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Brain and Heart Dynamics

Springer

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Editors

Brain and Heart Dynamics

With 73 Figures and 48 Tables

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ISBN 978-3-030-28007-9 ISBN 978-3-030-28008-6 (eBook)
ISBN 978-3-030-28009-3 (print and electronic bundle)
https://doi.org/10.1007/978-3-030-28008-6

This Springer imprint is published by the registered company Springer Nature Switzerland AG.
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

To Ottavia, Davide, Luca, Camilla, Wang Li, and Olivia: our next generations. They are love and drive to live for

Preface

Donatella said: “I’d like you all to write about how brain and heart talk to each other.” Pierluigi replayed by saying: “OK, I can collect a group of experts able to describe many, if not all, aspects of psyche and heart and how the first can drive the second.” Stefano added: “I can collect a group of experts describing all aspects of brain activity, pharmacology and the cardiovascular consequences of central neural disorders.” Being the cardiologist of the trio, Emilio felt like he was bound to be the target of the cross neural firing coming from above but he thought of the many years of great learning in neuro-cardiology. Emilio’s looping up was then: “Well guys, I’ll tell you how the heart is driving you both! The heart as a ‘sensing organ’ this is what I had learned from my great mentors who still guide me with their restless scientific life .” And this is how our great venture started.

The underlying understanding was that, in this arena, nothing is still and we were about to deal with “Brain Heart Dynamics” and the title was there! By joining our day-to-day scientific life, we had been sharing knowledge, going from the *invisible* orchestra to face autism to pharmacology of neural diseases to autonomic bidirectional drive of the heart. This is the deep soul of this reference book. We hope we fulfilled the goal that we pursued over 2 years of intensive work.

Moving along the index of the opera the reader will find, step by step, the description of the many ways by which the heart is sending its messages to the brain. This occurs within fractions of seconds so that neuromodulation of cardiovascular control can take place in a fraction of a second. Think about how many events the brain has to manage in a fraction of a second: we stand up in fraction of a second, maintaining cerebral perfusion against gravity that would take all blood to our feet. Emotions, as any other higher cerebral function. Need cardiovascular responses in a fraction of a second. Many aspects of our life run along this high-speed rail: at the time of any minor or, more so, severe perturbation of our mental process, anytime we take a pill or engage in exercise, when awake or sleeping. Of note, sleep is a time when most of our functions are under our autonomic nervous system’s control, but our mind process is reloading, and millions of data are reprocessed.

The entire life fluctuates in fractions of seconds, and this is the dynamic world still far from being understood that we aimed at describing in the 61 chapters that you’ll find available hereafter. We believe there is no need for a redundant recall of the importance of the continuing research on the

brain–heart interactions, but we would like to recall that this is the central drive of a whole, where any piece plays a role from the tip of the toe to the guts, the kidney, and edge of our hairs. One for all is the case of the novel use of electrical stimulation of the cervical vagus to effectively treat resistant epilepsy and depression. Eighty percent of the fibers travelling into the cervical vagus carries afferent information from all viscera to the CNS. This implies that the composite afferent information originating from the body can profoundly modulate the electrical and biochemical functions of the brain.

The take-home message we hope that the reader will save after working through the chapters of this reference book is, indeed, that our body operates in loops where the chief commander operates the driving and, in turn, is driven by the whole body. This is so because the heart and the rest of the body are designing its route. It seems sometimes as if somebody has indeed designed this beautiful functional architecture in the human body. Will the human being ever able to duplicate such architecture in her/his world? Meanwhile we hope you'll enjoy travelling along this book.

July 2020

Stefano Govoni
Pierluigi Politi
Emilio Vanoli

Acknowledgments

First, we would like to thank all contributors and section editors for making this book a reality!

An enormous thank to two great women who gave "brain and heart" to the conception of this opera: Donatella Rizza (see preface), who triggered the thought and drove the project to its approval, and Cristina Marelli, who supervised the project design and progression with her wonderful personality and bright mind. This work made it to its successful end because of the never-ending guidance by Shruti Datt: thank you so much. We want to express our profound gratitude to other fundamental contributors: Sandra Fabiani (Reference Publisher) for her continuous contribution over the entire period of manuscripts acquisition and management. We would also like to thank the Production PMs, Mr. Ragavan Rajasekaran and Ms. Madhivathani Madhi Maran, for their support in copyediting and typesetting.

Two years of wonderful work and learning! GRAZIE from the heart and brain!

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About the Editors

Stefano Govoni born in Milano, Italy, in 1950, is Full Professor of Pharmacology in the Department of Drug Sciences at the University of Pavia. He has worked in various Italian Universities (Bari, Brescia, Milano, Pavia) and back in 1979–81 at NIMH, St. Elizabeths hospital, Washington, D.C.

At the University of Pavia he has been director of the Department of Experimental and Applied Pharmacology, President of the Evaluation Office, Chancellor's Deputy for teaching activities, and Vice-Chancellor. Stefano Govoni has been Consultant for Biological Research Programs, Alzheimer Unit, FBF Hospital, Brescia; member of various ethical committees; and director of the Bioethical Committee of the San Matteo Hospital in Pavia, Italy.

Stefano Govoni has worked on brain aging and on Alzheimer's disease (AD) contributing to the definition of the neurobiology and physiology of beta amyloid and to the characterization of the antidementia drugs. In 2010, together with Emilio Vanoli, he started a search on the role of NGF in heart disease and is co-founder of a spin-off "Neuheart" working within this field. Recently he started a search on the therapeutic appropriateness of drugs used in nursing homes and in the elderly. In the period 2000–2011 he has been the national coordinator of a group of six laboratories belonging to various Italian universities (Pavia, Genoa, Catania, Florence, Foggia, Palermo) working on AD.

Stefano Govoni is author of more than 330 papers listed in Medline and some 20 books.

Pierluigi Politi is Full Professor of Psychiatry at the University of Pavia, Italy, and Head of Mental Health and Dependencies Department of ASST Pavia, the Regional Health Trust in Italy, and Head of the Specialization School in Psychiatry. He is also member of tEACH, the didactic subunit of International Association for Communication in Healthcare, and Full Member of the International Psychoanalytical Association.

His interest in heart and brain dynamics dates back to his Ph.D. years, when he supported the heart transplantation team at Pavia, Policlinico San Matteo Foundation; he provided evaluation of the candidates and follow-up of more than one thousand recipients. More recently, he focused his research and clinical work on autism spectrum disorders, through an intense cooperation with Cascina Rossago, the first Italian farm-community tailored for low-functioning people with autism. He thus developed bench to bedside research, besides new strategies of intervention, becoming a point of reference for the special talents in autism spectrum disorders. He also promoted some innovative job opportunities and a better quality of life in people belonging to this condition.

He authored/coauthored/edited 14 books, many books chapters, and some 140 papers on peer-reviewed journals. Being also an amateur jazz musician, he founded the Orchestra Invisibile (https://en.wikipedia.org/wiki/Orchestra_Invisibile) in 2005, a large jazz band, where one half of musicians belong to the autism spectrum condition.

Emilio Vanoli Graduated in Medicine with laude and specialization in Cardiology at the University of Milano. He has been involved in basic science and clinical research on autonomic nervous system cardiac control since his 4th year med school. Emilio was trained at the Centro Fisiologia Clinica and Ipertensione at the University of Milano, and he developed his research at the Department of Physiology at the University of Oklahoma HSC where he reached the position of adjunct Associate Professor of physiology and cardiology.

His major achievement here was the first experimental evidence of feasibility and efficacy of chronic implantable vagal stimulation in ischemic heart disease. Emilio is author and/or coauthor of 96 full-length papers and editor of 3 books. He is currently teaching at the International Harvey School of Medicine at the University of Pavia as Associate Professor of Cardiology in the Department of Molecular Medicine. He is sharing with Prof. Govoni the scientific direction of the academic spin-off named "Neu-Heart" whose first mission is active research on the Nerve Growth Factor (NGF). Clinically wise, he practiced as family doctor for 13 years in the Italian public healthcare system. Emilio was member of the intensive Coronary Care Unit staff at the IRCCS San Matteo Hospital in Pavia. He established his role in the area of autonomic treatment of heart failure as member of CIBIS II and III trials event committee.

Emilio is currently director of the outpatients Heart Failure Clinic at the IRCCS MultiMedica in Sesto San Giovanni (reference Cardiovascular Clinical Research Center for the Italian Ministry of Health Care) supported by extensive public funding to implement remote home monitoring of fragile patients.

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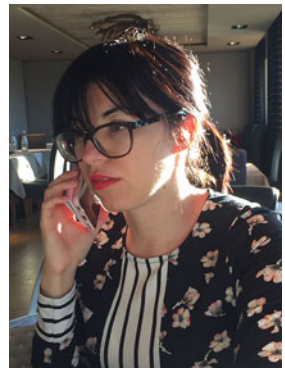

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Part I

Functional Anatomy and Molecular Basis of the Cardiac-Brain Axis

Brain-Heart Afferent-Efferent Traffic

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Veronica Dusi and Jeffrey L. Ardell

Contents

Abstract

The understanding of cardiac neuronal control has dramatically evolved in the last 50 years, both from an anatomical and a functional point of view. Cardiac neuronal control is mediated via a series of reflex control networks involving somata in the (i) intrinsic cardiac ganglia (heart), (ii) intrathoracic extracardiac ganglia (stellate, middle cervical), (iii) superior cervical ganglia, (iv) spinal cord, (v) brainstem, and (vi) higher centers. Each of these processing centers contains afferent, efferent, and local circuit neurons, which interact locally and in an interdependent fashion with the other levels

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*,
https://doi.org/10.1007/978-3-030-28008-6_2

to coordinate regional cardiac electrical and mechanical indices on a beat-to-beat basis. This neuronal control system shows plasticity and memory capacity, allowing it to maintain an adequate cardiac function in response to normal physiological stressors such as standing and exercise. Yet, pathological events such as myocardial ischemia as well as any other type of cardiac stressor may overcome the homeostatic capability of the system, leading to excessive sympathoexcitation coupled with withdrawal of central parasympathetic drive. In turn, autonomic dysregulation is central to the evolution of heart failure and the development of life-threatening arrhythmias. As such, understanding the anatomical and physiological basis for cardiac neuronal control is crucial to implement effectively novel neuromodulation therapies to mitigate the progression of cardiac diseases.

Keywords

Autonomic control · Autonomic imbalance · Cardiac neurons · Sympathetic system · Parasympathetic system

Introduction: Overview of Cardiac Neuronal Control

The complexity of cardiac neuraxis is broader than previously anticipated, both from a functional and a neurochemical point of view. For decades the leading theory assumed that cardiac neuronal control primarily resided within central neuronal projections that target peripheral postganglionic adrenergic and cholinergic motor neurons functionally behaving as antagonists among each other [1]. This hypothesis was referred to as centrally determined cardiac neuronal command [2–4]. The two major central cardiac autonomic outputs include: (i) parasympathetic efferent preganglionic neurons located in the medulla oblongata primarily in the ventral lateral component of the nucleus ambiguus [5–7] and (ii) sympathetic efferent preganglionic neurons located in caudal cervical and cranial thoracic spinal cord segments (intermediolateral cell column) ([8–10]). In such a scenario, the peripheral afferent arm was represented by sensory neuronal somata located in nodose and thoracic dorsal root ganglia [11, 12], which in turn projected to medullary and spinal cord second neurons [8], respectively. Cardiovascular afferent inputs also converge to forebrain neurons and cortical neurons – particularly those in the insular cortex [13, 14] leading to a tonic descendant influence on efferent stations. According to this view, the first integration of afferent inputs occurred either at a medullary level (for the nodose ganglia central projections) or at the spinal cord level (for the thoracic dorsal root ganglia central projections). On the other side, intrinsic cardiac ganglia located in fat pads on the heart were thought to only contain parasympathetic postganglionic neuronal bodies. The realization that an additional neuronal processing of cardiovascular inputs takes place at the peripheral level [15, 16], specifically through interconnected neurons in the thorax (intracardiac and extracardiac), led to a rethinking for the neural networks responsible for autonomic control of the heart. A turning point was the discovery that the neuronal soma contained in epicardial fat pads on the heart represented a complex and functionally independent neuronal network, including efferent neurons (both sympathetic and parasympathetic) as well as afferent neurons and interneurons [15]. The entire network started to be referred to as *the intrinsic cardiac nervous system (ICNS)*, or, reflecting its ability to allow for shorter-loop dynamic reflex control over regional cardiac function [17], the *little brain in the heart* [16]. From an anatomical point of view at least 10 major groupings of ganglionated Plexi have been associated with the human ICNS, although their delineation is not easy due to the continuum nature of the fat located at the base of adult human hearts. Most of these ganglia are located on the posterior surfaces of the atria and superior aspect of the ventricles. Overall, ICNS in humans is estimated to contain more than 14,000 neurons [18].

The presence of afferent neurons and interneurons, in addition to the efferent neurons, has been also demonstrated in other intrathoracic,

extracardiac ganglia, such as the cervical ganglia and the stellate ganglia. As such, the actual leading theory is that cardiac neuronal control is achieved through a hierarchal network whose organization can be simplified in three levels (Fig 1):

Level 1: CNS neurons (medullary and spinal cord neurons modulated by higher centers)
Level 2: Peripheral: extracardiac-intrathoracic neuronal pool and
Level 3: Peripheral: the ICNS. The peripheral levels (Levels 2 and 3) form cardio-centric reflex control loops, while the CNS (Level 1) engages central neural mechanisms for cardiac and peripheral vasculature regulation [15, 19]. In addition to the unraveling of the pivotal role of ICNS, the last decades brought about important steps forward in the understanding of the neuromodulators and the neurotransmitters involved in cardiac autonomic control as well as in cardiac innervation patterning.

In this chapter, the description of structural and functional organization of cardiac nervous system is focused on the peripheral aspects of this hierarchy. We will first describe what is currently known about the locations of cardiac afferent neurons in

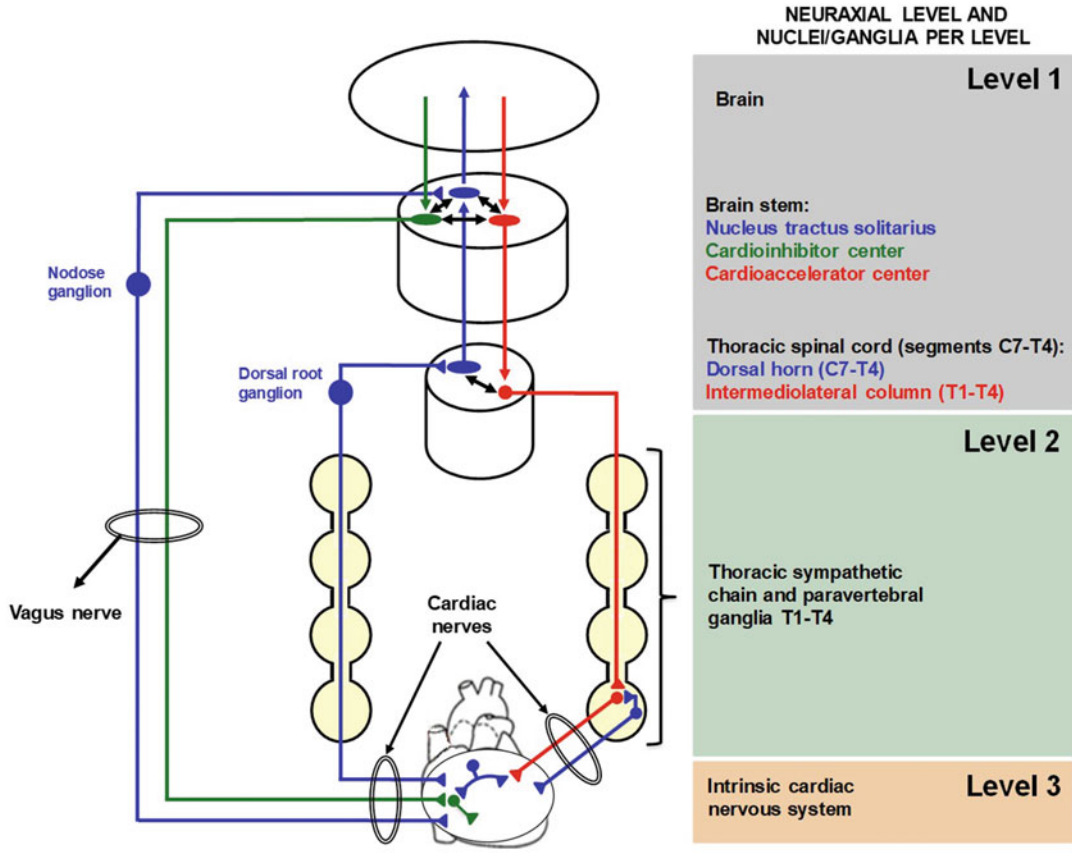

Fig. 1 Cardiac nervous system organization in humans. Blue: afferent nervous system with its ganglia: nodose ganglia and C7-T4 dorsal root ganglia (DRG). Green: parasympathetic efferent nervous system. Red: sympathetic efferent nervous system. All the afferent and efferent structures except for the autonomic nuclei in the central nervous system are bilateral, although mostly represented as unilateral for simplicity. Cardiac afferent fibers traveling across the paravertebral sympathetic ganglia (usually referred to as cardiac sympathetic afferent fibers) directly reach the DRG without having synapsis before. These fibers mediate cardio-cardiac sympathoexcitatory spinal reflexes that significantly increase the sympathetic output to the heart

dorsal root, nodose, intrathoracic extracardiac and intrinsic cardiac ganglia, along with their varied transduction capabilities. This will be followed by a summary of the roles that cardiac (adrenergic and cholinergic) efferent neurons play in motor control. The role of peripheral interactive local circuit neurons (LCNs) in the ICNS will be discussed as well. Finally, we will provide a deep insight into the structure/function characteristics of cardiac neuronal control in cardiac pathology, with a focus on myocardial ischemia-induced changes.

Structural and Functional Organization of the Cardiac Nervous System: Peripheral Signaling

Cardiac Afferent Neurons

Based on anatomical evidence, afferent neuronal somata whose sensory neurites projects on atrial, ventricular, and intrathoracic major intravascular tissues have been identified not only in nodose [20, 21] and dorsal root ganglia [20–23], but also in intrathoracic extracardiac ganglia such as the stellate ganglia and the middle cervical ganglia [12, 24, 25], and in intrinsic cardiac ganglia [26–28]. Intracardiac endings of these sensory neurons are concentrated in the sinoatrial nodal region, dorsal aspects of either atrium, endocardium of either ventricular outflow tract and in the papillary muscles of both ventricles [11, 29–32]. Vascular sensory endings are embedded in the fibrous coating of the major vessels adjacent to the heart [12, 33–36] and within the carotid sinus. Cardiac afferent fibers reaching the nodose ganglia travel along vagal nerve branches and are commonly referred to as cardiac parasympathetic afferent fibers. Cardiac afferent fibers reaching the dorsal root ganglia (DRG) travel across the paravertebral sympathetic ganglia (without having synapsis) and are commonly referred to as cardiac sympathetic afferent fibers. Primary cardiac-afferent projections from nodose ganglia project primarily into the nucleus tractus solitarius (NTS) to impact cardiac control; those from the DRG into the thoracic spinal cord dorsal horn [37]. From an embryological point of view, cardiac sensory neurons and cardiac efferent sympathetic neurons share the same origin from trunk neural crest cells [38, 39]. These two neuronal cell types also share important regulatory pathways such as the responsiveness to nerve growth factor (NGF) exposure, which is critical for their development. Indeed, cardiac nociceptive sensory nerves, the dorsal root ganglia, and the dorsal horn were found to be markedly retarded in NGF-deficient mice, whereas cardiac-specific overexpression of NGF rescues these deficits [40]. Thus, NGF synthesis in the heart is considered critical for the development of cardiac sensory nervous system [41].

The response of sensory endings to local mechanical and/or chemical milieu at the cardiac level is different depending on the cardiac region in which their neurites are located and the ganglion in which their various somata reside [12]. According to the type of stimuli they respond to, cardiac afferent neurons are classified as (i) mechanosensory, (ii) chemosensory, or (iii) multimodal (transducing both modalities) in nature. Mechanosensory and multimodal sensitive fibers are mostly myelinated (A delta type), while chemosensory fibers are mostly unmyelinated (C type). Power spectral analysis studies revealed that mechanical and chemical stimuli are transduced within different time domains both in specialized and in by multimodal fibers [42]. Mechanotransduction occurs fast (within few seconds), produces phasic activity in the afferent neurons, and shows a very limited memory. On the other side, chemotransduction generates relatively slow onset responses in afferent neurons, characterized by tonic (nonphasic) activity, relatively low frequencies, and memory [43]. This confers the capacity of individual afferent neurons to transduce differing stimuli at a particular time depending on the strength of the local milieu [42, 44, 45]. It is presumed that such multiple coding allows for limited populations of sensory neurons to transduce to second order neurons the status of regional cardiac mechanical and/or chemical milieus concomitantly [12].

Nodose Ganglion Cardiac Afferent Neurons

Nodose ganglia (otherwise known as inferior ganglia of the vagus nerve) are paired structures located within the jugular foramen where the vagus nerve exits the skull. Atrial and ventricular sensory neurites with central projection to nodose ganglion (usually referred to as parasympathetic afferent fibers) preferentially transduce regional chemical stimuli, with a smaller amount responding to mechanical stimuli or both modalities [22]. Nodose ganglia epicardial chemosensory fibers generate different central neuronal inputs as compared to mechanosensory fibers, both from a quantitative and a qualitative point of view. Chemical stimuli induce an order greater enhancement of activity of nodose ganglion cardiac afferent neurons. Than mechanical stimuli do. Moreover, the augmentation in activity elicited by chemical stimuli persists long after removal of the stimuli (up to 45 min), while mechanical stimuli exert short-lived effects [22]. Inputs from these receptors continuously participate to overall cardiovascular regulation on a beat to beat basis. They are not normally perceived by the sensorium but they may contribute to symptoms referred to the neck and jaw regions of the body during myocardial ischemia [49]. An experimental canine study showed that ventricular afferent neurons of the nodose ganglia are distinct from those in the DRG by having smaller size and a lacking immunoreactivity for substance P (SP), calcitonin gene-related peptide (CGRP), and/or neuronal nitric oxide synthase (nNOS) [20].

Dorsal Root Ganglion Cardiac Afferent Neurons

Cardiac related afferent neurons represent only a small percentage of dorsal root ganglia first-order neurons and they are primarily concentrated within the C6 to the T6 levels of the spinal column [21, 46]. Peripheral projections of these pseudo-unipolar neurons can be found in all four cardiac chambers, with a propensity for cranial ventricular regions [42]. Cardiac DRG afferent neurons mostly (∼95%) display multimodal transduction characteristics [42]. They transduce the cardiac milieu quite differently than nodose ganglion cardiac afferent neurons do [12], both in control states and during maximal level stimulation. In control states cardiac DRG afferent neurons discharge rate is higher (∼10 Hz) than nodose ganglion cardiac afferent neurons discharge rate (∼0.1 Hz) [47]. Upon maximal stimulation, their activity enhancement range is about +225% and +500% for mechanical and for chemical stimuli, respectively [48], as compared to +75% for both mechanical and chemical stimuli in the nodose ganglion cardiac afferent neurons. Individual DRG cardiac afferent neurons display a variety of activity patterns when transducing local mechanical versus chemical stimuli and when transducing multiple chemical stimuli simultaneously [12]. Thanks to this transduction capacity/plasticity, the number of DRG neurons required to transduce a constantly changing cardiac milieu to spinal neurons is minimized. At the molecular level, transient receptor potential vanilloid type 1 (TRPV1) receptors, due to their polymodal transducers capabilities, might significantly contribute to DRG cardiac afferent fibers properties. TRPV1 channels are expressed in DRG neurons that extend to both Aδ- and C-fibers. TRPV1 receptors are members of the big family of the transient receptor potential (TRP) channels, a class of non-specific cationic channels which has recently received a great attention in the cardiovascular field due to their capability to mediate pathological calcium-handlings in several cell types including cardiomyocytes, neurons, and endothelial cells [49].

Cardiovascular Afferent Neurons in Intrathoracic Extracardiac Ganglia and in Ganglionated Plexi

As already mentioned, sensitive pseudo-unipolar neurons have been identified in several intrathoracic ganglia [24, 50, 51]. Many afferent neurons mapped in the stellate and middle cervical ganglia transduce aortic arch wall dynamics; their collective active patterns reflect the pressure waves occurring during each cardiac cycle [24, 25, 50, 52]. On the other hand, a considerable fraction of cardiac sensory neurons is multimodal in nature,

transducing both mechanical and chemical stimuli. The later include adenosine, ATP, bradykinin, substance P, and various other peptides. It is also known that the transduction properties of their cardiac sensory neurites involve several ion species in situ [12].

Cardiac Motor Neurons

The two efferent branches of cardiac neuraxis, namely, the sympathetic and the parasympathetic division, control all cardiac functions: inotropy, chronotropy, dromotropy, bathmotropy, and lusitropy. In addition to that, it is now clear that sympathetic-parasympathetic interaction also affects inflammatory response onset, maintenance, and decay [53]. In general, sympathetic outputs to the heart are facilitatory, whereas parasympathetic outputs are inhibitory. The kinetics of the two autonomic divisions differ substantially. The vagal effects develop very rapidly, often within one heartbeat, and they decay quickly. Hence, the vagus nerves can exert beat-by-beat control of cardiac function. Conversely, the onset and the decay of the sympathetic effects are more gradual; only small changes are affected within the time of one cardiac cycle. When the two efferent branches act concomitantly, the effects are not additive algebraically, but complex interactions prevail. Such interactions may be mediated at multiple levels from the ICNS to the CNS; at the cardiac level they include both prejunctional and postjunctional interactions with respect to the neuro-effector junction [54]. As already mentioned, sympathetic efferent neurons share the same embryological origin as cardiac sensory neurons, represented by trunk neural crest cells. Trunk neural crest cells migrate and form sympathetic ganglia by mid-gestation, subsequently proliferating and differentiating into mature neurons [55]. In contrast, parasympathetic neurons derive from cardiac neural crest cells, which migrate into the developing heart and participate in septation of the outflow tract into the aorta and pulmonary trunk, development of aortic arch arteries, and the formation of cardiac ganglia [56–58].

Cardiac Sympathetic Efferent Neurons

Cardiac sympathetic preganglionic neurons have their soma in the intermediolateral column of the spinal cord (T1-T4 levels). Most of them synapses on postganglionic neurons located in the sympathetic cervical ganglia and upper thoracic paravertebral ganglia [7]. In humans, the lowest cervical ganglion (C8) and the highest thoracic ganglion (T1) are usually fused to constitute the left and the right stellate ganglia (also referred to as cervicothoracic ganglia). These structures convey the majority of cardiac sympathetic postganglionic fibers to the heart. The remaining postganglionic projections are provided by the left and right T2–T4 paravertebral ganglia. Sympathetic fibers arising from the right and from the left cervicothoracic ganglia have an asymmetrical, although largely overlapping distribution to the heart. The sinus node is under a predominant right-sided cervico-thoracic sympathetic innervation, while extracardiac sympathetic innervation to the atria and to the atrio-ventricular node is provided by both the right and left sympathetic chain [59]. From a functional point of view, the predominant role of right-sided sympathetic nerves over sinus node control has been consistently demonstrated at the preclinical level over years [60–62] and recently confirmed using very sophisticated optogenetic and viral vector strategies [63]. Finally, the right sympathetic chain was shown to mostly innervates the anterior surface of the ventricles, whereas the left chain was shown to mostly distributes to the posterior surface [64, 65], although a high degree of overlapping has been reported in canine and porcine hearts [66, 67]. Accordingly, despite most of the extracardiac sympathetic innervation to the left ventricle is provided, from a quantitative point of view, by the left sympathetic chain, a not neglectable contribution of right sympathetic nerves has been demonstrated as well [68].

As already mentioned, some (a minority) of sympathetic fibers synapses with sympathetic efferent postganglionic neurons located throughout the major atrial and ventricular ganglionated Plexi [27, 69–71]. This subgroup of intrinsic cardiac neurons contains mRNA and protein enzymes involved in catecholamine biosynthesis

[72, 73]. They are capable of augmenting cardiac function even when disconnected from higher centers of the cardiac nervous system [17, 26, 74, 75]. Of note, cardiac sympathetic control through postganglionic neurons in the ganglionated plexi work as an overall sympathetic neuronal network free from topographic boundaries, although preferential areas of influence have been suggested. Indeed, sympathetic efferent postganglionic neurons in each major ganglionated plexus exert control over electrical and mechanical indices throughout the atria and the ventricles [76–78]. This redundancy assures the persistence of enough adrenergic control over the heart even when the function of one ganglionated plexus is compromised.

From an anatomical point of view, sympathetic efferent postganglionic fibers travel along coronary arteries at the subepicardial level, predominantly in the ventricles with a base to apex gradient: sympathetic fibers are most dense near the base of the ventricles with fewer fibers running near the apex of the heart [79]. In addition to that, the distribution of sympathetic fibers to the myocardium was proved to be inhomogeneous in several animal species including pigs [80], dogs [81], and cats [82]. In these species a pronounced epicardial to endocardial sympathetic innervation gradient within ventricular walls has been observed, with sympathetic innervation being most abundant in the subepicardium. An intriguing regional exception is represented by the right ventricular outflow tract (RVOT), whose efferent sympathetic fibers were shown to run in canine not only in the subepicardium but also in the subendocardium [83]. Additionally, the main skeleton of the conduction system, which includes the sinoatrial node, the atrioventricular node, and the His bundle, is extensively innervated compared to the working myocardium with both sympathetic and parasympathetic efferent fibers. Of note, despite its clinical importance, the molecular mechanisms underlying sympathetic innervation density throughout ventricular walls have long been poorly understood. Lately [84] it was shown that cardiac sympathetic innervation is determined by the balance between neural chemoattraction and neuronal chemorepulsion, both of which occur in the heart at early stages of its development. NGF, which is a potent chemoattractant, is synthesized abundantly by cardiomyocytes and is induced by endothelin-1 upregulation in the heart. In contrast, semaphorin-3A (Sema3a), which is a neural chemorepellent, is expressed strongly in the trabecular (endocardial) layer in early stage embryos and at a lower level after birth, leading to epicardial-to-endocardial transmural sympathetic innervation patterning. Intriguingly, both Sema3a-deficient and Sema3a-overexpressing mice showed sudden death or lethal arrhythmias due to disruption of innervation patterning [85].

Finally, at the synaptic level, norepinephrine (NE) is the main, although not the sole neurotransmitter released by sympathetic efferent neurons. Neurotransmitters other than NE released by sympathetic efferent fibers are an area of intense research [86, 87]: at last three other co-transmitters have been identified in sympathetic nerves, including ATP, galanin, and neuropeptide Y (NPY). Co-release mainly occurs during high-frequency neuronal stimulation [88]. As opposed to the rapidly metabolized ATP, galanin and NPY are slowly diffusing molecules with a much longer half-life and duration of action compared with classical neurotransmitters. Both galanin [89] and NPY receptors (Y2-type) [90, 91] were localized on cholinergic vagal neurons projecting to the sinoatrial node and were found to be implicated in the long-lasting inhibition of vagally induced bradycardia evoked by sympathetic adrenergic stimulation [92]. NPY may also act directly on Y1 receptors on ventricular cardiomyocytes, affecting their electrophysiological properties. Intriguingly, Y1 receptors are coupled to both adenylyl cyclase (inhibited) and phospholipase C (activated). Optical mapping experiments in rats showed that NPY steepens the action potential duration restitution curve [86]. Very recently, in Langendorff-perfused rat hearts with intact innervation, Y1 receptor activation was associated with a significant reduction in ventricular fibrillation threshold despite metoprolol that was accompanied by increased amplitude and decreased duration of intracellular calcium transients [93]. Finally, NPY is also a potent vasoconstrictor [94].

Cardiac Parasympathetic Efferent Neurons

Parasympathetic efferent preganglionic soma mostly originates from the nucleus ambiguous within the medulla oblongata. Lesser numbers are located in the dorsal motor nucleus and the intermediate zone between these two medullary nuclei [6, 95–101]. Preganglionic neurons project axons via the vagus nerve and its multiple intrathoracic cardiopulmonary branches to efferent postganglionic parasympathetic neurons located in the numerous intrinsic cardiac ganglia. Postganglionic efferent parasympathetic neurons located in individual cardiac ganglia receive preganglionic inputs from both the right and left vagal trunks. As already mentioned, most of the ganglia of the human ICNS are located on the posterior surfaces of the atria and superior aspect of the ventricles, within epicardial fat pads. Each of them contains a variety of neurons that are associated with complex synaptology [18].

From a functional point of view, despite some suggestions [6, 102, 103] of a selective control from parasympathetic preganglionic neurons in one medullary region towards atrial versus ventricular ganglionated Plexi modulating specific cardiac indices (e.g., rate vs. conduction) have been provided, there is no conclusive evidence supporting this theory. On the contrary, several data support an integrative parasympathetic control of the heart, including the anatomical organization of cardiac parasympathetic efferent projections. On one side, vagal preganglionic neurons bilaterally project to multiple ganglionated plexi (divergence), on the other side, there are several interganglionic connections between the aggregates of intrinsic cardiac neurons [27, 104, 105] and postganglionic cholinergic neurons located within the various intrinsic cardiac ganglionated Plexi projecting to all regions of the heart. Therefore, it is currently believed that medullary preganglionic cholinergic neurons as well as postganglionic neurons located in each major intrinsic cardiac ganglion exert a widespread control over the various regions of the heart, rather than having a selective control on specific cardiac regions and/or indices [26, 43]. Yet, broad areas of preferential (but never selective) influence have been identified: nicotine sensitive neurons of atrial ganglionated Plexi modify primarily, but not exclusively, atrial tissues, whereas ventricular ones modify primarily, but not exclusively, ventricular tissues [106].

Following vagal preganglionic inputs, ICNS neurons mediate a reduction in several cardiac indices including sinus node rate, atrial contractility, atrial refractory period duration [107], atrioventricular nodal conduction, and ventricular contractile force [1, 108, 109]. Of note, since the first demonstration of functional parasympathetic efferent postganglionic projections to the ventricles [109], it is now well recognized that cholinergic efferent postganglionic neurons preferentially suppress ventricular endocardial contractile function, in particular that of the papillary muscles [65, 110, 111]. Along the same way, autonomic control of chronotropic function involves coordinated activities of the right atrial, posterior atrial, and dorsal atrial intrinsic cardiac ganglionated plexi [112, 113].

Taken together, these data demonstrate that neurons located in atrial or ventricular ganglionated plexi [18, 28, 114] target widely distributed regions throughout the heart [76–78, 106], supporting the thesis that the ICNS, as a whole, acts as a distributive control center [16, 43, 115]. Specifically, this functional anatomy has been emphasized to dispel the concept that one may ablate select neuronal populations with the presupposition that select cardiac modalities can be chronically targeted [116]. As matter of fact, animal data clearly showed that following discrete ablation of one element of the ICNS, the network adapts and functional control is restored [117].

Local Circuit Neurons

The term of local circuit neurons (LCNs) refers to neurons that are not directly conveying information about the cardiovascular milieu (cardiac afferent neurons) or having direct motor function (cardiac efferent neurons). Their main function is to allow for connection and processing functions within and between peripheral autonomic ganglia [15, 118]. As such, these neurons act as an integrating station between inputs from the heart and major intrathoracic vessels and descending inputs from central autonomic motor neurons. As

already mentioned, LCNs can be found throughout all intrathoracic ganglia, including those distributed on the heart [15, 16, 27]. They are constantly communicating one with the other, even when chronically disconnected from the central nervous system [22, 24, 26, 75]. The anatomical arrangement of LCNs reflects their function: rosettes of relatively large diameter neuronal somata (i.e., about 30 μmol/L) have been identified in intrathoracic extracardiac [134] and intrinsic cardiac [38, 129, 135, 179] ganglia. The majority of somata of LCNs projects axons within the ganglia in which they are located interdigitating primarily with of other neuronal somata within that ganglion; other subserve interganglionic coordination. Such anatomical arrangement concurs to the complex information processing that occurs within individual ganglionated Plexi at the level of the heart.

LCNs receive and process a variety of information. According to type of inputs they receive, LCNs have been classified in 3 main subgroups: efferent related LCNs, afferent related LCNs and convergent LCNs [27]. Efferent related LCNs receive inputs from one or both of efferent limbs (sympathetic and parasympathetic) of cardiac autonomic nervous system. Afferent related LCNs are involved in solely transducing regional cardiac, major intrathoracic vascular or the pulmonary milieus [26, 27]. Convergent LCNs integrate inputs from central sympathetic and/or parasympathetic efferent projections and afferent inputs. In addition, there are other populations of intrinsic cardiac LCNs that do not receive direct or indirect inputs from central or cardiovascular afferent sensory source [27], whose function to date remains unknown. Convergent LCN's are a major target for neuromodulation therapies [119].

Structural and Functional Organization of the Cardiac Nervous System: Central Signaling

Sensitive structures: First order cardiac afferent neurons of the nodose ganglia and the dorsal root ganglia synapse on second order neurons located in the NTS and in the dorsal horn of the spinal cord (laminae I, V [120] and VII [121] of the gray matter), respectively. Spinal cardiac afferent pathways are different according of whether they convey nociceptive inputs or not. Cardiac noxious inputs, as well as somatic and other visceral noxious inputs, follow the spinothalamic tract. This tract is the classical pain pathway that transmits information about noxious episodes to the thalamus and from there to areas of the cortex that are involved with pain perception [122]. Both myelinated and non-myelinated afferent fibers arising from the cardiopulmonary region were proved to excite spinothalamic tract cells in the T1-T5 segments [123, 124]. Non-noxious inputs converge on the NTS, as well as all visceral inputs other than the painful ones. The NTS conveys cardiac inputs to the hypothalamus and to the thalamus; on turn, the thalamus projects on cortical neurons – particularly those in the insular cortex [13, 14].

Motor structures: Central autonomic efferent network is composed of both hypothalamic and extra-hypothalamic nuclei [125]. The paraventricular nucleus (PVN) of the hypothalamus is a master controller of the autonomic nervous system and is one of the most important central sites involved in regulating sympathetic tone to the heart [125]. The PVN contains excitatory and inhibitory neurons, whose balance determines cardiac sympathetic tone [126]. In nonpathological conditions, the tonic inhibition of the PVN autonomic neurons is mediated by GABA- and NO-releasing neurons [127]. Subcortical extra-hypothalamic sites associated with control of sympathetic outflow include the central nucleus of the amygdala [128], the norepinephrine-containing neurons of the dorsal mesencephalon (locus coeruleus) and the rostral and caudal ventrolateral medulla [129, 130], and the serotonin-containing neurons of the pontine and medullary raphe nuclei [125, 131]. Subcortical extra-hypothalamic sites associated with control of parasympathetic outflow include the central nucleus of the amygdala [132, 133], the periaqueductal gray [134], the raphe nuclei, the parabrachial nucleus [135], and the dorsal motor nucleus of the vagus and the nucleus ambiguous [103]. Finally, limbic cortices, including the cingulate, orbitofrontal [136], insular and rhinal cortices, and the hippocampus, influence both sets of autonomic outflows [125, 132].

Neuraxial Transduction of Cardiac Pathology

Plasticity and memory capacity are crucial characteristics of cardiac neuraxis in the attempt to maintain an adequate cardiac function [16, 137] in response to physiological perturbations [19] of cardiovascular milieu. Yet, as any other homeostatic mechanism, they have a limit in their capability to properly respond to environmental stressors. When the demands of a deteriorated cardiac function exceed the homeostatic limit, either acutely or over longer time scales, neuronal plasticity and memory may lead to a profound disruption of cardiac neuraxis functional responses and hierarchy. This is typically the case of conditions such as heart failure or acute myocardial ischemia/infarction. For instance, the sensory transduction of regional ventricular ischemia can lead to enhanced excitability in network interactions because of reactive and maladaptive responses taking place at several levels of cardiac neuraxis, from the ICNS [138] to the insular cortex [43]. Excessive sympathoexcitation coupled with withdrawal of central parasympathetic drive reorganizes pre- and postsynaptic mechanisms [139–144]. At the cardiac level, the tissue ratio between parasympathetic and sympathetic fibers conveys important functional implications, because the two systems mutually antagonize one another, both at the presynaptic and at the postsynaptic level. Acetylcholine (ACh) inhibits NE release from sympathetic synapses [145, 146] and antagonizes NE effects at cellular levels. NPY and galanin released from sympathetic nerve terminals during high level sympathetic activity inhibit Ach release from parasympathetic terminals. Moreover, ACh also exerts direct anti-inflammatory and antiapoptotic effects at cardiac level through purinergic pathways [147]. With disease associated withdrawal of parasympathetic tone, the antiadrenergic, anti-inflammatory, and antiapoptotic protective effects mediated by parasympathetic activity are lost [148]. As such, autonomic dysregulation spanning from the peripheral to the central level is now recognized as fundamental contributor to the progression of cardiac pathology.

Neuraxial Transduction of Myocardial Ischemia and Infarction

The pathological activation of cardiac afferent neurons induced by acute myocardial ischemia and reperfusion leads to a powerful increase in sympathetic efferent drive to the heart [149]. The immediate consequence of this reflex, also known as cardiac sympathetic afferent reflex (CSAR), is a strong inotropic, vasopressor, and chronotropic response, aimed to sustain cardiac output. The inevitable adverse effect is a consistent increase in metabolic demand and in arrhythmic susceptibility. Indeed, the epicardium to endocardium gradient of sympathetic efferent fibers concur to explain the more severe electrophysiological disturbances observed in ventricular epicardium rather than endocardium during acute myocardial ischemia, including more pronounced changes in monophasic action potential [150] and greater prolongation of conduction time and refractory period [151]. Direct neural recordings of cardiac autonomic activity have proven that such an activation may occur within seconds after the onset of acute myocardial ischemia and may affect survival according to whether the pro-arrhythmic action of sympathetic activity or the protective action of vagal activation is predominant [152]. Accordingly, several preclinical studies throughout the years consistently showed that the interruption of CSAR at any level (afferent [153, 154] or efferent [155, 156]) and by any mean (surgical or chemical neuronal ablation) was associated with protection towards ischemia-related ventricular arrhythmias as well as other detrimental effects of excessive sympathoexcitation. For example, selective chemical ablation of TRPV1-expressing afferent fibers by application of resiniferatoxin (a toxic activator of the TRPV1 channels) provided powerful protective effects against ischemia-induced ventricular arrhythmias in dogs [157, 158] as well as against the adverse cardiac remodeling and autonomic dysfunction induced by myocardial infarction (MI) in rats [159]. Of note, the involvement of cardiomyocytes in the neuraxial transduction of acute myocardial ischemia is crucial. First, they are the main source [160] of ischemic metabolites

such as lactic acid, bradykinin (BK), prostaglandins, adenosine, and reactive oxygen species (ROS) that constitute powerful stimuli for cardiac afferent nerve endings. Second, they are able to produce neurotrophic factors such as NGF, that has strong impact on neuronal phenotype and innervation densities [137, 161].

Neural remodeling processes begin in a few minutes/hours after an acute coronary occlusion and may lead to denervation, nerve sprouting, and sympathetic hyperinnervation [161]. After a transmural myocardial infarction, sympathetic denervation occurs not only within the dense scar, but also in the viable myocardium surrounding the scar and in remote regions [162, 163]. The denervated myocardium is characterized by an increased susceptibility to catecholamines, also known as denervation supersensitivity [164], resulting in an exaggerated refractoriness shortening when exposed to catecholamines perfusion and a subsequent increase in arrhythmic vulnerability. The hyper-innervated myocardium is characterized by a constitutively abnormal afferent signaling combined with a very patchy distribution of sympathetic efferent fibers [165]. NGF plays a pivotal role in the neural regeneration processes occurring after an ischemic cardiac insult. Experimental data in conscious dogs documented that NGF infusion in the left stellate ganglion induces a significant nerve sprouting (evaluated by the analysis of the tyrosine-hydroxylase (TH) and the growth-associated protein 43 (GAP43) markers) at the cardiac level, potentially leading to excessive expression of cardiac innervations, ventricular fibrillation (VF), and sudden cardiac death [166, 167]. A spontaneous augmentation of NGF has been documented in the myocardial site of injury in experimental dogs, together with an increase in NGF protein and NGF mRNA. Specifically, NGF protein arises very quickly in the infarct site, while NGF mRNA takes 3 days to reach its peak [168]. Furthermore, the transcardiac concentration (difference between coronary sinus and aorta) of NGF increases just after the myocardial infarction, long before the expression of NGF mRNA, thus suggesting a rapid release from storage areas [168]. Early NGF increase is mostly observed in the border zone of the myocardial lesion. Notably, a spontaneous raise in NGF and GAP43 expression was found in the LSG without a parallel increase in mRNA content, supporting the idea of a retrograde axonal transport of NGF and GAP43 from the infarcted site to the LSG [168]. From the LSG, the nerve sprouting signal induces a generalized enhancement in cardiac nerve density (hyperinnervation) throughout the heart (including both ventricles and atria), especially at the noninfarcted left ventricular free-wall sites [168]. Cardiac nerve sprouting peak was observed at 1 week after MI [168]. Accordingly, stellate ganglion nerve activity (SGNA) was shown to rapidly increase within a few seconds after myocardial infarction and to continue over the following weeks [169]. Increased SGNA was associated with intramyocardial nerve sprouts and increased neuronal size and synaptic density in the LSG, as much as in the right stellate ganglion (RSG) [140, 169, 170]. NGF production by itself was found to be related with CSAR. Indeed, in a rat experimental model where during ischemia, NGF myocardial levels increased significantly within 60 min of occlusion and plateau by 6 h, sympathetic deafferentation by pharmacological blockade of dorsal roots resulted in a dramatic reduction in NGF expression [171]. This would suggest that NGF expression during myocardial ischemia is indeed regulated by sympathetic reflexes [171]. Of note, despite such demonstrated importance of NGF in sympathetic neural remodeling, the upstream molecules that regulate NGF expression *in vivo* are still largely unknown. Intriguingly, endothelin-1 (ET-1), an endothelium-derived vasoactive peptide released in the early hours of acute myocardial infarction and associated with poor prognosis and no-reflow phenomenon [172], was found to specifically upregulate NGF expression in primary cultured cardiomyocytes among several cardiac hypertrophic factors [173]. In contrast, mechanical stretch and α-1-adrenergic stimulation were shown to downregulate NGF expression via activation of the calcineurin-NFAT pathway in cardiomyocytes, resulting in decreased neurite outgrowth [174].

Finally, beyond activating strong sympathetic extracardiac reflexes, acute myocardial ischemia

has a deep and only partially unraveled impact on the ICNS which, as already mentioned, is the convergence point for cardiac neural control. Back in 2000 [175], only 3 years after the first description of ICNS anatomy in humans [18], it was shown that intrinsic cardiac (IC) neurons from humans with ischemic heart disease contain inclusions and vacuoles and display degenerative changes in their dendrites and axons. Subsequently, *in vitro* intracellular studies of IC neurons derived from chronic MI animals showed enhanced excitability, altered synaptic efficacy, and adaptive changes in neurochemical phenotypes and neuromodulation [143]. Yet, the knowledge on the functional consequences of such changes on neural signaling *in vivo* in the context of a healed infarct has been very limited since recent years. In 2016, by using advanced techniques of *in vivo* neuronal recording and processing, it was clearly shown that MI induces a profound functional as well as structural remodeling of the ICNS [165]. Afferent neural signals from the infarcted region to IC neurons were attenuated, while those from border and remote regions were preserved post-MI, giving rise to a "neural sensory border zone." Convergent IC local circuit (processing) neurons were shown to have enhanced transduction capacity following MI. Overall, functional network connectivity within the ICNS was proved to be reduced post-MI. Another very important piece in the puzzle was added in 2017 [176]. As already mentioned, the vast majority, albeit not the entirety, of ICNS efferent neurons is constituted by parasympathetic neurons. Therefore, the characterization of MI impact on ICNS structure and connectivity is expected to consistently increase our understating of the mechanisms underlying parasympathetic dysfunction during and after MI. Indeed, in a post-MI porcine model it was shown [176] that in contrast to NE levels, cardiac acetylcholine levels remain preserved in border zones and viable myocardium of infarcted hearts. Yet, *in vivo* neuronal recordings of infarcted animals demonstrated abnormalities in firing frequency of parasympathetic neurons. ICNS neurons that were activated by left vagal nerve stimulation (VNS) displayed a low basal firing frequency, while neurons that were suppressed by left VNS had abnormally high basal activity. Additionally, although the total number of convergent and efferent parasympathetic neurons, as well as the primary relationships of these neurons, was unchanged between normal and infarcted hearts, the proportion of convergent LCNs that would normally receive only parasympathetic input decreased, and the proportion receiving sympathetic input increased, providing evidence for increased sympathetic drive coupled with lack of parasympathetic drive. These data suggest that parasympathetic cardiac neuronal network remains anatomically intact after MI but undergoes a functional remodeling compromising the final sympathetic/parasympathetic balance at the tissutal (cardiac) level. Supporting this theory, in the same model it was demonstrated that augmenting parasympathetic drive with cervical vagal nerve stimulation reduced ventricular arrhythmia inducibility by decreasing ventricular excitability and heterogeneity of repolarization of infarct border zones, an area with known proarrhythmic potential. The authors concluded that preserved acetylcholine levels and intact parasympathetic neuronal pathways could explain the electrical stabilization of infarct border zones observed with vagal nerve stimulation, providing insight into its antiarrhythmic benefit. Of note, the antiarrhythmic effects of vagal stimulation/activity towards ischemia/reperfusion related arrhythmias as well as post-MI related arrhythmias have been consistently documented in both anesthetized [177–180] and conscious [181–183] animals starting from the 70s.

Yet, what still needs to be explained is why post-MI anatomical denervation seems to mostly affect sympathetic efferent fibers while sparing the parasympathetic ones. It has been suggested [176] that this behavior reflects differences in the physiological regulation of sympathetic as compared to parasympathetic innervation processes. Postganglionic sympathetic fibers mostly originate from neurons located farther from the heart, and their reinnervation may be hindered by different molecules than cholinergic fibers, whose cell bodies are anatomically closer. Accordingly, NGF was proved to play a pivotal role in sympathetic fiber development, maintenance and sprouting, while parasympathetic nerve development is, at least in part,

dependent on glial cell line-derived neurotrophic factor (GDNF) signaling [184]. Finally, cholinergic transdifferentiation might play a role in the preserved ACh levels observed post-MI [185].

Neuraxial Transduction in Heart Failure

There is growing appreciation of the fact that, independently form the cause of heart failure, pathological changes occur not only in the cardiac musculature, but also in the neurohumoral control system that modulates the musculature [186, 187]. Neuronal remodeling can occur at multiple levels of cardiac neuraxis, from the ICNS, to intrathoracic extracardiac neurons, extending up to central neural processing circuits associated with the arterial baroreflex [188]. Alterations in neurohumoral control also include the renin-angiotensin-aldosterone system and circulating catecholamines [189]. Consistently with experimental evidence in the field of acute myocardial ischemia, neuronal remodeling has been associated with an increased arrhythmic susceptibility also in the setting of heart failure [137, 190].

At the cardiac level, various abnormalities in sympathetic efferent fibers terminals, including sustained sympathetic activation and decreased NE levels have been detected in the setting of heart failure [191, 192]. These effects have been attributed to increased NE turnover and spillover [193–196] and to malfunctions in the reuptake of NE [194, 197–199]. In addition, downregulation of tyrosine hydroxylase (TH), the rate-limiting enzyme for NE synthesis in sympathetic neurons [200, 201], and anatomic denervation itself [201–203] were also implicated in the synaptic terminal abnormalities. As already mentioned, excessive sympathoexcitation is coupled with withdrawal of central parasympathetic drive, leading to a pre- and postsynaptic reorganization of both branches of cardiac autonomic nervous system.

The production of several cardiac hypertrophic factors such as angiotensin II [204], ET-1 [205], leukemia inhibitory factor (LIF) [185], NGF [202, 206, 207], other growth factors [208], cytokines [209] and chemokines [53] is disrupted in the failing heart, influencing sympathetic activity, function, plasticity, and phenotype by a complex crosstalk. Specifically, NGF seems to have a dynamic, biphasic behavior potentially correlated with nerve sprouting and cardiac nerve regeneration. As already mentioned, NGF plasma levels increase abruptly in the first hours after an ischemic attack, while, instead, they decline in a chronic heart failure disease due to catecholaminergic (mostly alfa-mediated) inhibition [202]. Experimental evidence describes a progressive decrease in cardiac NGF expression over time after a coronary occlusion [210], following a prolonged exposure to elevated concentrations of catecholamine. Similarly, noradrenaline prolonged infusion in dogs is associated to a reduction in NGF and in its receptor TrkA, both at mRNA and protein levels [203].

Concluding Summary

The dynamic interplay between the neurohumoral control systems and the heart is central to not only our ability to respond to everyday stressor, but also to the progression of cardiac diseases. Through a mechanistic understanding of the adverse remodeling of the nervous system coupled to the myocyte substrate, focused neuromodulation therapies can be designed to mitigate disease progression and improve the morbidity/mortality outcome for patients. Such approaches may include such things as surgical removal of the T1–T4 levels of the paravertebral chain to treat intractable ventricular tachycardia [211–213], to bioelectric interventions targeted to the afferents of the carotid sinus [214, 215] and vagal nerve stimulation for treatment of atrial fibrillation [216, 217] and heart failure [218, 219].

Cross-References

- ▶ Adrenoceptor Blockers
- ▶ Brain-Heart Communication
- ▶ Neural Effects on Cardiac Electrophysiology
- ▶ Neuromodulation for Chronic Refractory Angina
- ▶ Nociception, Sympathetic Nervous System, and Inflammation
- ▶ When the Heart Hurts

References

1. Levy MN. Sympathetic-parasympathetic interactions in the heart. Circ Res. 1971; https://doi.org/10.1161/01.RES.29.5.437.
2. Ross JP. Cardiovascular innervation. By G.A.G. Mitchell, O.B.E., T.D., M.B., Ch.M., D.Sc., Professor of Anatomy, University of Manchester. Foreword by Sir Geoffrey Jefferson, C.B.E., M.S., M.Ch., M.Sc., LL.D., F.R.C.P., F.R.C.S., F.A.C.S., F.R.S., Emeritus Prof. J Bone Joint Surg Br. 1956. https://doi.org/10.1302/0301-620x.38b3.787.
3. Potts JT, Mitchell JH. Synchronization of somatosympathetic outflows during exercise: role for a spinal rhythm generator. J Physiol. 1998;508(Pt 3):646. https://doi.org/10.1111/j.1469-7793.1998.646bp.x.
4. Williamson JW, Fadel PJ, Mitchell JH. New insights into central cardiovascular control during exercise in humans: a central command update. Exp Physiol. 2006;91:51–8. https://doi.org/10.1113/expphysiol.2005.032037.
5. Coote JH. Myths and realities of the cardiac vagus. J Physiol. 2013;591:4073–85. https://doi.org/10.1113/jphysiol.2013.257758.
6. Gray AL, Johnson TA, Lauenstein JM, Newton SS, Ardell JL, Massari VJ. Parasympathetic control of the heart. III. Neuropeptide Y-immunoreactive nerve terminals synapse on three populations of negative chronotropic vagal preganglionic neurons. J Appl Physiol. 2004;96:2279–87. https://doi.org/10.1152/japplphysiol.00621.2003.
7. Hopkins DA, Armour JA. Localization of sympathetic postganglionic and parasympathetic preganglionic neurons which innervate different regions of the dog heart. J Comp Neurol. 1984. https://doi.org/10.1002/cne.902290205.
8. Foreman RDD, De Jongste MJL, Linderoth B. Integrative control of cardiac function by cervical and thoracic spinal neurons. In: Armour JA, Ardell JL, editors. Basic and clinical neurocardiology. New York: Oxford University Press; 2004. p. 153–86.
9. Levy M, Martin P. Neural control of the heart. In: Berne RM, editor. Handbook of physiology: section 2: cardiovascular system, vol. 1. Bethesda: The American Physiological Society; 1979. p. 581–620.
10. Buckley U, Yamakawa K, Takamiya T, Armour JA, Shivkumar K, Ardell JL. Targeted stellate decentralization: implications for sympathetic control of ventricular electrophysiology. Heart Rhythm. 2016;13:282–8. https://doi.org/10.1016/j.hrthm.2015.08.022.
11. Paintal AS. Vagal sensory receptors and their reflex effects. Physiol Rev. 1973. https://doi.org/10.1152/physrev.1973.53.1.159.
12. Armour J, Kember G. Cardiac sensory neurons. In: Armour JA, Ardell JL, editors. Basic and clinical neurocardiology. New York: Oxford University Press; 2004. p. 79–117.
13. Harper RM, Kumar R, Macey PM, Ogren JA, Richardson HL. Functional neuroanatomy and sleep-disordered breathing: implications for autonomic regulation. Anat Rec. 2012;295:1385–95. https://doi.org/10.1002/ar.22514.
14. Oppenheimer SM, Gelb A, Girvin JP, Hachinski VC. Cardiovascular effects of human insular cortex stimulation. Neurology. 1992;42:1727–32. https://doi.org/10.1212/wnl.42.9.1727.
15. Armour JA. Cardiac neuronal hierarchy in health and disease. Am J Phys Regul Integr Comp Phys. 2004;287:R262–71. https://doi.org/10.1152/ajpregu.00183.2004.
16. Armour JA. Potential clinical relevance of the "little brain" on the mammalian heart. Exp Physiol. 2008;93:165–76. https://doi.org/10.1113/expphysiol.2007.041178.
17. Murphy DA, O'Blenes S, Hanna BD, Armour JA. Capacity of intrinsic cardiac neurons to modify the acutely autotransplanted mammalian heart. J Heart Lung Transplant. 1994;13:847.
18. Armour JA, Murphy DA, Yuan BX, Macdonald S, Hopkins DA. Gross and microscopic anatomy of the human intrinsic cardiac nervous system. Anat Rec. 1997;247:289–98. https://doi.org/10.1002/(SICI)1097-0185(199702)247:2<289::AID-AR15>3.0.CO;2-L.
19. Kember G, Armour JA, Zamir M. Neural control of heart rate: the role of neuronal networking. J Theor Biol. 2011;277:41–7. https://doi.org/10.1016/j.jtbi.2011.02.013.
20. Hoover DB, Shepherd AV, Southerland EM, Armour JA, Ardell JL. Neurochemical diversity of afferent neurons that transduce sensory signals from dog ventricular myocardium. Auton Neurosci Basic Clin. 2008;141:38–45. https://doi.org/10.1016/j.autneu.2008.04.010.
21. Hopkins DA, Armour JA. Ganglionic distribution of afferent neurons innervating the canine heart and cardiopulmonary nerves. J Auton Nerv Syst. 1989;26:213–22. https://doi.org/10.1016/0165-1838(89)90170-7.
22. Armour JA, Huang MH, Pelleg A, Sylvén C. Responsiveness of in situ canine nodose ganglion afferent neurones to epicardial mechanical or chemical stimuli. Cardiovasc Res. 1994;28:1218–25. https://doi.org/10.1093/cvr/28.8.1218.
23. Vance WH, Bowker RC. Spinal origins of cardiac afferents from the region of the left anterior descending artery. Brain Res. 1983;258:96–100. https://doi.org/10.1016/0006-8993(83)91230-1.
24. Armour JA. Synaptic transmission in the chronically decentralized middle cervical and stellate ganglia of the dog. Can J Physiol Pharmacol. 1983;258:96–100. https://doi.org/10.1139/y83-171.
25. Armour JA. Activity of in situ stellate ganglion neurons of dogs recorded extracellularly. Can J Physiol Pharmacol. 1986;64:101–11. https://doi.org/10.1139/y86-016.
26. Ardell JL, Butler CK, Smith FM, Hopkins DA, Armour JA. Activity of *in vivo* atrial and ventricular neurons in chronically decentralized canine hearts.

Am J Physiol Heart Circ Physiol. 1991;260:H713–21. https://doi.org/10.1152/ajpheart.1991.260.3.h713.
27. Beaumont E, Salavatian S, Southerland EM, Vinet A, Jacquemet V, Armour JA, et al. Network interactions within the canine intrinsic cardiac nervous system: implications for reflex control of regional cardiac function. J Physiol. 2013;591:4515–33. https://doi.org/10.1113/jphysiol.2013.259382.
28. Yuan B-X, Ardell JL, Hopkins DA, Losier AM, Armour JA. Gross and microscopic anatomy of the canine intrinsic cardiac nervous system. Anat Rec. 1994;239:75–87. https://doi.org/10.1002/ar.1092390109.
29. Armour JA. Physiological behavior of thoracic cardiovascular receptors. Am J Phys. 1973;225:177–85. https://doi.org/10.1152/ajplegacy.1973.225.1.177.
30. Paintal AS. A study of ventricular pressure receptors and their role in the Bezold reflex. Q J Exp Physiol Cogn Med Sci. 1955;40:348–63. https://doi.org/10.1113/expphysiol.1955.sp001135.
31. Paintal AS. A study of right and left atrial receptors. J Physiol. 1953;120:596–610. https://doi.org/10.1113/jphysiol.1953.sp004920.
32. Paintal AS, Damodaran VN, Guz A. Mechanism of excitation of type J receptors. Acta Neurobiol Exp (Wars). 1973;33:15–9.
33. Malliani A, Lombardi F. Consideration of the fundamental mechanisms eliciting cardiac pain. Am Heart J. 1982;103:575–8. https://doi.org/10.1016/0002-8703(82)90352-0.
34. Malliani A, Lombardi F, Pagani M, Recordati G, Schwartz PJ. Spinal sympathetic reflexes in the cat and the pathogenesis of arterial hypertension. Clin Sci Mol Med Suppl. 1975;2:269–70. https://doi.org/10.1042/cs048259s.
35. Peters SR, Kostreva DR, Armour JA, Zuperku EJ, Igler FO, Coon RL, et al. Cardiac, aortic, pericardial, and pulmonary vascular receptors in the dog. Cardiology. 1980;65:85–100. https://doi.org/10.1159/000170798.
36. Ursino M, Magosso E. Role of short-term cardiovascular regulation in heart period variability: a modeling study. Am J Physiol Heart Circ Physiol. 2003;284:H1479–93. https://doi.org/10.1152/ajpheart.00850.2002.
37. Ardell JL, Andresen MC, Armour JA, Billman GE, Chen PS, Foreman RD, et al. Translational neurocardiology: preclinical models and cardioneural integrative aspects. J Physiol. 2016;594:3877–909. https://doi.org/10.1113/JP271869.
38. Kimura K, Ieda M, Fukuda K. Development, maturation, and transdifferentiation of cardiac sympathetic nerves. Circ Res. 2012;110:325–36. https://doi.org/10.1161/CIRCRESAHA.111.257253.
39. Hasan W. Autonomic cardiac innervation: development and adult plasticity. Organogenesis. 2013;9:176–93. https://doi.org/10.4161/org.24892.
40. Ieda M, Kanazawa H, Ieda Y, Kimura K, Matsumura K, Tomita Y, et al. Nerve growth factor is critical for cardiac sensory innervation and rescues neuropathy in diabetic hearts. Circulation. 2006;114:2351–63. https://doi.org/10.1161/CIRCULATIONAHA.106.627588.
41. Kuruvilla R, Zweifel LS, Glebova NO, Lonze BE, Valdez G, Ye H, et al. A neurotrophin signaling cascade coordinates sympathetic neuron development through differential control of TrkA trafficking and retrograde signaling. Cell. 2004;118:243–5. https://doi.org/10.1016/j.cell.2004.06.021.
42. Huang MH, Horackova M, Negoescu RM, Wolf S, Armour JA. Polysensory response characteristics of dorsal root ganglion neurones that may serve sensory functions during myocardial ischaemia. Cardiovasc Res. 1996;32:503–15. https://doi.org/10.1016/0008-6363(96)00108-3.
43. Ardell JL, Armour JA. Neurocardiology: structure-based function. Compr Physiol. 2016;6:1635–53. https://doi.org/10.1002/cphy.c150046.
44. Foreman RD. Mechanisms of cardiac pain. Annu Rev Physiol. 1999;61:143–67. https://doi.org/10.1146/annurev.physiol.61.1.143.
45. Foreman RD, Blair RW, Holmes HR, Armour JA. Correlation of ventricular mechanosensory neurite activity with myocardial sensory field deformation. Am J Phys Regul Integr Comp Phys. 1999;276:R979–89. https://doi.org/10.1152/ajpregu.1999.276.4.r979.
46. Ellison JP, Hibbs RG. An ultrastructural study of mammalian cardiac ganglia. J Mol Cell Cardiol. 1976;8:89–101. https://doi.org/10.1016/0022-2828(76)90023-7.
47. Huang MH, Sylven C, Horackova M, Armour JA. Ventricular sensory neurons in canine dorsal root ganglia: effects of adenosine and substance P. Am J Phys Regul Integr Comp Phys. 1995;269:R318–24. https://doi.org/10.1152/ajpregu.1995.269.2.r318.
48. Kember GC, Fenton GA, Armour JA, Kalyaniwalla N. Competition model for aperiodic stochastic resonance in a Fitzhugh-Nagumo model of cardiac sensory neurons. Phys Rev E Stat Phys Plasmas Fluids Relat Interdiscip Topics. 2001;63:041911. https://doi.org/10.1103/PhysRevE.63.041911.
49. Falcón D, Galeano-Otero I, Calderón-Sánchez E, Del Toro R, Martín-Bórnez M, Rosado JA, et al. TRP channels: current perspectives in the adverse cardiac remodeling. Front Physiol. 2019; https://doi.org/10.3389/fphys.2019.00159.
50. Armour JA. Neuronal activity recorded extracellularly in chronically decentralized in situ canine middle cervical ganglia. Can J Physiol Pharmacol. 1986;64:1038–46. https://doi.org/10.1139/y86-177.
51. Bosnjak Kampine ZJJP. Cardiac sympathetic afferent cell bodies are located in the peripheral nervous system of the cat. Circ Res. 1989;64:554–62. https://doi.org/10.1161/01.res.64.3.554.
52. Ardell JL, Cardinal R, Vermeulen M, Armour JA. Dorsal spinal cord stimulation obtunds the capacity of intrathoracic extracardiac neurons to transduce myocardial ischemia. Am J Phys Regul Integr Comp

Phys. 2009;297:R470–7. https://doi.org/10.1152/ajpregu.90821.2008.
53. Dusi V, Ghidoni A, Ravera A, De Ferrari GM, Calvillo L. Chemokines and heart disease: a network connecting cardiovascular biology to immune and autonomic nervous systems. Mediat Inflamm. 2016;2016 https://doi.org/10.1155/2016/5902947.
54. Levy MN. Neural control of cardiac function. Baillieres Clin Neurol. 1997;6:227–44.
55. Loring JF, Erickson CA. Neural crest cell migratory pathways in the trunk of the chick embryo. Dev Biol. 1987;121:220–36. https://doi.org/10.1016/0012-1606(87)90154-0.
56. Creazzo TL, Godt RE, Leatherbury L, Conway SJ, Kirby ML. Role of cardiac neural crest cells in cardiovascular development. Annu Rev Physiol. 1998;60:267–86. https://doi.org/10.1146/annurev.physiol.60.1.267.
57. Farrell M, Waldo K, Li YX, Kirby ML. A novel role for cardiac neural crest in heart development. Trends Cardiovasc Med. 1999;103:1499–507. https://doi.org/10.1016/S1050-1738(00)00023-2.
58. Waldo K, Zdanowicz M, Burch J, Kumiski DH, Stadt HA, Godt RE, et al. A novel role for cardiac neural crest in heart development. J Clin Invest. 1999;9:214–20. https://doi.org/10.1172/JCI6501.
59. Geis WP, Kaye MP, Randall WC. Major autonomic pathways to the atria and S-A and A-V nodes of the canine heart. Am J Phys. 1973;224:202–8. https://doi.org/10.1152/ajplegacy.1973.224.1.202.
60. Randall WC, Rohse WG. The augmentor action of the sympathetic cardiac nerves. Circ Res. 1956;4:470–5. https://doi.org/10.1161/01.RES.4.4.470.
61. Chauhan RA, Coote J, Allen E, Pongpaopattanakul P, Brack KE, Ng GA. Functional selectivity of cardiac preganglionic sympathetic neurones in the rabbit heart. Int J Cardiol. 2018;264:70–8. https://doi.org/10.1016/j.ijcard.2018.03.119.
62. Schwartz PJ, Stone HL. Effects of unilateral stellectomy upon cardiac performance during exercise in dogs. Circ Res. 1979;44:637–45. https://doi.org/10.1161/01.RES.44.5.637.
63. Rajendran PS, Challis RC, Fowlkes CC, Hanna P, Tompkins JD, Jordan MC, et al. Nat Commun. 2019; https://doi.org/10.1038/s41467-019-09770-1.
64. Yanowitz F, Preston JB, Abildskov JA. Functional distribution of right and left stellate innervation to the ventricles. Production of neurogenic electrocardiographic changes by unilateral alteration of sympathetic tone. Circ Res. 1966;18:416–28. https://doi.org/10.1161/01.RES.18.4.416.
65. Randall WC, Armour JA, Geis WP, Lippincott DB. Regional cardiac distribution of the sympathetic nerves. Fed Proc. 1972;31:1999–208.
66. Haws CW, Burgess MJ. Effects of bilateral and unilateral stellate stimulation on canine ventricular refractory periods at sites of overlapping innervation. Circ Res. 1978;42:195–8. https://doi.org/10.1161/01.RES.42.2.195.
67. Janse MJ, Schwartz PJ, Wilms-Schopman F, Peters RJ, Durrer D, et al. Circulation. 1985;72:585–95. https://doi.org/10.1161/01.CIR.72.3.585.
68. Vaseghi M, Zhou W, Shi J, Ajijola OA, Hadaya J, Shivkumar K, et al. Sympathetic innervation of the anterior left ventricular wall by the right and left stellate ganglia. Heart Rhythm. 2012;9:1303–9. https://doi.org/10.1016/j.hrthm.2012.03.052.
69. Gagliardi M, Randall WC, Bieger D, Wurster RD, Hopkins DA, Armour JA. Activity of *in vivo* canine cardiac plexus neurons. Am J Physiol Heart Circ Physiol. 1988;255:H789–800. https://doi.org/10.1152/ajpheart.1988.255.4.h789.
70. Thompson GW, Collier K, Ardell JL, Kember G, Armour JA. Functional interdependence of neurons in a single canine intrinsic cardiac ganglionated plexus. J Physiol. 2000;528:561–71. https://doi.org/10.1111/j.1469-7793.2000.00561.x.
71. Waldmann M, Thompson GW, Kember GC, Ardell JL, Armour JA. Stochastic behavior of atrial and ventricular intrinsic cardiac neurons. J Appl Physiol. 2006;101:413–9. https://doi.org/10.1152/japplphysiol.01346.2005.
72. Hoover DB, Isaacs ER, Jacques F, Hoard JL, Pagé P, Armour JA. Localization of multiple neurotransmitters in surgically derived specimens of human atrial ganglia. Neuroscience. 2009;164:1170–9. https://doi.org/10.1016/j.neuroscience.2009.09.001.
73. Horackova M, Armour JA, Byczko Z. Distribution of intrinsic cardiac neurons in whole-mount guinea pig atria identified by multiple neurochemical coding. A confocal microscope study. Cell Tissue Res. 1999;297:409–21. https://doi.org/10.1007/s004410051368.
74. Armour JA, Collier K, Kember G, Ardell JL. Differential selectivity of cardiac neurons in separate intrathoracic autonomic ganglia. Am J Phys Regul Integr Comp Phys. 1998;274:R939–49. https://doi.org/10.1152/ajpregu.1998.274.4.r939.
75. Murphy DA, Thompson GW, Ardell JL, McCraty R, Stevenson RS, Sangalang VE, et al. The heart reinnervates after transplantation. Ann Thorac Surg. 2000;69:1769–81. https://doi.org/10.1016/S0003-4975(00)01240-6.
76. Butler CK, Smith FM, Cardinal R, Murphy DA, Hopkins DA, Armour JA. Cardiac responses to electrical stimulation of discrete loci in canine atrial and ventricular ganglionated plexi. Am J Physiol Heart Circ Physiol. 1990;259:H1365–73. https://doi.org/10.1152/ajpheart.1990.259.5.h1365.
77. Butler CK, Smith FM, Nicholson J, Armour JA. Cardiac effects induced by chemically activated neurons in canine intrathoracic ganglia. Am J Physiol Heart Circ Physiol. 1990;259:H1108–17. https://doi.org/10.1152/ajpheart.1990.259.4.h1108.
78. Cardinal R, Pagé P, Vermeulen M, Ardell JL, Armour JA. Spatially divergent cardiac responses to nicotinic stimulation of ganglionated plexus neurons in the canine heart. Auton Neurosci Basic Clin.

2009;145:55–62. https://doi.org/10.1016/j.autneu.2008.11.007.
79. Habecker BA, Anderson ME, Birren SJ, Fukuda K, Herring N, Hoover DB, et al. Molecular and cellular neurocardiology: development, and cellular and molecular adaptations to heart disease. J Physiol. 2016;594:3853–75. https://doi.org/10.1113/JP271840.
80. Holmgren S, Abrahamsson T, Almgren O. Adrenergic innervation of coronary arteries and ventricular myocardium in the pig: fluorescence microscopic appearance in the normal state and after ischemia. Basic Res Cardiol. 1985;80:18–26. https://doi.org/10.1007/BF01906740.
81. Dahlström A, Mya-Tu M, Fuxe K, Zetterström BE. Observations on adrenergic innervation of dog heart. Am J Phys. 1965;209:689–92. https://doi.org/10.1152/ajplegacy.1965.209.4.689.
82. Jacobowitz D, Cooper T, Barner HB. Histochemical and chemical studies of the localization of adrenergic and cholinergic nerves in normal and denervated cat hearts. Circ Res. 1967;20:289–98. https://doi.org/10.1161/01.RES.20.3.289.
83. Ito M, Zipes DP. Efferent sympathetic and vagal innervation of the canine right ventricle. Circulation. 1994;90:1459–68. https://doi.org/10.1161/01.CIR.90.3.1459.
84. Ieda M, Kimura K, Kanazawa H, Fukuda K. Regulation of cardiac nerves: a new paradigm in the management of sudden cardiac death? Curr Med Chem. 2008;15:1731–6. https://doi.org/10.2174/092986708784872339.
85. Ieda M, Kanazawa H, Kimura K, Hattori F, Ieda Y, Taniguchi M, et al. Sema3a maintains normal heart rhythm through sympathetic innervation patterning. Nat Med. 2007;13:604–12. https://doi.org/10.1038/nm1570.
86. Herring N. Autonomic control of the heart: going beyond the classical neurotransmitters. Exp Physiol. 2015;100:354–8. https://doi.org/10.1113/expphysiol.2014.080184.
87. Dusi V, De Ferrari GM, Schwartz PJ. There are 100 ways by which the sympathetic nervous system can trigger life-threatening arrhythmias. Eur Heart J. 2020. https://doi.org/10.1093/eurheartj/ehz950.
88. Burnstock G. Do some nerve cells release more than one transmitter? Neuroscience. 1976;1:239–48. https://doi.org/10.1016/0306-4522(76)90054-3.
89. Herring N, Cranley J, Lokale MN, Li D, Shanks J, Alston EN, et al. The cardiac sympathetic co-transmitter galanin reduces acetylcholine release and vagal bradycardia: Implications for neural control of cardiac excitability. J Mol Cell Cardiol. 2012;52:667–76. https://doi.org/10.1016/j.yjmcc.2011.11.016.
90. Potter E. Presynaptic inhibition of cardiac vagal postganglionic nerves by neuropeptide Y. Neurosci Lett. 1987;83:101–6. https://doi.org/10.1016/0304-3940(87)90223-0.
91. Smith-White MA, Herzog H, Potter EK. Role of neuropeptide Y Y2 receptors in modulation of cardiac parasympathetic neurotransmission. Regul Pept. 2002;103:105–1. https://doi.org/10.1016/S0167-0115(01)00368-8.
92. Potter EK. Prolonged non-adrenergic inhibition of cardiac vagal action following sympathetic stimulation: neuromodulation by neuropeptide Y? Neurosci Lett. 1985;54:117–21. https://doi.org/10.1016/S0304-3940(85)80065-3.
93. Kalla M, Hao G, Tapoulal N, Tomek J, Liu K, Woodward L, et al. The cardiac sympathetic co-transmitter neuropeptide Y is pro-arrhythmic following ST-elevation myocardial infarction despite beta-blockade. Eur Heart J. 2019. https://doi.org/10.1093/eurheartj/ehz852.
94. Edvinsson L, Copeland JR, Emson PC, McCulloch J, Uddman R. Nerve fibers containing neuropeptide Y in the cerebrovascular bed: immunocytochemistry, radioimmunoassay, and vasomotor effects. J Cereb Blood Flow Metab. 1987;7:45–57. https://doi.org/10.1038/jcbfm.1987.7.
95. Geis GS, Wurster RD. Cardiac responses during stimulation of the dorsal motor nucleus and nucleus ambiguus in the cat. Circ Res. 1980;46:606–11. https://doi.org/10.1161/01.RES.46.5.606.
96. Geis GS, Wurster RD. Horseradish peroxidase localization of cardiac vagal preganglionic somata. Brain Res. 1980;182:19–30. https://doi.org/10.1016/0006-8993(80)90827-6.
97. Hopkins DA, Armour JA. Medullary cells of origin of physiologically identified cardiac nerves in the dog. Brain Res Bull. 1982; https://doi.org/10.1016/0361-9230(82)90073-9.
98. Kalia M, Mesulam M-M. Brain stem projections of sensory and motor components of the vagus complex in the cat: I. The cervical vagus and nodose ganglion. J Comp Neurol. 1980;8:359–65. https://doi.org/10.1002/cne.901930210.
99. Kalia M, Mesulam M-M. Brain stem projections of sensory and motor components of the vagus complex in the cat: II. Laryngeal, tracheobronchial, pulmonary, cardiac, and gastrointestinal branches. J Comp Neurol. 1980;193:467–508. https://doi.org/10.1002/cne.901930211.
100. McAllen RM, Spyer KM. The location of cardiac vagal preganglionic motoneurones in the medulla of the cat. J Physiol. 1976;258:187–204. https://doi.org/10.1113/jphysiol.1976.sp011414.
101. Hopkins DA, Armour JA. Brainstem cells of origin of physiologically identified cardiopulmonary nerves in the rhesus monkey (*Macaca mulatta*). J Auton Nerv Syst. 1998;68:21–32. https://doi.org/10.1016/S0165-1838(97)00112-4.
102. Dickerson LW, Rodak DJ, Fleming TJ, Gatti PJ, Massari VJ, McKenzie JC, et al. Parasympathetic neurons in the cranial medial ventricular fat pad on the dog heart selectively decrease ventricular contractility. J Auton Nerv Syst. 1998;70:129–41. https://doi.org/10.1016/S0165-1838(98)00048-4.
103. Gatti PJ, Johnson TA, Massari VJ. Can neurons in the nucleus ambiguus selectively regulate cardiac rate

and atrio-ventricular conduction? J Auton Nerv Syst. 1996;57:123–7. https://doi.org/10.1016/0165-1838(95)00104-2.
104. Gray AL, Johnson TA, Ardell JL, Massari VJ. Parasympathetic control of the heart. II. A novel interganglionic intrinsic cardiac circuit mediates neural control of heart rate. J Appl Physiol. 2004;96:2273–8. https://doi.org/10.1152/japplphysiol.00616.2003.
105. Mcallen RM, Salo LM, Paton JFR, Pickering AE. Processing of central and reflex vagal drives by rat cardiac ganglion neurones: an intracellular analysis. J Physiol. 2011;589:5801–18. https://doi.org/10.1113/jphysiol.2011.214320.
106. Yuan BX, Ardell JL, Hopkins DA, Armour JA. Differential cardiac responses induced by nicotine sensitive canine atrial and ventricular neurones. Cardiovasc Res. 1993;27:760–9. https://doi.org/10.1093/cvr/27.5.760.
107. Inoue H, Zipes DP. Changes in atrial and ventricular refractoriness and in atrioventricular nodal conduction produced by combinations of vagal and sympathetic stimulation that result in a constant spontaneous sinus cycle length. Circ Res. 1987;60:942–51. https://doi.org/10.1161/01.RES.60.6.942.
108. Ardell JL, Rajendran PS, Nier HA, KenKnight BH, Armour JA. Central-peripheral neural network interactions evoked by vagus nerve stimulation: functional consequences on control of cardiac function. Am J Physiol Heart Circ Physiol. 2015;309:H1740–52. https://doi.org/10.1152/ajpheart.00557.2015.
109. Reeves TJ, Hefner LL. The effect of vagal stimulation on ventricular contractility. Trans Assoc Am Phys. 1961;74:260–70.
110. Armour JA, Randall WC. *In vivo* papillary muscle responses to cardiac nerve stimulation. Proc Soc Exp Biol Med. 1970;133:948–52. https://doi.org/10.3181/00379727-133-34601.
111. Brandys JC, Randall WC, Armour JA. Functional anatomy of the canine mediastinal cardiac nerves located at the base of the heart. Can J Physiol Pharmacol. 1986;64:152–62. https://doi.org/10.1139/y86-023.
112. Ardell JL, Randall WC. Selective vagal innervation of sinoatrial and atrioventricular nodes in canine heart. Am J Physiol Heart Circ Physiol. 1986;251:H764–73. https://doi.org/10.1152/ajpheart.1986.251.4.h764.
113. Furukawa Y, Hoyano Y, Chiba S. Parasympathetic inhibition of sympathetic effects on sinus rate in anesthetized dogs. Am J Physiol Heart Circ Physiol. 1996;71:H44–50. https://doi.org/10.1152/ajpheart.1996.271.1.h44.
114. Arora RC, Waldmann M, Hopkins DA, Armour JA. Porcine intrinsic cardiac ganglia. Anat Rec A Discov Mol Cell Evol Biol. 2003;271:249–58. https://doi.org/10.1002/ar.a.10030.
115. Armour JA. Functional anatomy of intrathoracic neurons innervating the atria and ventricles. Heart Rhythm. 2010;7:994–6. https://doi.org/10.1016/j.hrthm.2010.02.014.
116. Scherlag BJ, Patterson E, Po SS. The neural basis of atrial fibrillation. J Electrocardiol. 2006;39:S180–3. https://doi.org/10.1016/j.jelectrocard.2006.05.021.
117. Leiria TLL, Glavinovic T, Armour JA, Cardinal R, de Lima GG, Kus T. Longterm effects of cardiac mediastinal nerve cryoablation on neural inducibility of atrial fibrillation in canines. Auton Neurosci Basic Clin. 2011;161:68–74. https://doi.org/10.1016/j.autneu.2010.12.006.
118. Arora R, Ardell JL, Armour JA. Cardiac denervation and cardiac function. Curr Interv Cardiol Rep. 2000;2(3):188–195.
119. Salavatian S, Beaumont E, Longpré JP, Armour JA, Vinet A, Jacquemet V, et al. Vagal stimulation targets select populations of intrinsic cardiac neurons to control neurally induced atrial fibrillation. Am J Physiol Heart Circ Physiol. 2016;311:H1311–20. https://doi.org/10.1152/ajpheart.00443.2016.
120. Cervero F, Connell LA. Distribution of somatic and visceral primary afferent fibres within the thoracic spinal cord of the cat. J Comp Neurol. 1984;230:88–98. https://doi.org/10.1002/cne.902300108.
121. Kuo DC, Oravitz JJ, DeGroat WC. Tracing of afferent and efferent pathways in the left inferior cardiac nerve of the cat using retrograde and transganglionic transport of horseradish peroxidase. Brain Res. 1984;321:111–8. https://doi.org/10.1016/0006-8993(84)90686-3.
122. Willis WD. The pain system. The neural basis of nociceptive transmission in the mammalian nervous system. Pain Headache. 1985;8:1–346. https://doi.org/10.1136/jnnp.48.7.728.
123. Ammons WS, Girardot MN, Foreman RD. Effects of intracardiac bradykinin on T2-T5 medial spinothalamic cells. Am J Phys. 1985;249:R147–52. https://doi.org/10.1152/ajpregu.1985.249.2.r147.
124. Blair RW, Weber RN, Foreman RD. Characteristics of primate spinothalamic tract neurons receiving viscerosomatic convergent inputs in T3-T5 segments. J Neurophysiol. 1981;46:797–811. https://doi.org/10.1152/jn.1981.46.4.797.
125. Benarroch EE. The central autonomic network: functional organization, dysfunction, and perspective. Mayo Clin Proc. 1993;68:988–1001. https://doi.org/10.1016/S0025-6196(12)62272-1.
126. Saper CB, Loewy AD, Swanson LW, Cowan WM. Direct hypothalamo-autonomic connections. Brain Res. 1976;117:305–12. https://doi.org/10.1016/0006-8993(76)90738-1.
127. Pyner S. The paraventricular nucleus and heart failure. Exp Physiol. 2014;99:332–9. https://doi.org/10.1113/expphysiol.2013.072678.
128. Saha S. Role of the central nucleus of the amygdala in the control of blood pressure: descending pathways to medullary cardiovascular nuclei. Clin Exp Pharmacol Physiol. 2005;32:450–6. https://doi.org/10.1111/j.1440-1681.2005.04210.x.
129. Jansen ASP, Wessendorf MW, Loewy AD. Transneuronal labeling of CNS neuropeptide and

monoamine neurons after pseudorabies virus injections into the stellate ganglion. Brain Res. 1995;683:1–24. https://doi.org/10.1016/0006-8993(95)00276-V.
130. Koganezawa T, Shimomura Y, Terui N. The role of the RVLM neurons in the viscero-sympathetic reflex: a mini review. Auton Neurosci Basic Clin. 2008. https://doi.org/10.1016/j.autneu.2008.03.007.
131. Dampney RAL. Functional organization of central pathways regulating the cardiovascular system. Physiol Rev. 1994;74:323–64. https://doi.org/10.1152/physrev.1994.74.2.323.
132. Sakaki M, Yoo HJ, Nga L, Lee TH, Thayer JF, Mather M. Heart rate variability is associated with amygdala functional connectivity with MPFC across younger and older adults. NeuroImage. 2016;139:44–52. https://doi.org/10.1016/j.neuroimage.2016.05.076.
133. Thayer JF, Lane RD. A model of neurovisceral integration in emotion regulation and dysregulation. J Affect Disord. 2000;61:201–16. https://doi.org/10.1016/S0165-0327(00)00338-4.
134. Geis GS, Kozelka JW, Wurster RD. Organization and reflex control of vagal cardiomotor neurons. J Auton Nerv Syst. 1981;3:437–50. https://doi.org/10.1016/0165-1838(81)90080-1.
135. Lane RD, McRae K, Reiman EM, Chen K, Ahern GL, Thayer JF. Neural correlates of heart rate variability during emotion. NeuroImage. 2009;44:213–22. https://doi.org/10.1016/j.neuroimage.2008.07.056.
136. Bandler R, Keay KA, Floyd N, Price J. Central circuits mediating patterned autonomic activity during active vs. passive emotional coping. Brain Res Bull. 2000;53:95–104. https://doi.org/10.1016/S0361-9230(00)00313-0.
137. Fukuda K, Kanazawa H, Aizawa Y, Ardell JL, Shivkumar K. Cardiac innervation and sudden cardiac death. Circ Res. 2015;116:2005–19. https://doi.org/10.1161/CIRCRESAHA.116.304679.
138. Arora RC, Armour JA. Adenosine A1 receptor activation reduces myocardial reperfusion effects on intrinsic cardiac nervous system. Am J Phys Regul Integr Comp Phys. 2003;284:R1314–21. https://doi.org/10.1152/ajpregu.00333.2002.
139. Schwartz PJ, Pagani M, Lombardi F, Malliani A, Brown AM. A cardiocardiac sympathovagal reflex in the cat. Circ Res. 1973;32:215–20. https://doi.org/10.1161/01.RES.32.2.215.
140. Ajijola OA, Yagishita D, Reddy NK, Yamakawa K, Vaseghi M, Downs AM, et al. Remodeling of stellate ganglion neurons after spatially targeted myocardial infarction: neuropeptide and morphologic changes. Heart Rhythm. 2015;12:1027–35. https://doi.org/10.1016/j.hrthm.2015.01.045.
141. Gardner RT, Wang L, Lang BT, Cregg JM, Dunbar CL, Woodward WR, et al. Targeting protein tyrosine phosphatase σ after myocardial infarction restores cardiac sympathetic innervation and prevents arrhythmias. Nat Commun. 2015;6:6235. https://doi.org/10.1038/ncomms7235.
142. Hardwick JC, Baran CN, Southerland EM, Ardell JL. Remodeling of the guinea pig intrinsic cardiac plexus with chronic pressure overload. Am J Phys Regul Integr Comp Phys. 2009;297:R859–66. https://doi.org/10.1152/ajpregu.00245.2009.
143. Hardwick JC, Ryan SE, Beaumont E, Ardell JL, Southerland EM. Dynamic remodeling of the guinea pig intrinsic cardiac plexus induced by chronic myocardial infarction. Auton Neurosci Basic Clin. 2014;181:4–12. https://doi.org/10.1016/j.autneu.2013.10.008.
144. Lu CJ, Hao G, Nikiforova N, Larsen HE, Liu K, Crabtree MJ, et al. CAPON modulates neuronal calcium handling and cardiac sympathetic neurotransmission during dysautonomia in hypertension. Hypertension. 2015;65:1288–97. https://doi.org/10.1161/HYPERTENSIONAHA.115.05290.
145. Vanhoutte PM, Verbeuren TJ. Inhibition by acetylcholine of the norepinephrine release evoked by potassium in canine saphenous veins. Circ Res. 1976;39:263–9. https://doi.org/10.1161/01.res.39.2.263.
146. Levy MN, Blattberg B. Effect of vagal stimulation on the overflow of norepinephrine into the coronary sinus during cardiac sympathetic nerve stimulation in the dog. Circ Res. 1976;38:81–4. https://doi.org/10.1161/01.res.38.2.81.
147. Calvillo L, Vanoli E, Andreoli E, Besana A, Omodeo E, Gnecchi M, et al. Vagal stimulation, through its nicotinic action, limits infarct size and the inflammatory response to myocardial Ischemia and reperfusion. J Cardiovasc Pharmacol. 2011;58:500–7. https://doi.org/10.1097/FJC.0b013e31822b7204.
148. Hanna P, Shivkumar K, Ardell JL. Calming the nervous heart: autonomic therapies in heart failure. Card Fail Rev. 2018;4:92–8. https://doi.org/10.15420/cfr.2018.20.2.
149. Malliani A, Schwartz PJ, Zanchetti A. A sympathetic reflex elicited by experimental coronary occlusion. Am J Phys. 1969;217:703–9. https://doi.org/10.1152/ajplegacy.1969.217.3.703.
150. Taggart P, PMI S, Spear DW, Drake HF, Swanton RH, Manuel RW. Simultaneous endocardial and epicardial monophasic action potential recordings during brief periods of coronary artery ligation in the dog: Influence of adrenaline, beta blockade and alpha blockade. Cardiovasc Res. 1988;22:900–9. https://doi.org/10.1093/cvr/22.12.900.
151. Williams DO, Scherlag BJ, Hope RR, El-Sherif N, Lazzara R. The pathophysiology of malignant ventricular arrhythmias during acute myocardial ischemia. Circulation. 1974;50:1163–72. https://doi.org/10.1161/01.CIR.50.6.1163.
152. Schwartz PJ, La Rovere MT, Vanoli E. Autonomic nervous system and sudden cardiac death: experimental basis and clinical observations for post-myocardial infarction risk stratification. Circulation. 1992;85:177–91.
153. Schwartz PJ, Foreman RD, Stone HL, Brown AM. Effect of dorsal root section on the arrhythmias

associated with coronary occlusion. Am J Phys. 1976;231:923–8. https://doi.org/10.1152/ajplegacy.1976.231.3.923.
154. Lujan HL, Krishnan S, di Carlo SE. Cardiac spinal deafferentation reduces the susceptibility to sustained ventricular tachycardia in conscious rats. Am J Phys Regul Integr Comp Phys. 2011;301:R775–82. https://doi.org/10.1152/ajpregu.00140.2011.
155. Schwartz PJ, Stone HL. Left stellectomy in the prevention of ventricular fibrillation caused by acute myocardial ischemia in conscious dogs with anterior myocardial infarction. Circulation. 1980;62:1256–65. https://doi.org/10.1161/01.CIR.62.6.1256.
156. Lujan HL, Palani G, Zhang L, DiCarlo SE. Targeted ablation of cardiac sympathetic neurons reduces the susceptibility to ischemia-induced sustained ventricular tachycardia in conscious rats. Am J Physiol Heart Circ Physiol. 2010;298:H1330–9. https://doi.org/10.1152/ajpheart.00955.2009.
157. Zhou M, Liu Y, He Y, Xie K, Quan D, Tang Y, et al. Selective chemical ablation of transient receptor potential vanilloid 1 expressing neurons in the left stellate ganglion protects against ischemia-induced ventricular arrhythmias in dogs. Biomed Pharmacother. 2019;120:109500. https://doi.org/10.1016/j.biopha.2019.109500.
158. Zhou M, Liu Y, Xiong L, Quan D, He Y, Tang Y, et al. Cardiac sympathetic afferent denervation protects against ventricular arrhythmias by modulating cardiac sympathetic nerve activity during acute myocardial infarction. Med Sci Monit. 2019;25:1984–93. https://doi.org/10.12659/MSM.914105.
159. Wang HJ, Wang W, Cornish KG, Rozanski GJ, Zucker IH. Cardiac sympathetic afferent denervation attenuates cardiac remodeling and improves cardiovascular dysfunction in rats with heart failure. Hypertension. 2014;64:745–55. https://doi.org/10.1161/HYPERTENSIONAHA.114.03699.
160. Tjen-A-Looi SC, Fu LW, Longhurst JC. Xanthine oxidase, but not neutrophils, contributes to activation of cardiac sympathetic afferents during myocardial ischaemia in cats. J Physiol. 2002;543:327–36. https://doi.org/10.1113/jphysiol.2001.013482.
161. D'Elia E, Pascale A, Marchesi N, Ferrero P, Senni M, Govoni S, et al. Novel approaches to the post-myocardial infarction/heart failure neural remodeling. Heart Fail Rev. 2014;19:611–9. https://doi.org/10.1007/s10741-013-9415-6.
162. Barber MJ, Mueller TM, Henry DP, Felten SY, Zipes DP. Transmural myocardial infarction in the dog produces sympathectomy in noninfarcted myocardium. Circulation. 1983;67:787–96. https://doi.org/10.1161/01.CIR.67.4.787.
163. Inoue H, Zipes DP. Time course of denervation of efferent sympathetic and vagal nerves after occlusion of the coronary artery in the canine heart. Circ Res. 1988;62:1111–20. https://doi.org/10.1161/01.RES.62.6.1111.
164. Inoue H, Zipes DP. Results of sympathetic denervation in the canine heart: supersensitivity that may be arrhythmogenic. Circulation. 1987;75:877–87. https://doi.org/10.1161/01.CIR.75.4.877.
165. Rajendran PS, Nakamura K, Ajijola OA, Vaseghi M, Armour JA, Ardell JL, et al. Myocardial infarction induces structural and functional remodelling of the intrinsic cardiac nervous system. J Physiol. 2016;594(2):321–41. https://doi.org/10.1113/JP271165.
166. Chen PS, Chen LS, Cao JM, Sharifi B, Karagueuzian HS, Fishbein MC. Sympathetic nerve sprouting, electrical remodeling and the mechanisms of sudden cardiac death. Cardiovasc Res. 2001;50:409–16. https://doi.org/10.1016/S0008-6363(00)00308-4.
167. Voroshilovsky O, Qu Z, Lee MH, Ohara T, Fishbein GA, Huang HLA, et al. Mechanisms of ventricular fibrillation induction by 60-Hz alternating current in isolated swine right ventricle. Circulation. 2000;102:1569–74. https://doi.org/10.1161/01.CIR.102.13.1569.
168. Zhou S, Chen LS, Miyauchi Y, Miyauchi M, Kar S, Kangavari S, et al. Mechanisms of cardiac nerve sprouting after myocardial infarction in dogs. Circ Res. 2004;95:76–83. https://doi.org/10.1161/01.RES.0000133678.22968.e3.
169. Han S, Kobayashi K, Joung B, Piccirillo G, Maruyama M, Vinters HV, et al. Electroanatomic remodeling of the left stellate ganglion after myocardial infarction. J Am Coll Cardiol. 2012;59:954–61. https://doi.org/10.1016/j.jacc.2011.11.030.
170. Ajijola OA, Yagishita D, Patel KJ, Vaseghi M, Zhou W, Yamakawa K, et al. Focal myocardial infarction induces global remodeling of cardiac sympathetic innervation: neural remodeling in a spatial context. Am J Physiol Heart Circ Physiol. 2013;59:954–61. https://doi.org/10.1152/ajpheart.00434.2013.
171. Zhang H, Yuan X, Jin PF, Hou JF, Wang W, Wei YJ, et al. Alteration of parasympathetic/sympathetic ratio in the infarcted myocardium after schwann cell transplantation modified electrophysiological function of heart: a novel antiarrhythmic therapy. Circulation. 2010. https://doi.org/10.1161/CIRCULATIONAHA.109.922740.
172. Eitel I, Nowak M, Stehl C, Adams V, Fuernau G, Hildebrand L, et al. Endothelin-1 release in acute myocardial infarction as a predictor of long-term prognosis and no-reflow assessed by contrast-enhanced magnetic resonance imaging. Am Heart J. 2010; https://doi.org/10.1016/j.ahj.2010.02.019.
173. Ieda M, Fukuda K, Hisaka Y, Kimura K, Kawaguchi H, Fujita J, et al. Endothelin-1 regulates cardiac sympathetic innervation in the rodent heart by controlling nerve growth factor expression. J Clin Invest. 2004. https://doi.org/10.1172/JCI200419480.
174. Rana OR, Saygili E, Meyer C, Gemein C, Krüttgen A, Andrzejewski MG, et al. Regulation of nerve growth factor in the heart: the role of the calcineurin-NFAT pathway. J Mol Cell Cardiol. 2009. https://doi.org/10.1016/j.yjmcc.2008.12.006.
175. Hopkins DA, Macdonald SE, Murphy DA, Armour JA. Pathology of intrinsic cardiac neurons from ischemic human hearts. Anat Rec. 2000. https://doi.org/

10.1002/1097-0185(20000801)259:4<424::AID-AR60>3.0.CO;2-J.
176. Vaseghi M, Salavatian S, Rajendran PS, Yagishita D, Woodward WR, Hamon D, et al. Parasympathetic dysfunction and antiarrhythmic effect of vagal nerve stimulation following myocardial infarction. JCI Insight. 2017. https://doi.org/10.1172/jci.insight.86715.
177. Kent KM, Smith ER, Redwood DR, Epstein SE. Electrical stability of acutely ischemic myocardium. Influences of heart rate and vagal stimulation. Circulation. 1973. https://doi.org/10.1161/01.CIR.47.2.291.
178. Myers RW, Pearlman AS, Hyman RM, Goldstein RA, Kent KM, Goldstein RE, et al. Beneficial effects of vagal stimulation and bradycardia during experimental acute myocardial ischemia. Circulation. 1974. https://doi.org/10.1161/01.CIR.49.5.943.
179. Corr PB, Gillis RA. Role of the vagus nerves in the cardiovascular changes induced by coronary occlusion. Circulation. 1974. https://doi.org/10.1161/01.CIR.49.1.86.
180. Zuanetti G, De Ferrari GM, Priori SG, Schwartz PJ. Protective effect of vagal stimulation on reperfusion arrhythmias in cats. Circ Res. 1987. https://doi.org/10.1161/01.RES.61.3.429.
181. Billman GE, Schwartz PJ, Stone HL. The effects of daily exercise on susceptibility to sudden cardiac death. Circulation. 1984. https://doi.org/10.1161/01.CIR.69.6.1182.
182. Vanoli E, De Ferrari GM, Stramba-Badiale M, Hull SS, Foreman RD, Schwartz PJ. Vagal stimulation and prevention of sudden death in conscious dogs with a healed myocardial infarction. Circ Res. 1991;68:1471–81.
183. Billman GE, Kukielka M. Effects of endurance exercise training on heart rate variability and susceptibility to sudden cardiac death: protection is not due to enhanced cardiac vagal regulation. J Appl Physiol. 2006. https://doi.org/10.1152/japplphysiol.01328.2005.
184. Hiltunen JO, Laurikainen A, Airaksinen MS, Saarma M. GDNF family receptors in the embryonic and postnatal rat heart and reduced cholinergic innervation in mice hearts lacking ret or GFRα2. Dev Dyn. 2000. https://doi.org/10.1002/1097-0177(2000)9999:9999<::AID-DVDY1031>3.0.CO;2-P.
185. Kanazawa H, Ieda M, Kimura K, Arai T, Kawaguchi-Manabe H, Matsuhashi T, et al. Heart failure causes cholinergic transdifferentiation of cardiac sympathetic nerves via gp130-signaling cytokines in rodents. J Clin Invest. 2010. https://doi.org/10.1172/JCI39778.
186. Schwartz PJ, De Ferrari GM. Sympathetic-parasympathetic interaction in health and disease: abnormalities and relevance in heart failure. Heart Fail Rev. 2011. https://doi.org/10.1007/s10741-010-9179-1.
187. Gronda E, Vanoli E, Sacchi S, Grassi G, Ambrosio G, Napoli C. Risk of heart failure progression in patients with reduced ejection fraction: mechanisms and therapeutic options. Heart Fail Rev. 2019. https://doi.org/10.1007/s10741-019-09823-z.
188. Zucker IH, Patel KP, Schultz HD. Neurohumoral stimulation. Heart Fail Clin. 2012. https://doi.org/10.1016/j.hfc.2011.08.007.
189. Mill JG, Stefanon I, dos Santos L, Baldo MP. Remodeling in the ischemic heart: the stepwise progression for heart failure. Braz J Med Biol Res. 2011. https://doi.org/10.1590/S0100-879X2011007500096.
190. Dusi V, Zhu C, Ajijola OA. Neuromodulation approaches for cardiac arrhythmias: recent advances. Curr Cardiol Rep. 2019;21:32. https://doi.org/10.1007/s11886-019-1120-1.
191. Chidsey CA, Braunwald E, Morrow AG, Mason DT. Myocardial norepinephrine concentration in man. Effects of reserpie and of congestive heart failure. N Engl J Med. 1963. https://doi.org/10.1056/NEJM196309262691302.
192. Chidsey CA, Kaiser GA, Sonnenblick EH, Spann JF, Braunwald E. Cardiac norepinephrine stores in experimental heart failure in the dog. J Clin Invest. 1964;43:2386–93. https://doi.org/10.1172/JCI105113.
193. Chidsey CA, Braunwald E, Morrow AG. Catecholamine excretion and cardiac stores of norepinephrine in congestive heart failure. Am J Med. 1965. https://doi.org/10.1016/0002-9343(65)90211-1.
194. Eisenhofer G, Friberg P, Rundqvist B, Quyyumi AA, Lambert G, Kaye DM, et al. Cardiac sympathetic nerve function in congestive heart failure. Circulation. 1996. https://doi.org/10.1161/01.CIR.93.9.1667.
195. Leimbach WN, Wallin BG, Victor RG, Aylward PE, Sundlöf G, Mark AL. Direct evidence from intraneural recordings for increased central sympathetic outflow in patients with heart failure. Circulation. 1986. https://doi.org/10.1161/01.CIR.73.5.913.
196. Hasking GJ, Esler MD, Jennings GL, Burton D, Johns JA, Korner PI. Norepinephrine spillover to plasma in patients with congestive heart failure: evidence of increased overall and cardiorenal sympathetic nervous activity. Circulation. 1986. https://doi.org/10.1161/01.CIR.73.4.615.
197. Liang C, Fan THM, Sullebarger JT, Sakamoto S. Decreased adrenergic neuronal uptake activity in experimental right heart failure. A chamber-specific contributor to beta-adrenoceptor downregulation. J Clin Invest. 1989. https://doi.org/10.1172/JCI114294.
198. Backs J, Haunstetter A, Gerber SH, Metz J, Borst MM, Strasser RH, et al. The neuronal norepinephrine transporter in experimental heart failure: evidence for a posttranscriptional downregulation. J Mol Cell Cardiol. 2001. https://doi.org/10.1006/jmcc.2000.1319.
199. Münch G, Rosport K, Bültmann A, Baumgartner C, Li Z, Laacke L, et al. Cardiac overexpression of the norepinephrine transporter uptake-1 results in marked improvement of heart failure. Circ Res. 2005. https://doi.org/10.1161/01.RES.0000186685.46829.E5.
200. Pool PE, Covell JW, Levitt M, Gibb J, Braunwald E. Reduction of cardiac tyrosine hydroxylase activity in experimental congestive heart failure. Its role in the depletion of cardiac norepinephrine stores. Circ Res. 1967. https://doi.org/10.1161/01.RES.20.3.349.

201. Himura Y, Felten SY, Kashiki M, Lewandowski TJ, Delehanty JM, Liang CS. Cardiac noradrenergic nerve terminal abnormalities in dogs with experimental congestive heart failure. Circulation. 1993. https://doi.org/10.1161/01.CIR.88.3.1299.
202. Kimura K, Kanazawa H, Ieda M, Kawaguchi-Manabe H, Miyake Y, Yagi T, et al. Norepinephrine-induced nerve growth factor depletion causes cardiac sympathetic denervation in severe heart failure. Auton Neurosci Basic Clin. 2010. https://doi.org/10.1016/j.autneu.2010.02.005.
203. Qin F, Vulapalli RS, Stevens SY, Liang CS. Loss of cardiac sympathetic neurotransmitters in heart failure and NE infusion is associated with reduced NGF. Am J Physiol Heart Circ Physiol. 2002. https://doi.org/10.1152/ajpheart.00319.2001.
204. Zhang DY, Anderson AS. The sympathetic nervous system and heart failure. Cardiol Clin. 2014. https://doi.org/10.1016/j.ccl.2013.09.010.
205. Liu JL, Pliquett RU, Brewer E, Cornish KG, Shen YT, Zucker IH. Chronic endothelin-1 blockade reduces sympathetic nerve activity in rabbits with heart failure. Am J Phys Regul Integr Comp Phys. 2001. https://doi.org/10.1152/ajpregu.2001.280.6.r1906.
206. Hassankhani A, Steinhelper ME, Soonpaa MH, Katz EB, Taylor DA, Andrade-Rozental A, et al. Overexpression of NGF within the heart of transgenic mice causes hyperinnervation, cardiac enlargement, and hyperplasia of ectopic cells. Dev Biol. 1995. https://doi.org/10.1006/dbio.1995.1146.
207. Kimura K, Ieda M, Kanazawa H, Yagi T, Tsunoda M, Ninomiya SI, et al. Cardiac sympathetic rejuvenation: a link between nerve function and cardiac hypertrophy. Circ Res. 2007. https://doi.org/10.1161/01.RES.0000269828.62250.ab.
208. Kreusser MM, Buss SJ, Krebs J, Kinscherf R, Metz J, Katus HA, et al. Differential expression of cardiac neurotrophic factors and sympathetic nerve ending abnormalities within the failing heart. J Mol Cell Cardiol. 2008. https://doi.org/10.1016/j.yjmcc.2007.10.019.
209. Parrish DC, Alston EN, Rohrer H, Nkadi P, Woodward WR, Schütz G, et al. Infarction-induced cytokines cause local depletion of tyrosine hydroxylase in cardiac sympathetic nerves: experimental physiology-research paper. Exp Physiol. 2010. https://doi.org/10.1113/expphysiol.2009.049965.
210. Kaye DM, Vaddadi G, Gruskin SL, Du XJ, Esler MD. Reduced myocardial nerve growth factor expression in human and experimental heart failure. Circ Res. 2000;86:E80–4. https://doi.org/10.1161/01.res.86.7.e80.
211. Dusi V, De Ferrari GM, Pugliese L, Schwartz PJ. Cardiac sympathetic denervation in channelopathies. Front Cardiovasc Med. 2019. https://doi.org/10.3389/fcvm.2019.00027.
212. Vaseghi M, Barwad P, Malavassi Corrales FJ, Tandri H, Mathuria N, Shah R, et al. Cardiac sympathetic denervation for refractory ventricular arrhythmias. J Am Coll Cardiol. 2017;69:3070–80. https://doi.org/10.1016/j.jacc.2017.04.035.
213. Dusi V, Sorg JM, Gornbein J, Gima J, Yanagawa J, Lee JM, et al. Prognostic impact of atrial rhythm and dimension in patients with structural heart disease undergoing cardiac sympathetic denervation for ventricular arrhythmias. Heart Rhythm. 2020; [Online ahead of print]. https://doi.org/10.1016/j.hrthm.2019.12.007.
214. Gronda E, Seravalle G, Brambilla G, Costantino G, Casini A, Alsheraei A, et al. Chronic baroreflex activation effects on sympathetic nerve traffic, baroreflex function, and cardiac haemodynamics in heart failure: a proof-of-concept study. Eur J Heart Fail. 2014;16:977–83. https://doi.org/10.1002/ejhf.138.
215. Gronda E, Francis D, Zannad F, Hamm C, Brugada J, Vanoli E. Baroreflex activation therapy: a new approach to the management of advanced heart failure with reduced ejection fraction. J Cardiovasc Med. 2017;18:641–9. https://doi.org/10.2459/JCM.0000000000000544.
216. Stavrakis S, Humphrey MB, Scherlag BJ, Hu Y, Jackman WM, Nakagawa H, et al. Low-level transcutaneous electrical vagus nerve stimulation suppresses atrial fibrillation. J Am Coll Cardiol. 2015;10:867–75. https://doi.org/10.1016/j.jacc.2014.12.026.
217. Stavrakis S, Stoner JA, Humphrey MB, Morris L, Filiberti A, Reynolds JC, et al. TREAT AF (Transcutaneous electrical vagus nerve stimulation to suppress atrial fibrillation): a randomized clinical trial. JACC Clin Electrophysiol. 2020;6:282–91. https://doi.org/10.1016/j.jacep.2019.11.008.
218. Konstam MA, Udelson JE, Butler J, Klein HU, Parker JD, Teerlink JR, et al. Impact of autonomic regulation therapy in patients with heart failure: ANTHEM-HFrEF pivotal study design. Circ Heart Fail. 2019;12(11):e005879. https://doi.org/10.1161/CIRCHEARTFAILURE.119.005879.
219. De Ferrari GM, Dusi V. Vagal stimulation in the treatment of heart failure. G Ital Cardiol. 2015;16:157–64.

Brain-Heart Communication

2

Hardware and Software Strategies Through Nerves and Humoral Factors

Alessia Pascale and Stefano Govoni

Contents

Abstract

The tight crosstalk between heart and brain is becoming increasingly recognized as the underlying mutual mechanisms are better identified, having a potential impact for clinical approach. Cardiac control is achieved by means of a three-level hierarchical neuronal network (central nervous system neurons, extracardiac-intrathoracic neurons, and intrinsic cardiac nervous system), where all the components work together to fulfill the physiological demands. However, each component of this network can undergo pathologic-mediated changes due to the transduction of altered sensory inputs originating from a deteriorating heart. A key role in the maintenance of cardiovascular homeostasis is played by the autonomic nervous system with its sympathetic and parasympathetic branches, which operate in a reciprocal manner. Heart rate best mirrors the relative balance between these two systems, and especially heart rate variability has emerged as a key parameter that reflects the health status of a given individual. Neural reflexes (i.e., the baroreceptor reflex) and several neuromodulators released from the heart itself or coming from other

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*,
https://doi.org/10.1007/978-3-030-28008-6_4

sites, as well as neurotrophins, also contribute to cardiovascular homeostasis and will be considered in the present chapter. A deeper understanding of heart-brain interactions will facilitate the prompt recognition and management of cardiac diseases, as well as of neurologic disorders associated to heart dysfunction, and, at the same time, will help in optimizing the therapeutic approach.

Keywords

Heart-brain crosstalk · Cardiac function · Heart rate variability · Angiotensin · Natriuretic peptide · Neurotrophin

Introduction

Since the ancient Greeks, reason (brain) and sentiment (heart) have been considered as separate functions often depicted in a constant battle aimed at controlling the human psyche; however, it is becoming more and more clear that the brain and the heart interact in a dynamic and complex relationship. The French physiologist Claude Bernard (1813–1878) was one of the first scientists to systematically investigate the interactions between the peripheral organs and the nervous system, and over 150 years ago, he proposed the existence of an intimate connection between the brain and the heart. Since then, a number of experimental and clinical studies have highlighted the presence of a complex network of cortical and subcortical areas engaged in the control and processing of the cardiovascular function [1]. Notably, a medical specialty focused in brain-heart interactions has emerged, namely neurocardiology, which specifically refers to the (patho)physiological interplay of the nervous and cardiovascular systems.

Proof for a role of brain and higher centers in modulating the autonomic control of the cardiovascular function includes anecdotal reports throughout the ages, especially pointing to an association with mental stress. In humans, the pattern of the sympathetic response during mental stress preferentially involves the heart, and short-term mental stress results in a significant enhancement in heart rate, blood pressure, and muscle sympathetic nerve activity [2]. Accordingly, consisting evidence correlates chronic emotional stress to the development of cardiovascular diseases. For instance, a study by Mittleman and collaborators [3] showed a more than double relative risk of acute myocardial infarction in the 2 h subsequent to an anger episode with respect to no anger events. These episodes of anger-associated cardiac death risk have been confirmed also by others [4]. Moreover, on the day of the Northridge earthquake that struck the Los Angeles area in 1994, there was an abrupt rise, in comparison to average days, in the number of cardiac episodes leading to sudden death [5]. There is even a report documenting that the excitement of watching sport can have dramatic consequences on the autonomic regulation of the heart; indeed, during the 2006 soccer World Cup hosted by Germany, a doubling of hospital admissions for acute coronary events (including myocardial infarction) was observed among German spectators watching their team playing important matches [6]. Within this context, it is known that both arrhythmia and sudden cardiac death are characterized by a diurnal variation associated with more elevated morning levels of catecholamines [7, 8]; however, in working individuals, a Monday morning peak has also been described, which suggests a relationship to work-related mental stress [9].

There is growing evidence about the heart-brain mutual relationship also with potential outcomes for clinical treatment. It should be recalled that the brain is very sensitive to changes in cerebral blood flow, with both hypo- and hyperperfusion having severe consequences such as stroke. For this reason, in physiologic conditions, the effect of changes in mean arterial pressure is well buffered in the brain by several mechanisms that ensure, as much as possible, the maintenance of perfusion within healthy limits (cerebral autoregulation) [10]. However, these protective mechanisms may fail in pathologic conditions. For example, transient ischemic attacks and cerebrovascular accidents are often induced by cardiac arrhythmias and/or congestive heart failure [11, 12]. Atrial fibrillation may produce cognitive disorders that anticipate transient

ischemic attacks and cerebrovascular accidents. Moreover, atrial fibrillation is a risk factor for cognitive deficit and hippocampal atrophy, even in the absence of stroke [13] (see ▶ Chap. 5, "Cognitive Decline in Elderly Patients with Hypertensive Heart Disease").

On the other side, neurologic disorders as well can have cardiac manifestations. For instance, subarachnoid bleeding may provoke pronounced electrocardiographic alterations and even ventricular fibrillation, probably depending upon QT-interval prolongation [14]. Arrhythmias are also commonly associated with stroke and include atrial fibrillation and sinus bradycardia. Such complications might be caused by focal cerebral injury; for instance, atrial fibrillation has been related to brainstem hemorrhage, while sinus bradycardia is a common arrhythmia found in patients with supratentorial intracerebral hemorrhage [15]. Notably, even though it is often difficult to recognize whether a newly reported atrial fibrillation is the cause or the consequence of stroke, cardiac monitoring and ECG is recommended in patients with acute stroke [16]. A wide spectrum of cardiac arrhythmias, some of them life threatening, may also arise from central autonomic disorders. For example, sympathetic hyperactivity leads to both supraventricular and ventricular tachycardia, while vagal hyperactivity results in bradyarrhythmias, including atrioventricular block; further, sympathetic or vagal hyperactivity may trigger atrial fibrillation. In addition, several links have been underlined between seizures and cardiac dysfunction, including cardiac arrhythmias [17].

Overall, these findings suggest that a deeper understanding of the cardiac complications linked to neurologic disorders will facilitate the prompt recognition and management of cardiac diseases and, at the same time, will help in optimizing the therapeutic approach.

Evidence of Heart-Brain Interactions: The Hardware

Cardiac control is attained by means of a three-level hierarchical network: (1) central nervous system neurons [medullary (the medulla oblongata, often just called medulla, constitutes the lower half of the brainstem continuous with the spinal cord) and spinal cord neurons regulated by higher centers], (2) extracardiac-intrathoracic neurons, and (3) the intrinsic cardiac nervous system. All these network components act together with the task to assure that the cardiac output meets blood flow requirements. Indeed, in response to normal physiological stressors, such as dynamic exercise and orthostatic stress, changes in cardiovascular afferent inputs involve both central and peripheral reflexes that, in turn, regulate motor outputs to fulfill body demands. Therefore, this system guarantees the presence of a fine-tuned control of the sympathetic-parasympathetic balance in the heart, under both normal and stressed states, in the short (beat-to-beat), intermediate (minutes to hours), and long term (days to years). However, it should be emphasized that, although this cardiac hierarchical control is capable of adjusting as a consequence of physiologic perturbations, it may be unable to respond adequately to the needs of a deteriorating heart, such as occurring in slowly progressing heart failure or to sudden changes in demand as following myocardial infarction [18].

The anterior cingulate cortex, anterior insula, amygdala, several hypothalamic nuclei project to medullary (especially the rostral ventrolateral medulla) and spinal nuclei, either directly or via a relay in the periaqueductal gray matter, playing a key role in modulating the cardiovascular function. Indeed, these cerebral structures regulate the force of contraction and heart rate through the sympathetic and parasympathetic nervous system in response to emotional and stressful events, and in homeostatic reflexes [17].

Laboratory studies have emphasized the central implication of the insular cortex in the management of heart's activity. The insular cortex is a complex structure that has been involved in several functions and in the pathophysiology of various neurologic disorders. Its importance in heart control is underscored by the fact that ischemic or hemorrhagic strokes that particularly involve this cerebral area can manifest with cardiac arrhythmias or myocardial injury that may be potential causes of sudden death. With respect to insular cortex function, it has been reported that

the stimulation of the caudal portion of the posterior insula produces bradycardia, while tachycardia is evoked by the stimulation of the rostral posterior insula. Moreover, stimulation of the right insula increases the sympathetic tone, whereas stimulation of the left insula results in a rise of the parasympathetic tone ("the laterality hypothesis"), a phenomenon that can be also ascribed to the lateralized distribution of the baroreceptor units [1, 19]. However, it should be mentioned that, even though a number of findings suggest a lateralization of the autonomic cardiovascular control at cortical level, and mainly at the insular cortex [20], the laterality in humans is still under debate [1].

On the other side, afferent cardiovascular inputs, conveyed by layer I of the dorsal horn or the nucleus of the solitary tract neurons (a brainstem structure), reach via thalamus the cortical areas [17]. Moreover, the afferent inputs due to changes in arterial pressure and blood gas content reflexively (i.e., via baroreceptors) modulate the activity of the pertinent visceral motor pathways and, finally, of target cardiac and vascular smooth muscles.

A key role in the maintenance of cardiovascular homeostasis is played by the autonomic nervous system with its sympathetic and parasympathetic branches (Fig. 1). The sympathetic innervation of the heart arises from the preganglionic neurons located in caudal cervical and cranial thoracic spinal cord segments (the intermediolateral column), which receive tonic excitatory glutamatergic inputs from the rostral ventrolateral medulla (another brainstem structure). The cardiac preganglionic sympathetic

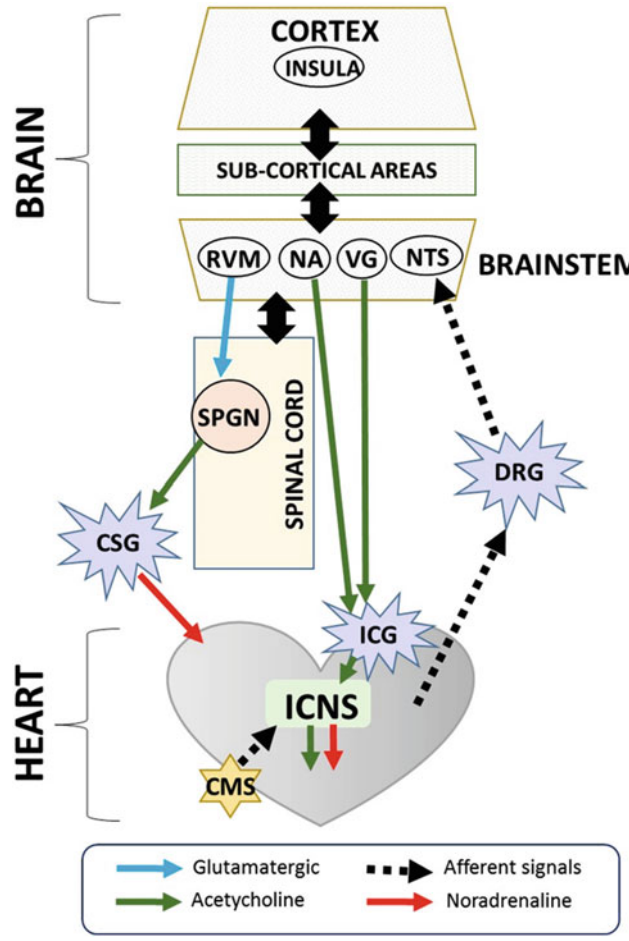

Fig. 1 *Brain-heart crosstalk.* Simplified representation of the main pathways involved in brain-heart mutual interaction. See text for further details. *CSG* cervicothoracic stellate ganglia, *CMS* chemosensory and mechanosensory neurons, *DRG* dorsal root ganglion, *ICG* intrinsic cardiac ganglia, *ICNS*, intrinsic cardiac nervous system, *NA* nucleus ambiguous, *NTS* nucleus of the solitary tract, *RVM* rostral ventrolateral medulla, *SPGN* sympathetic preganglionic neurons, *VG* vagus nerve

neurons are cholinergic and, via small myelinated axons, synapse on noradrenergic neurons of the cervicothoracic stellate ganglia (located bilaterally to the thoracic vertebrae) that, in turn, innervate the heart through the superior, middle, and inferior cardiac nerves [21]. Notably, the cardiac left-to-right distribution of sympathetic nerves is asymmetrical and displays interindividual variability. The noradrenergic postganglionic axons innervate the heart conduction network, atria and ventricles, being heterogeneous and less dense in the cardiac apex [1]. Therefore, sympathetic activation positively influences cardiac indices throughout the atria and ventricles, such as heart rate as well as electrical and mechanical indices. Indeed, augmented sympathetic tone increases cardiac chronotropism, dromotropism, and inotropism.

The parasympathetic preganglionic neurons originate in the dorsal motor nucleus of the vagus nerve and in the nucleus ambiguous in the medulla, projecting to postganglionic neurons within the intrinsic cardiac ganglia. Notably, within these ganglia, the mechanisms underlying the transmission and regulation of the neuronal activity are not completely clear, and it appears that this site is more complex than a simple relay station [1]. The parasympathetic nerves project to the atrial conduction system and to the ganglionated plexus of myocardium that through the intrinsic cardiac nervous system (see below) control ventricular contractility (although the effects are less prominent with respect to those mediated by the sympathetic nerves) [22]. The activation of cholinergic neurons determines a reduction in atrial rate, atrioventricular nodal conduction, atrial and ventricular contractility. To this regard, it has been supposed that the cardiac motor neurons located in the dorsal motor nucleus of the vagus are mainly involved in the regulation of heart inotropism while those placed in the nucleus ambiguous primarily control heart rate [23].

Armour JA studies revealed that the heart also possesses a complex intrinsic cardiac nervous system (ICNS) constituted by an intricate network of various types of neurons, neurotransmitters, proteins, and supporting cells similarly to the brain; for this reason, he introduced the concept of "the little brain on the heart" [24]. Historically, it was believed that intrinsic ganglia were simple relay stations for parasympathetic signals and therefore would only contain cholinergic markers. Instead, over the years, it has been documented that these ganglia show immunoreactivity for a number of neuromodulators and neurotransmitters such as vasoactive intestinal peptide, tyrosine hydroxylase (responsible for the production of noradrenaline), neuropeptide Y (NPY), substance P, and calcitonin gene-related peptide. Intrinsic cardiac nerves innervate the atria, interatrial septum, and the ventricles [25]. It should be mentioned that, besides demonstrating the presence of such a complex mix of neurotransmitters/neuromodulators, the exact role and destiny in physiopathological conditions of each one has not been fully characterized. This intrinsic nervous system integrates inputs from the brain and other centers throughout the body with messages coming from cardiac sensory neurites and elaborates the appropriate signals to be sent to the sinoatrial and atrioventricular nodes as well as to the cardiac muscles. However, the intrinsic nervous system is also able to operate and process information independently of the brain, since it possesses all the neuronal elements to function autonomously, such as efferent (sympathetic and parasympathetic), afferent, and local neurons. This organization explains why a transplanted heart can work, having an autonomous "coordinated" activity through the ICNS and responding/releasing humoral factors even if lacking of direct neuronal connections. Indeed, in a transplanted heart, the nerve fibers connecting the heart to the brain do not reconnect for a prolonged time, if at all. Nevertheless, due to the intrinsic nervous system, the transplanted heart is capable to function in the new host.

Terminals of cardiac sensory neurons, localized in the dorsal root ganglion, are found not only at epicardial sites but also in the ventricular myocardium. As mentioned, the sensory signals originating within the heart are transmitted to the higher centers, especially to the nucleus of the solitary tract, via cardiac afferent nerves (see also Fig. 1), primarily composed by thinly myelinated Aδ-fibers and nonmyelinated C-fibers. For

instance, the cardiac sensory nervous system is responsible for pain perception and for triggering a protective cardiovascular response in the course of myocardial ischemia [26]. Moreover, the intrinsic cardiac afferent sensory neurons transmit mechanical and chemical information concerning the heart to the ICNS.

Cardiac pathology implicates maladaptive interactions occurring not only at cardiomyocyte level but also at any level of the neuronal network engaged in heart control, from the intrinsic nervous system to the higher cerebral centers. Indeed, each component of this network can undergo pathologic-mediated changes due to the transduction of altered sensory inputs originating from a deteriorating heart. These altered signals generate a sort of central-peripheral conflict among the neurons within the hierarchical network, which is the foundation of the maladaptive neurohumoral response to a diseased heart and of cardiac pathology evolution. For example, an excessive stimulation of intrinsic cardiac neuron subpopulations can trigger arrhythmias, or altered neuronal heart activities, associated with cardiac electrophysiological changes, are a fundamental contributor to sudden cardiac death [18, 25, 27]. Atrial fibrillation is the most common cardiac arrhythmia and the importance of the ICNS in its genesis is underscored by the fact that recent developments in treatments have revolved around ablation of the ICNS [28]. However, such ablation therapy does not take into account the level of plasticity of the nerves and ganglia within the ICNS. Indeed, following atrial fibrillation, a significant remodeling of the neurons within the ICNS occurs, such as increased levels of sympathetic neurons and augmented acetylcholine (ACh) labelled neurons, which can alter the effects of this type of therapy. The reorganization and remodeling of the ICNS has been also reported after myocardial ischemia, where it primarily occurs within noninfarcted regions, probably with the purpose of enabling the ICNS to cope with the damage, thus allowing the maintenance of cardiac function. With time, the compromised blood supply to intrinsic cardiac neurons induces pathological and degenerative changes, providing an anatomical basis for altered ganglionic control. During the early stage of heart failure, there is little or no substantial alterations in ICNS function; in contrast, late stage heart failure is accompanied by neuronal hypertrophy, where neurons are less excitable and may fail to reach their excitability threshold [25]. It is not clear whether neuronal hypertrophy is causally associated with cardiac hypertrophy and whether the same neuro-humoral signals control either events or whether they are independently regulated. Within this context, nerve growth factor (NGF) may have a key involvement [29]. Nevertheless, it should be stressed that, in general, remodeling can occur at various levels starting from the intrinsic nervous system up to the central neuronal circuits and can also involve changes in the neuro-humoral control including, as well, circulating catecholamines and the renin-angiotensin-aldosterone system [18].

The Signaling Pathways: The Software

The sympathetic and parasympathetic branches of the cardiac autonomic nervous system operate in a reciprocal manner to modulate heart rate and conduction velocity especially acting on the cardiac conduction tissue, where heart rate best mirrors the relative balance between these two systems (see Box 1). Moreover, both branches innervate atrial and ventricular cardiomyocytes, thus influencing the force of contraction and relaxation [30].

The sympathetic cardiac effects are mediated by noradrenaline (also called norepinephrine; Fig. 2a) through metabotropic β1 receptors (the predominant β receptor subtype found in mammalian hearts) located on the myocytes. These adrenergic receptors are coupled to stimulatory heterotrimeric (formed by α, β, and γ subunits) guanine nucleotide-binding proteins (G_s proteins). The G_s activation following agonist binding facilitates the exchange of bound GDP (guanosine diphosphate) for GTP (guanosine triphosphate) on the α subunit, which is the rate-limiting step in G protein activation, and the dissociation of the α subunit

itself from the βγ subunits. The activated GTP-bound $G_s\alpha$ subunit can thus directly interact with the adenylyl cyclase leading to an increase of the intracellular levels of the second messenger cyclic adenosine monophosphate (cAMP) which, in turn, activates protein kinase A (PKA; also known as cAMP-dependent protein kinase). PKA is a family of tetrameric enzymes consisting of two regulatory and two catalytic subunits; the binding of four cAMP molecules to the two inhibitory regulatory subunits produces a conformational change causing the release of the two activated catalytic subunits. Once released, these latter can phosphorylate several intracellular substrates, such as L-type Ca^{2+} channels and delayed rectifier K^+ channels, which results in the shortening of the duration of the action potential necessary for heart rate and conduction velocity enhancement [31, 32]. The action of cAMP on pacemaker channels is thought to be the primary mechanism implicated in the sympathetic-induced rise in heart rate [33], while the effect of PKA activity on Ca^{2+} channels significantly contributes to the sympathetic regulation of cardiac muscle contraction [34]. Notably, pacemaker channels, also referred as hyperpolarization-activated cyclic nucleotide–gated (HCN) channels, are nonselective voltage-gated cation channels located in the plasma membranes of cardiac cells that help to generate rhythmic activity. Ca^{2+} channel activity plays also a determinant role in cardiac action potential duration, and a sympathetic-induced increase of the L-type Ca^{2+} current, in the absence of other modifications, can produce a substantial prolongation of the action potential. This last event, if left unchecked, may potentially trigger the development of arrhythmias [35].

Within this general context, it should be also taken into account that changes, on genetic bases, in the features of cardiac channels, including sensitivity to drugs, may also lead to heart pathology, as detailed elsewhere [36, 37].

The parasympathetic component of the autonomic nervous system is also engaged in the physiological regulation of cardiac function (Fig. 2b); indeed, besides being able to regulate the contractile force, it significantly influences the initiation as well as the propagation of electrical impulses. The axon terminals release ACh that primarily binds to the metabotropic muscarinic M_2 receptors, thus changing the ion channel activity (see below) and resulting in a decrease in heart rate and contractility; it also takes part in slowing impulse conduction mainly through the atrioventricular node. The M_2 receptor is considered to be the predominant muscarinic receptor subtype expressed in cardiac muscle.

The majority of the changes in cardiac ion channel function coupled to M_2 receptor activation involve two main mechanisms: a direct G protein-dependent regulation or an indirect modulation of cAMP-dependent responses. The direct signaling pathway implicates the coupling of M_2 receptors to inward rectifying K^+ (GIRK) channels, primarily expressed in atrial, sinoatrial node, and atrioventricular node cells, through the inhibitory pertussis toxin-sensitive G protein Gi [reviewed in 35]. The indirect route entails the inhibition of cAMP-dependent responses and it represents the mechanism most often associated with muscarinic receptor stimulation. Notably, the capability of M_2 receptor to hinder cAMP-dependent responses has been termed "accentuated antagonism" [38], referring to the fact that the inhibitory response following M_2 receptor stimulation is more evident or becomes manifest in the presence of β-adrenergic receptor activation (this is especially true with regard to the effects on ventricular function). The understanding of this indirect pathway originated from the observation that the inhibitory effects mediated by ACh do not always correlate with changes in cAMP levels, thus leading to the speculation that this neurotransmitter might antagonize cAMP-dependent responses through the stimulation of phosphatase activity and the increase of protein dephosphorylation [35]. Within this context, it should be also mentioned that it has been proposed that nitric oxide may play an obligatory role in mediating M_2 inhibition of cAMP-dependent responses through a mechanism that implicates a cGMP (cyclic guanosine monophosphate)-dependent regulation of the activity of type 2 phosphodiesterase (PDE2), resulting in an enhancement in

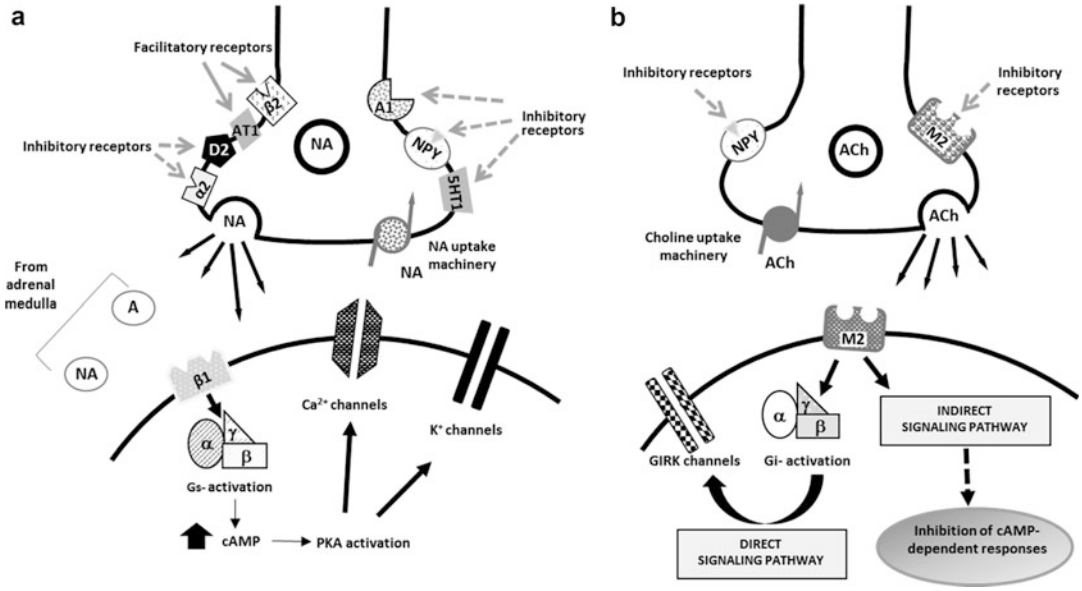

Fig. 2 *Autonomic nervous system control of the heart at a glance.* The figure depicts the main noradrenergic (**a**) and cholinergic (**b**) signaling pathways. The interplay between presynaptic inhibitory and stimulatory auto- and hetero-receptors, only briefly summarized in the figure, indicates that the intra-synaptic regulatory mechanisms may have a fundamental role in the fine-tuning of cardiac activity and heart rate variability. Even if the effect of pathology and drugs has not been systematically investigated, both these conditions can impact on this regulatory system. A detailed review on the presynaptic human receptors has been recently published by Schlicker et al. [42]. *A* adrenaline, *A1* adenosine-type 1 receptor, *ACh* acetylcholine, *AT1* Ang II–type 1 receptor, *cAMP* cyclic adenosine monophosphate, *D2* dopamine-type 2 receptor, *5HT1* serotonin-type 1 receptor, *GIRK channels* inward rectifying K^+ channels, *M2* muscarinic acetylcholine receptor 2, *NA* noradrenaline, *NPY* neuropeptide Y receptor, *PKA* protein kinase A

cAMP breakdown. However, the involvement of nitric oxide in mediating this inhibitory response is not clear [35].

Although it is not the focus of this chapter, it should be mentioned that the various neuromodulators listed above, and in particular those associated with an increase in cAMP and PKA activation, may trigger, in addition to beat-to-beat control, long-term changes through the modulation of gene expression, an aspect that may be relevant in cardiac remodeling [39–41].

The balance between parasympathetic and sympathetic activity is also affected by neural reflexes (i.e., the baroreceptor reflex) and by several neuromodulators released from the heart itself or coming from other sites such as the kidney and the coronary vessels (i.e., natriuretic peptides and angiotensin II) and the adrenal medulla (i.e., adrenaline), as well as by neurotrophins.

Box 1 Heart Rate Variability

The cardiovascular regulatory stations in the spinal cord and in the medulla integrate the information from the higher centers with the afferent signals coming from the cardiovascular system to adjust blood pressure and heart rate (HR) through the sympathetic and parasympathetic efferent branches. Indeed HR, evaluated at any given time, reflects the net effect of sympathetic (which accelerates HR) and parasympathetic (which slows down HR) nerve signals, the latter predominating during normal daily activities, when resting or sleeping. Nevertheless, efferent sympathetic and parasympathetic signals are integrated within the activity of the intrinsic

(continued)

Box 1 (continued)
cardiac nervous system, which also takes into account the afferent inputs originating from the mechanosensitive and chemosensory neurons within the heart, thus contributing as a whole to beat-to-beat changes [43]. However, it should be emphasized that any biological process, even in "steady-state" conditions, is not static, but it is the result of dynamic interactions at multiple levels. For instance, the cardiac rhythm is highly variable and not monotonously regular as previously thought. Indeed, the irregular profile of the heartbeat is easily evident when considering heart rate on a beat-to-beat basis rather than simply calculating its mean value. Notably, the term heart rate variability (HRV) is used to define the change in the time intervals between consecutive heartbeats, and it is a measure of neurocardiac function resulting from heart-brain crosstalk and autonomic nervous system dynamics. Following a rise in HR, HRV decreases since less time is available for heartbeats variability; the opposite occurs when HR declines, since in this case, more time is available for heartbeats to vary. Within an organism, an optimal HRV level reflects a healthy status and an intrinsic self-regulatory adaptability. An excessive instability, such as in presence of arrhythmias, is detrimental for an efficient physiological functioning; on the other side, too little HRV is an index of inappropriate functioning at various levels of the self-regulatory systems that are unable to adapt to the current context [44]. For instance, reduced HRV has been reported to be the most important risk factor of postmyocardial infarction death [45] and the strongest independent predictor of coronary atherosclerosis progression [46]. A decrease in HRV has also been observed among older adults with depression [47]. Notably, HRV declines with senescence, therefore, in the context of risk prediction, aged-adjusted values should be considered [48].

Reflexes and Modulators: A Complex Network Affecting Cardiac Function

The Baroreceptor Reflex

An efficient regulation of central blood volume and arterial pressure is essential to guarantee an optimal cardiovascular homeostasis. Indeed, an inadequate control of mean arterial pressure has significant pathophysiological implications such as end organ damage, syncope, and stroke. Such regulation requires the intervention of neural sensors that direct afferent information to the brainstem and higher brain regions for central integration, thus allowing the genesis of a proper autonomic response [49].

The baroreceptors are highly specialized stretch-sensitive receptors designated to monitor variations in blood pressure that transmit to the brainstem. Specifically, high-pressure baroreceptors, which are responsible for sensing changes in the mean arterial pressure, are distributed in the aorta and in the carotid artery, while low-pressure baroreceptors, which sense changes in central blood volume, are localized in the cardiopulmonary regions including the walls of the atria, ventricles, and intrathoracic vessels [50]. Both sets of afferent baroreceptor inputs travel to the brainstem converging bilaterally to the caudal region of the solitary tract nucleus, located within the medulla. In turn, the solitary tract nucleus integrates and transmits this information to other autonomic medullary areas that dictate parasympathetic and sympathetic outflow to the heart and blood vessels. For instance, as a consequence of a transient reduction in blood pressure (resulting in a decreased firing rate of the baroreceptors), the parasympathetic outflow is inhibited whereas the sympathetic one is promoted, and vice versa.

The clinical relevance of the cerebral cortex, especially the insular cortex, on proper blood pressure regulation has been revealed from studies in stroke patients who show impaired baroreceptor reflex sensitivity [51]. Moreover, evidence from animal models has underscored the critical role of supramedullary centers in baroreflex control of the cardiovascular system [49]. The cardiac arm of the baroreceptor reflex modulates (shortening or prolongation) the cardiac period as a function of changes in the baroreceptor input, generally constituted by blood pressure variations. Of interest, a reduction with senescence in cardiovagal (=cardiac response vagally mediated) baroreflex sensitivity has been documented [50]. With regard to the underlying mechanisms, age-dependent changes affecting any component of the cardiac baroreflex arc may be implicated. In particular, literature data indicate a compromised vagal control in humans with aging including a drop in M_2 receptors and a diminished responsiveness of the heart to muscarinic activation [reviewed in 52].

Adrenaline

The sympathetic system also acts by secretion of adrenaline (also named epinephrine) and noradrenaline from the adrenal medulla, the central part of the adrenal gland. Here, the chromaffin cells secrete approximately 20% noradrenaline and 80% adrenaline, which then reach the heart through the circulation causing an increase in heart rate and in cardiac contractility signaling trough β-adrenoceptors [53].

The adrenal gland receives input from the sympathetic nervous system via preganglionic fibers and can be considered as a specialized sympathetic ganglion with the unique feature to secrete neurohormones directly into the blood. Chromaffin cells are postganglionic sympathetic neurons partially deprived of their typical characteristics like axons and dendrites that release their hormones into the bloodstream by exocytosis [54].

It should be mentioned that the release of catecholamines is regulated by presynaptic α_2 autoreceptors, which inhibit their further release in adrenergic nerves in the central and in the sympathetic nervous system, including the adrenal gland. Moreover, catecholamines secretion by chromaffin cells is strongly regulated by adrenal gland cortex as well. Specifically, glucocorticoids affect chromaffin cells differentiation and characterization; indeed, during development, glucocorticoids are crucial for the sustained expression of phenylethanolamine *N*-methyltransferase, the enzyme that converts noradrenaline into adrenaline thus allowing the acquirement of the adrenergic phenotype versus the noradrenergic one [55]. Furthermore, it has been reported that, in the adult, glucocorticoids determine diverse expression of α_2 receptors subtypes, namely α_{2A} and α_{2C}, in the brain during chronic stress, suggesting that they could influence not only the adrenergic/noradrenergic phenotype but also adrenergic receptors expression thus cooperating in sympathetic overdrive related diseases [56].

An elevated sympathetic tone accompanied with increased levels of circulating and synaptic catecholamines is a key feature of heart failure. Indeed, an augmented sympathetic nervous activity is a useful and compensatory mechanism to maintain, in the early phase of heart failure, cardiac output by increasing heart rate and cardiac contractility. However, considering that adrenergic receptors undergo agonist-dependent desensitization and downregulation, when β receptors become irresponsive to catecholamines, this chronic stimulation triggers heart failure progression and its consequent detrimental systemic effects [53, 57].

Angiotensin II

The heart-kidney interaction is fundamental for the maintenance of cardiovascular homeostasis. Indeed, in healthy individuals, hemodynamic changes in either organ may influence the other one. This relationship is finely tuned by neurohumoral activity, which includes the systemic renin-angiotensin system.

Since the discovery of renin by Tigerstedt and Bergman in 1898 [58], the importance of the systemic renin-angiotensin system in the maintenance of extracellular volume homeostasis and blood pressure has been well known. This system

requires the interaction of multiple organs, which first involves the liver for the production of the precursor protein named angiotensinogen. Angiotensinogen is subsequently converted by renin, a protease produced by the renal juxtaglomerular apparatus, to the decapeptide angiotensin I (Ang I) that, in turn, undergoes a second cleavage operated by the angiotensin converting enzyme (ACE), located on the endothelium and especially on the lung endothelium, to finally originate angiotensin II (Ang II). Ang II is a potent vasoactive peptide that, mainly through the G protein-coupled receptor AT1 (Ang II–type 1), increases cytosolic Ca^{2+} concentrations thus inducing arterioles to constrict, and resulting in augmented arterial blood pressure with a consequent impact on cardiac activity. Ang II stimulates as well the secretion of aldosterone, the main mineralocorticoid hormone, from the adrenal cortex. Aldosterone, acting on the nuclear mineralocorticoid receptors localized on the distal tubule and the collecting duct of the kidney nephron, increases the reabsorption of sodium ions from the tubular fluid back into the blood, thus further contributing to blood pressure enhancement [updated in 59].

During hypertension, myocardial ischemia, and heart failure, the persistent activation of the renin-angiotensin system is engaged in vascular and cardiac remodeling, such as left ventricular hypertrophy and fibrosis. Accordingly, ACE inhibitors and AT1 blockers (ARBs) show beneficial effects in hypertensive subjects and an improvement of cardiac function and remodeling in patients with heart failure [60].

Experimental evidence supports the notion that a local renin-angiotensin system is present in various organs including heart and kidney. Specifically, Ang II is locally produced in the myocardium and is able to enhance, through AT1 receptors, sympathetic activity by inhibiting the parasympathetic neurotransmission [61]. Moreover, Ang II gradients across the heart are elevated in patients with heart failure [62]. Concerning the availability of angiotensinogen, although the presence of its mRNA has been demonstrated in human heart, studies performed in isolated perfused hearts suggest that the majority of the cardiac angiotensinogen is taken up from the circulation [63]. With regard to the origin of cardiac renin in the normal heart, evidence indicates that its uptake from plasma represents the primary source of the enzyme, although cardiac renin production, which increases following myocardial infarction, has been reported as well [60]. Recent findings show that, in intact left ventricle of adult rats, intracellular renin causes a depolarization of ventricular fibers and a reduction in action potential duration and cardiac refractoriness, with consequent generation of triggered activity. Specifically, the shortening of the action potential has been associated with an enhancement in total potassium current. Of note, these effects of intracellular renin may be especially relevant in pathological conditions, such as myocardial ischemia, when cardiac excitability is already elevated [64].

It should be also taken into consideration that plasma Ang II can directly activate cerebral angiotensinergic pathways, thus further contributing to the increase of sympathetic activity [65; see also Box 2].

Recent findings indicate that the ACE2/Ang (1–7)/Mas receptor pathway critically contributes to oppose many effects of Ang II at cardiovascular and renal levels. ACE2 is an enzyme highly homologous to ACE, which can form the peptide Ang (1–7) directly or indirectly from either the decapeptide Ang I or from Ang II. Ang (1–7), acting via the G protein-coupled Mas receptor, hinders several Ang II actions, including its proliferative and profibrotic effects as well as those on blood pressure [60, 66].

Box 2 Angiotensinergic Pathways in the Brain

In the brain, the angiotensinergic pathways significantly contribute to the control of cardiovascular homeostasis through the activation of sympathetic activity. These pathways originate from neurons in the circumventricular organs in the forebrain located outside the blood-brain barrier, such as the organum vasculosum of the lamina terminalis and the subfornical organ, that project to the rostral

(continued)

Box 2 (continued)
ventrolateral medulla and the paraventricular nucleus in the brainstem [65]. In these major cardiovascular regulatory nuclei, Ang II interacts with AT1 receptors that have been found at both pre- and postsynaptic level, although it should be mentioned that, within the local brain renin-angiotensin system, Ang III (generated via aminopeptidase A from Ang II) seems to play a key role acting upon AT1 receptors as well [67]. Moreover, aldosterone, which is produced at hypothalamic level and behaves as slow neuromodulator via mineralocorticoid receptors, amplifies Ang II/III downstream responses [68]. The blockade of these cerebral Ang II-mediated cascades may thus represent a potential therapeutic strategy for heart failure and hypertension treatment [65]. Regarding the origin of angiotensin, a recent review challenges the concept of local angiotensin generation in the brain, while proposing a blood origin of the peptide, possibly resulting in augmented levels following blood–brain barrier disruption (for example, due to hypertension) [69]. Indeed, although angiotensinogen mRNA can be detected in brain tissue, the levels of the corresponding protein are very low; further, the formation of this substrate often occurs at unusual intracellular locations where it cannot be cleaved by secreted renin. Moreover, also the levels detected in the brain of renin and its inactive precursor, prorenin, seem not in favor of a local Ang II synthesis [69].

Natriuretic Peptides

Natriuretic peptides (NPs), although genetically distinct, are a family of structurally and functionally related peptides, which include atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), and C-type natriuretic peptide (CNP). NPs are secreted in response to enhanced cardiac wall stress to counteract the effects of renin-angiotensin system and sympathetic nervous system activation [70]. The production and secretion of ANP and BNP, which behave as cardiac peptide hormones, occurs in the atria and the ventricles of the heart, whereas CNP acts as a vascular relaxing peptide and is primarily produced and secreted from the vessels endothelium and the male genital glands [71]. NPs regulate different metabolic and physiological functions, such as diuresis, natriuresis, and vasodilation, by signaling through three membrane receptors, namely, NPR-A, NPR-B and NPR-C. NPR-A and NPR-B are guanylyl cyclase-associated receptors, while NPR-C is coupled to G_i and leads to inhibition of adenylyl cyclase or activation of phospholipase C. Noteworthy, NPR-C is mainly a clearance receptor primarily implicated in the clearance or degradation of these hormones [72]. NPs can be also degraded by the protease neprilysin (which has a higher affinity for ANP and CNP than for BNP). The importance of this enzyme in NPs degradation is underscored by the fact that the simultaneous blockage of neprilysin and angiotensin II receptors represents a new therapeutic approach in the management of heart failure [73].

ANP and BNP are endowed with hemodynamic and anti-remodeling actions and are critically involved in the regulation of intravascular blood volume and vascular tone [74, 75]. Indeed, given their actions of vasodilation, diuresis, natriuresis, inhibition of renin secretion and aldosterone synthesis, they play a key role as cardioprotective hormones under pathologic conditions such as hypertension, heart failure, coronary artery disease, left ventricular hypertrophy, and cerebrovascular accidents or stroke [74, 76]. Accordingly, a deficiency in these circulating peptides may contribute to enhancing the susceptibility to the risk of cardiovascular diseases. Furthermore, during heart failure, there is an increase in the plasma levels of ANP and BNP as a compensatory mechanism, and their use in diagnosis and prognosis is well established, especially in patients with heart failure with reduced ejection fraction. Studies have also demonstrated that, in patients with chronic heart failure, acute administration of these

peptides can improve left ventricular function, suggesting their potential usefulness as short-term therapeutic agents [77, 78].

Neurotrophins

Neurotrophins (NTs) are soluble factors released by postsynaptic target tissues that regulate retrogradely neurite outgrowth, survival, and synaptogenesis of innervating neurons. The classical NTs family include four structurally related protein members: NGF, brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT-3), and neurotrophin 4/5 (NT-4/5) that are involved in several functions within the nervous system, such as survival, synaptic plasticity, axonal growth, and differentiation. All NTs are expressed by the mammalian heart and strong evidence has emerged that they exert essential cardiovascular functions. Notably, the heart is innervated by sympathetic, parasympathetic, and sensory neurons that rely upon NTs for their early development and in the establishment of mature properties, taking part to the maintenance of cardiovascular homeostasis [79].

The gene product is a larger size precursor, the proneurotrophin, which is subsequently cleaved by proteases to originate the mature form. NTs signal via two distinct classes of cell surface receptors: the p75 neurotrophin receptor (p75NTR) and the Trk subfamily of tyrosine kinase receptors. p75NTR is a transmembrane glycoprotein belonging to the tumor necrosis receptor superfamily that exhibits effects ranging from trophism to programmed cell death. It displays a low affinity for each mature neurotrophin; instead, all the proneurotrophins bind p75NTR with high affinity leading, in many cells, to the promotion of apoptosis. The mature NTs interact with high affinity with three distinct Trk receptors: TrkA, preferentially activated by NGF, TrkB, principally stimulated by BDNF and NT-4/5, and TrkC bound by NT-3 [80–82]. These tyrosine kinase receptors undergo dimerization following agonist binding, resulting in the activation, via transphosphorylation, of the kinase domain and in the triggering of down-stream cascades that propagate the signal [79, 82]. The internalization of plasma membrane receptors is now widely recognized as part of the signaling process. Indeed, the so-called "signaling endosomes" have been suggested as a way to bridge long distances and to transfer neurotrophin signal from the axons to cell bodies to control transcriptional events [81, 83].

The most studied and best-known NTs, also at cardiac level, are certainly BDNF and NGF.

BDNF is synthesized by both developing and mature sympathetic neurons, and preganglionic neurons express TrkB [84]. It has been reported to be able to modulate heart rate and blood pressure via the autonomic nervous system [85]. Specifically, in rats, the injection of BDNF, but not NGF, into the rostral ventrolateral medulla causes a blood pressure drop [86]. Furthermore, it has been described that when autonomic nervous system neurons are cultured with cardiac myocytes, they form synapses on the myocytes and the exposure to BDNF enhances acetylcholine release from the autonomic nervous system neurons and diminishes cardiac myocyte beat frequency [87]. In addition, BDNF has been documented to exert a protective role in the heart by inducing angiogenesis, upregulating prosurvival factors, and promoting the neovascularization of ischemic tissue by recruiting endothelial cells and modulating their survival. Consistently, disturbances in its synthesis are associated with cardiovascular system diseases such as arrhythmias, myocardial infarction, high blood pressure, and atherogenesis [26]. BDNF also possesses antioxidant activity by promoting the activation of detoxifying enzymes. With this regard, in the border zone of the ischemic area, it may protect sensory and sympathetic neurites against reactive oxygen species (ROS) harmful action [26]. Indeed, ROS are released during reperfusion after myocardial infarction and are detrimental to cardiac cells; moreover, they could also damage sensory and sympathetic neurites. Therefore, BDNF upregulation may represent a compensatory cardiac response to face neuronal injury by suppressing ROS effects in nerve terminals [88].

NGF is produced by parasympathetic neurons also and its expression can be modulated by sympathetic innervation [89]. Within the heart, it is released by cardiac myocytes, which express its

specific receptor on their cellular membrane, and has a pleiotropic effect favoring neoangiogenesis and giving protection to the ill myocardium [90]. Notably, NGF seems to induce angiogenesis by increasing the expression of vascular endothelial growth factor A (VEGF-A) and by activating Akt intracellular cascades leading to nitric oxide production [79]. Both NGF expression and release can change in pathologic conditions. For instance, NGF levels increase in several inflammatory and autoimmune states together with the accumulation of immune system cells. Indeed, NGF can be released by both of the two types of cells contributing to the inflammatory process, namely structural cells (i.e., fibroblasts, smooth muscle cells, and epithelial cells) and hematopoietic-immune system cells (i.e., lymphocytes, mast cells, and macrophages) that infiltrate into the site of inflammation [81].

A number of studies indicate the ability of NGF to induce nerve sprouting within the heart, leading to increased sympathetic outflow and a more elevated risk of ventricular arrhythmias and sudden cardiac death [91]. Pathological cardiac hyperinnervation and enlargement have also been described in transgenic mice selectively overexpressing NGF in the heart [92]. Noteworthy, this neurotrophin dramatically rises after myocardial infarction, whereas its levels decline along with advanced heart failure and ventricular dysfunction. This bimodal NGF profile in acute versus chronic settings brings about the hypothesis that NGF modulation may represent a novel pharmacological target for intervention in various stages of ischemic heart disease [91].

Conclusions

The importance of the crosstalk between heart and brain has increasingly emerged, as the underlying mutual mechanisms become better understood. This strict dialogue is crucial to guarantee an optimal cardiovascular homeostasis and to assure that the cardiac output meets blood flow requirements. The heart-brain interaction is finely modulated by neuro-humoral activity, including atrial natriuretic peptides, renin-angiotensin aldosterone system, and neurotrophins, which can also represent an important pharmacological target. Therefore, the comprehension of this complex network is relevant not only to go deeper into cardiovascular physiology but also will facilitate the prompt recognition and management of cardiac diseases, as well as of neurologic disorders associated to heart dysfunction, thus allowing a more suitable intervention in pathologic states (see ▶ Chap. 61, "Neural Effects on Cardiac Electrophysiology"). Further, neuromodulation-based approaches, which target selected nexus points for cardiac control, offer unique opportunities to positively implement the therapeutic outcomes and to expand biomarkers useful for diagnosis as well as targets upon which direct new drugs, allowing a more fine-tuning of these complex regulatory systems.

Cross-References

- ▶ Cognitive Decline in Elderly Patients with Hypertensive Heart Disease
- ▶ Neural Effects on Cardiac Electrophysiology

References

1. Tahsili-Fahadan P, Geocadin RG. Heart-Brain axis: effects of neurologic injury on cardiovascular function. Circ Res. 2017;120(3):559–72.
2. Fontes MA, Filho ML, Santos Machado NL et al. Asymmetric sympathetic output: the dorsomedial hypothalamus as a potential link between emotional stress and cardiac arrhythmias. Auton Neurosci. 2017;207:22. pii:S1566-0702(16)30228-4.
3. Mittleman MA, Maclure M, Sherwood JB, et al. Triggering of acute myocardial infarction onset by episodes of anger. Determinants of Myocardial Infarction Onset Study Investigators. Circulation. 1995;92(7):1720–17254.
4. Lampert R, Shusterman V, Burg M, et al. Anger-induced T-wave alternans predicts future ventricular arrhythmias in patients with implantable cardioverter-defibrillators. J Am Coll Cardiol. 2009;53(9):774–8.
5. Leor J, Poole WK, Kloner RA. Sudden cardiac death triggered by an earthquake. N Engl J Med. 1996;334:413–9.
6. Wilbert-Lampen U, Leistner D, Greven S, et al. Cardiovascular events during World Cup soccer. N Engl J Med. 2008;358(5):475–83.

7. Lampert R, Rosenfeld L, Batsford W, et al. Circadian variation of sustained ventricular tachycardia in patients with coronary artery disease and implantable cardioverter-defibrillators. Circulation. 1994;90:241–7.
8. Tofler GH, Gebara OC, Mittleman MA, et al. Morning peak in ventricular tachyarrhythmias detected by the time of implantable cardiverter-defibrillator therapy. Circulation. 1995;92:1203–8.
9. Peters RW, McQuillan S, Resnick SK, et al. Increased Monday incidence of lifethreatening ventricular arrhythmias. Circulation. 1996;94:1346–9.
10. Warnert EA, Hart EC, Hall JE, et al. The major cerebral arteries proximal to the Circle of Willis contribute to cerebrovascular resistance in humans. J Cereb Blood Flow Metab. 2016;36(8):1384–95.
11. van der Wall EE. New insights in prevention, diagnosis and treatment of stroke: its relation with atrial fibrillation. Neth Hear J. 2012;20(4):141–2.
12. Verheugt FW. Antithrombotic therapy in heart failure. Neth Hear J. 2012;20(4):176–8.
13. van der Wall EE, van Gilst WH. Neurocardiology: close interaction between heart and brain. Neth Hear J. 2013;21(2):51–2.
14. Chatterjee S. ECG changes in subarachnoid haemorrhage: a synopsis. Neth Hear J. 2011;19(1):31–4.
15. Talman WT. Cardiovascular regulation and lesions on the central nervous system. Ann Neurol. 1985;18(1):1–13.
16. Adams HP Jr, del Zoppo G, Alberts MJ, et al. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. Circulation. 2007;115(20):e478–534.
17. Palma JA, Benarroch EE. Neural control of the heart. Recent concepts and clinical correlations. Neurology. 2014;8(3):261–71.
18. Ardell JL, Armour JA. Neurocardiology: structure-based function. Compr Physiol. 2016;6(4):1635–53.
19. Oppenheimer SM, Saleh TM, Wilson JX, et al. Plasma and organ catecholamine levels following stimulation of the rat insular cortex. Brain Res. 1992;569(2):221–8.
20. Oppenheimer S, Cechetto D. The insular cortex and the regulation of cardiac function. Compr Physiol. 2016;6(2):1081–133.
21. Kawashima T. The autonomic nervous system of the human heart with special reference to its origin, course, and peripheral distribution. Anat Embryol. 2005;209:425–38.
22. Hoover DB, Ganote CE, Ferguson SM, et al. Localization of cholinergic innervation in guinea pig heart by immunohistochemistry for high-affinity choline transporters. Cardiovasc Res. 2004;62(1):112–21.
23. Gatti PJ, Johnson TA, Phan P, et al. The physiological and anatomical demonstration of functionally selective parasympathetic ganglia located in discrete fat pads on the feline myocardium. J Auton Nerv Syst. 1995;51(3):255–9.
24. Armour JA. The little brain on the heart. Cleve Clin J Med. 2007;74(Suppl 1):S48–51.
25. Wake E, Brack K. Characterization of the intrinsic cardiac nervous system. Auton Neurosci. 2016;199:3–16.
26. Pius-Sadowska E, Machaliński B. BDNF – a key player in cardiovascular system. J Mol Cell Cardiol. 2017;110:54–60.
27. Fukuda K, Kanazawa H, Aizawa Y, et al. Cardiac innervation and sudden cardiac death. Circ Res. 2015;116(12):2005–19.
28. Choi EK, Chen PS. Is the atrial neural plexis a therapeutic target in atrial fibrillation? Methodist Debakey Cardiovasc J. 2015;11(2):82–6.
29. Singh S, Sayers S, Walter JS, et al. Hypertrophy of neurons within cardiac ganglia in human, canine, and rat heart failure: the potential role of nerve growth factor. J Am Heart Assoc. 2013;2(4):e000210.
30. Hasan W. Autonomic cardiac innervation: development and adult plasticity. Organogenesis. 2013;9(3):176–93.
31. Bers DM. Cardiac excitation-contraction coupling. Nature. 2002;415(6868):198–205.
32. Marx SO, Kurokawa J, Reiken S, et al. Requirement of a macromolecular signaling complex for beta adrenergic receptor modulation of the KCNQ1-KCNE1 potassium channel. Science. 2002;295(5554):496–9.
33. Accili EA, Proenza C, Baruscotti M, et al. From funny current to HCN channels: 20 years of excitation. News Physiol Sci. 2002;17:32–7.
34. Tsien RW. Cyclic AMP and contractile activity in heart. Adv Cyclic Nucleotide Res. 1977;8:363–420.
35. Harvey RD, Belevych AE. Muscarinic regulation of cardiac ion channels. Br J Pharmacol. 2003;139(6):1074–84.
36. Fernández-Falgueras A, Sarquella-Brugada G, Brugada J, et al. Cardiac channelopathies and sudden death: recent clinical and genetic advances. Biology (Basel). 2017;6(1). pii: E7
37. Schwartz PJ, Ackerman MJ, Wilde AAM. Channelopathies as causes of sudden cardiac death. Card Electrophysiol Clin. 2017;9(4):537–49.
38. Levy MN. Sympathetic – parasympathetic interactions in the heart. Circ Res. 1971;29(5):437–45.
39. Cheng X, Ji Z, Tsalkova T, Mei F. Epac and PKA: a tale of two intracellular cAMP receptors. Acta Biochim Biophys Sin Shanghai. 2008;40(7):651–62.
40. Fujita T, Umemura M, Yokoyama U, et al. The role of Epac in the heart. Cell Mol Life Sci. 2017;74(4):591–606.

41. Schmidt M, Dekker FJ, Maarsingh H. Exchange protein directly activated by cAMP (epac): a multidomain cAMP mediator in the regulation of diverse biological functions. Pharmacol Rev. 2013;65(2):670–709.
42. Schlicker E, Feuerstein T. Human presynaptic receptors. Pharmacol Ther. 2017;172:1–21.
43. Shaffer F, McCraty R, Zerr CL. A healthy heart is not a metronome: an integrative review of the heart's anatomy and heart rate variability. Front Psychol. 2014;5:1040.
44. McCraty R, Shaffer F. Heart rate variability: new perspectives on physiological mechanisms, assessment of self-regulatory capacity, and health risk. Glob Adv Health Med. 2015;4(1):46–61.
45. Wolf MM, Varigos GA, Hunt D, Sloman JG. Sinus arrhythmia in acute myocardial infarction. Med J Aust. 1978;2(2):52–3.
46. Huikuri HV, Jokinen V, Syvänne M, et al. Heart rate variability and progression of coronary atherosclerosis. Arterioscler Thromb Vasc Biol. 1999;9(8):1979–85.
47. Brown L, Karmakar C, Gray R, et al. Heart rate variability alterations in late life depression: a meta-analysis. J Affect Disord. 2018;235:456–66.
48. Umetani K, Singer DH, McCraty R, Atkinson M. Twenty-four hour time domain heart rate variability and heart rate: relations to age and gender over nine decades. J Am Coll Cardiol. 1998;31(3):593–601.
49. Kimmerly DS. A review of human neuroimaging investigations involved with central autonomic regulation of baroreflex-mediated cardiovascular control. Auton Neurosci. 2017;207:10. pii: S1566-0702(17)30117-0.
50. Monahan KD. Effect of aging on baroreflex function in humans. Am J Phys Regul Integr Comp Phys. 2007;293(1):R3–12.
51. Sykora M, Diedler J, Rupp A, et al. Impaired baroreceptor reflex sensitivity in acute stroke is associated with insular involvement, but not with carotid atherosclerosis. Stroke. 2009;40:737–74.
52. Pascale A, Govoni S. Cerebral aging: implications for the heart autonomic nervous system regulation. In: Gronda E, Vanoli E, Costea A, editors. Heart failure management: the neural pathways. Cham: Springer International Publishing; 2016. p. 115–27.
53. De Lucia C, Femminella GD, Gambino G, et al. Adrenal adrenoceptors in heart failure. Front Physiol. 2014;5:246.
54. Haase M, Willenberg HS, Bornstein SR. Update on the corticomedullary interaction in the adrenal gland. Endocr Dev. 2011;20:28–37.
55. Hodel A. Effects of glucocorticoids on adrenal chromaffin cells. J Neuroendocrinol. 2001;13(2):216–20.
56. Flügge G, van Kampen M, Meyer H, et al. Alpha2A and alpha2C-adrenoceptor regulation in the brain: alpha2A changes persist after chronic stress. Eur J Neurosci. 2003;17(5):917–28.
57. Port JD, Bristow MR. Altered beta-adrenergic receptor gene regulation and signaling in chronic heart failure. J Mol Cell Cardiol. 2001;33(5):887–905.
58. Tigerstedt R, Bergman PG. Niere und kreislauf. Skand Arch Physiol. 1898;8:223–71.
59. Yang T, Xu C. Physiology and pathophysiology of the intrarenal renin-angiotensin system: an update. J Am Soc Nephrol. 2017;28(4):1040–9.
60. De Mello WC. Local renin angiotensin aldosterone systems and cardiovascular diseases. Med Clin North Am. 2017;101(1):117–27.
61. Kawada T, Yamazaki T, Akiyama T, et al. Angiotensin II attenuates myocardial interstitial acetylcholine release in response to vagal stimulation. Am J Physiol Heart Circ Physiol. 2007;293(4):H2516–22.
62. Serneri GG, Boddi M, Cecioni I, et al. Cardiac angiotensin II formation in the clinical course of heart failure and its relationship with left ventricular function. Circ Res. 2001;88(9):961–8.
63. Danser AH, van Kesteren CA, Bax WA, et al. Prorenin, renin, angiotensinogen, and angiotensin-converting enzyme in normal and failing human hearts. Evidence for renin binding. Circulation. 1997;96(1):220–6.
64. De Mello WC. Intracellular renin alters the electrical properties of the intact heart ventricle of adult Sprague Dawley rats. Regul Pept. 2013;181:45–9.
65. Leenen F, Blaustein MP, Hamlyn J. Update on angiotensin II: new endocrine connections between the brain, adrenal glands and the cardiovascular system. Endocr Connect. 2017;6(7):R131–45.
66. Santos RA, Simoes e Silva AC, Maric C, et al. Angiotensin-(1-7) is an endogenous ligand for the G protein-coupled receptor Mas. Proc Natl Acad Sci U S A. 2003;100(14):8258–63.
67. Zini S, Fournie-Zaluski MC, Chauvel E, et al. Identification of metabolic pathways of brain angiotensin II and III using specific aminopeptidase inhibitors: predominant role of angiotensin III in the control of vasopressin release. Proc Natl Acad Sci U S A. 1996;93(21):11968–73.
68. Huang BS, Zheng H, Tan J, et al. Regulation of hypothalamic renin-angiotensin system and oxidative stress by aldosterone. Exp Physiol. 2011;96(10):1028–38.
69. Uijl E, Ren L, Danser AHJ. Angiotensin generation in the brain: a re-evaluation. Clin Sci (Lond). 2018;132(8):839–50.
70. von Lueder TG, Atar D, Krum H. Current role of neprilysin inhibitors in hypertension and heart failure. Pharmacol Ther. 2014;144(1):41–9.
71. Suga SI, Itoh H, Komatsu Y, et al. Regulation of endothelial production of C-type natriuretic peptide by interaction between endothelial cells and macrophages. Endocrinology. 1998;139(4):1920–6.
72. Santhekadur PK, Kumar DP, Seneshaw M, et al. The multifaceted role of natriuretic peptides in metabolic syndrome. Biomed Pharmacother. 2017;92:826–35.
73. Havakuk O, Elkayam U. Angiotensin receptor-neprilysin inhibition. J Cardiovasc Pharmacol Ther. 2017;22(4):356–64.

74. Nishikimi T, Maeda N, Matsuoka H. The role of natriuretic peptides in cardio protection. Cardiovasc Res. 2006;69:318–28.
75. Volpe M. Natriuretic peptides and cardio-renal disease. Int J Cardiol. 2014;176:630–9.
76. Yoshimura M, Yasue H, Ogawa H. Pathophysiological significance and clinical application of ANP and BNP in patients with heart failure. Can J Physiol Pharmacol. 2001;79:730–5.
77. Pandit K, Mukhopadhyay P, Ghosh S, et al. Natriuretic peptides: diagnostic and therapeutic use. Indian J Endocrinol Metab. 2011;15:S345–53.
78. Rubattu S, Triposkiadis F. Resetting the neurohormonal balance in heart failure (HF): the relevance of the natriuretic peptide (NP) system to the clinical management of patients with HF. Heart Fail Rev. 2017;22(3):279–88.
79. Caporali A, Emanueli C. Cardiovascular actions of neurotrophins. Physiol Rev. 2009;89:279–308.
80. Bothwell M. NGF, BDNF, NT3, and NT4. Handb Exp Pharmacol. 2014;220:3–15.
81. Govoni S, Pascale A, Amadio M, et al. NGF and heart: is there a role in heart disease? Pharmacol Res. 2011;63(4):266–77.
82. Skaper SD. The biology of neurotrophins, signalling pathways, and functional peptide mimetics of neurotrophins and their receptors. CNS Neurol Disord Drug Targets. 2008;7:46–62.
83. Scott-Solomon E, Kuruvilla R. Mechanisms of neurotrophin trafficking via Trk receptors. Mol Cell Neurosci. 2018;91:25. pii: S1044-7431(18) 30014–30019.
84. Causing CG, Gloster A, Aloyz R, et al. Synaptic innervation density is regulated by neuron-derived BDNF. Neuron. 1997;18(2):257–67.
85. Wan R, Weigand LA, Bateman R, et al. Evidence that BDNF regulates heart rate by a mechanism involving increased brainstem parasympathetic neuron excitability. J Neurochem. 2014;129(4):573–80.
86. Wang H, Zhou XF. Injection of brain-derived neurotrophic factor in the rostral ventrolateral medulla increases arterial blood pressure in anaesthetized rats. Neuroscience. 2002;112(4):967–75.
87. Yang B, Slonimsky JD, Birren SJ. A rapid switch in sympathetic neurotransmitter release properties mediated by the p75 receptor. Nat Neurosci. 2002;5(6):539–45.
88. Hildreth V, Anderson RH, Henderson DJ. Autonomic innervation of the developing heart: origins and function. Clin Anat. 2009;22(1):36–46.
89. Hasan W, Smith PG. Nerve growth factor expression in parasympathetic neurons: regulation by sympathetic innervation. Eur J Neurosci. 2000;12:4391–7.
90. Meloni M, Caporali A, Graiani G, et al. Nerve growth factor promotes cardiac repair following myocardial infarction. Circ Res. 2010;106(7):1275–84.
91. D'Elia E, Pascale A, Marchesi N, et al. Novel approaches to the post-myocardial infarction/heart failure neural remodeling. Heart Fail Rev. 2014;19(5):611–9.
92. Hassankhani A, Steinhelper ME, Soonpaa MH, et al. Overexpression of NGF within the heart of transgenic mice causes hyperinnervation, cardiac enlargement, and hyperplasia of ectopic cells. Dev Biol. 1995;169(1):309–21.

The Cardiorenal Cross Talk

3

The Autonomic Pathway Regulating the Cardiocirculatory Balance

Edoardo Gronda and Emilio Vanoli

Contents

Abstract

The autonomic nervous system (ANS) controls essential physiologic functions, including heart rate, blood pressure, and body fluid volume regulation [1]. It is now well understood that the ANS is specifically designed to maintain body homeostasis eliciting organ-specific responses in the face of external challenges [2]. This complex task is accomplished by continuous and instantaneous interactions of its two limbs: the sympathetic and parasympathetic ones. As a matter of fact, the so-called sympatho-vagal interaction is the key mechanism able to warrant all needed adjustments to any aspect of the physiological activity of the entire body. Any alteration or maladaptive response of the ANS to physiological or pathological events (from simple position changes to compensatory responses to acute myocardial ischemia, for instance) results in disease development or progression. Specific to the cardiorenal axis is the fact that congestion due to intravascular overload is the most potent driver of sympathetic nervous system activation that increases arterial vascular resistance and organ hypoperfusion. In this context, kidneys are

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*,
https://doi.org/10.1007/978-3-030-28008-6_3

severely blood supply deprived and react to the higher intra-parenchimal vascular resistance by increasing the sympathetic response and the neuro-hormonal activation, with major consequence in fluid retention. The overall effect worsens heart function and target organs damage contributing to maintain and to aggravate heart failure progression.

Keywords

Cardio-renal axis · Heart failure · Autonomic nervous system

Introduction

The autonomic nervous system (ANS) controls essential physiologic functions, including heart rate, blood pressure, and body fluid volume regulation [1]. It is now well understood that the ANS is specifically designed to maintain body homeostasis eliciting organ-specific responses in the face of external challenges [2]. This complex task is accomplished by continuous and instantaneous interactions of its two limbs: the sympathetic and parasympathetic ones. As a matter of fact, the so-called sympatho-vagal interaction is the key mechanism able to warrant all needed adjustments to any aspect of the physiological activity of the entire body. Any alteration or maladaptive response of the ANS to physiological or pathological events (from simple position changes to compensatory responses to acute myocardial ischemia, for instance) results in disease development or progression. Meaningful examples of this concept are the apparently paradoxical vagal activation during symptomatic hypotension leading to the so-called "vasovagal" syncope or the occurrence of ventricular fibrillation during acute myocardial ischemia facilitated by an excessive sympathetic response to the physiological quest for support originating from the suffering heart.

Within the sensor ANS apparatus, the baroreceptorial one plays a predominant role in maintaining cerebral perfusion. This latter has, indeed, to be maintained at any cost even in condition of low cardiac output. The most critical consequence of this functional setting is that, when cardiac output is low, the ANS responses support cerebral perfusion by cutting blood supply to all the other organs but the heart. Among these many others, the kidney is the one bound to pay the higher price as its hypoperfusion causes a progressive and, at a certain point, irreversible damage that, at the end, will accelerate the cardiac disease progression toward end-stage heart failure.

Among the ANS differential organ effects, a critical one is the integrated response to increase sodium concentration and water retention aimed at regulating circulatory volume.

The physiological interaction between the heart and kidney is based on this pivotal mechanism, and its dysregulation is prominently involved in causing the cardiorenal syndrome (CRS), arterial hypertension, and heart failure (HF) (Fig. 1).

Experimental evidence describes the increase in brain sodium concentration in conscious sheep leading to simultaneous increase in cardiac sympathetic nerve activity (SNA) and arterial pressure. In a normally functioning system, an increase in afferent renal nerve activity results in a reflex reduction in efferent renal SNA, thus promoting renin secretion decrease, renal vasodilatation, and renal sodium excretion [1]. The experimental observation logical inference is that the inhibition of renal SNA is the homeostatic response to a sodium load, aimed at restoring normal sodium concentration and circulatory volume.

These effects are organ-specific and are mediated via a neural pathway that includes an angiotensinergic synapse and specialized neural centers in the medulla oblongata and in the paraventricular nucleus of the hypothalamus [3, 4].

In contrast with the physiological scenario, in the experimental animal models of HF induced by rapid pacing, the cardiac and renal SNA activities increased to similar, almost maximal, levels, and the reflex response of cardiac SNA to changes in blood volume was significantly attenuated [1, 5], thus reflecting a loss of reflex neural inhibitory circuits.

These data are coherent with the fact that in HF, a decreased arterial pressure results in a lesser or null baroreflex inhibition of SNA, which, together with the loss of an inhibitory response to the

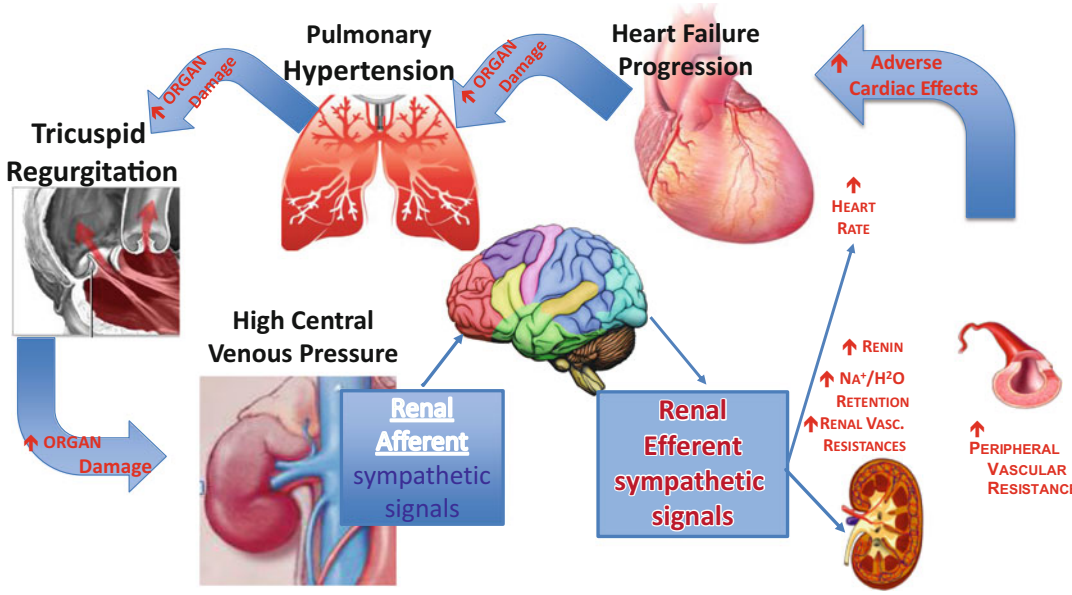

Fig. 1 The cardiorenal engagement in heart failure progression. Heart failure leads to increased cardiac filling pressures that, in turn, drive backward pressure increase in lung circulation and in central venous system, leading to vascular congestion. The ensue of tricuspid regurgitation led by high pulmonary pressure is the marker of right ventricular failure and addresses the loss of all cardiac compensatory mechanism. Congestion due to intravascular overload is the most potent driver of sympathetic nervous system activation that increases arterial vascular resistance and organ hypoperfusion. Kidneys react to the higher intra-parenchimal vascular resistance by increasing the sympathetic response and the neuro-hormonal activation, with major consequence in fluid retention. The overall effect worsens heart function and target organs damage contributing to maintain and to aggravate heart failure progression

increased volume and cardiac pressures, contributes to the heightened, because unconstrained, sympathetic activity typical of HF [1].

Excessive and unrestrained cardiac sympathetic drive is undoubtedly a major contributing factor to the pathogenesis of hypertension and to the progression of HF. Importantly, much of the excessive SNA in these conditions targets the kidney, where it leads to inappropriate sodium retention, renin stimulation, and diminished renal function. In addition, the kidney itself is abundantly innervated by the sympathetic fibers and acts both as an afferent signaling source and as a target of sympathetic efferent activation. The key element in causing opposite effects on renal sympathetic efferent activity is the source of the afferent sympathetic signal. In physiological conditions, afferent traffic originating from receptors located in the renal pelvis inhibits efferent sympathetic traffic. On the opposite, afferent information originating from the renal parenchyma (often due to hypoperfusion) stimulates efferent sympathetic activity, as measurable by the increased renal norepinephrine spillover (NE) together with an increase in plasma renin activity. Overall, in hypertension as well as in HF, the kidney is both target and contributor to increased SNA [6].

Measurements of Autonomic Nervous System Activity

One important challenge to the understanding of the in/out autonomic interactions between the heart and the kidney is the ability to detect and size the individual regional SNA activity.

For this purpose sympathetic nerve recording techniques and radiotracer-derived measurements of NE spillover into the plasma from individual organs have been used. Limitations are recognized in each technique, and it's recommended they be used together [7].

Microneurography provides instantaneous multiunit recordings of electrical activity in sympathetic nerves, but assessment may be skewed by interpreter's bias [8, 9], and repeated detection is advised to provide data reproducibility.

The NE spillover method provides objective measure of the release of this neurotransmitter from internal organs where microneurography is not feasible [10–12]. During constant rate infusion of titrated NE, output of endogenous NE from a given organ (NE "spillover") can be measured by isotope dilution according to the formula:

$$\text{Regional norepinephrine spillover} = [(C_V - C_A) + C_A E]\,PF$$

where C_V and C_A address the plasma concentrations of NE in the organ's venous and arterial plasma, E is the fractional extraction of titrated NE while the blood is flowing through the organ, and PF is the organ plasma flow [7]. The spillover represents the amount of released NE that exceeds the reuptake capability by the neural endings.

Given the complexity of the above-presented measures of ANS system activity, attention has been directed to noninvasive indirect markers of the autonomic balance between its two limbs. In this prospective the analysis of heart rate variability (HRV), specifically in the frequency domain, allows a gross but effective estimate of the cardiac autonomic balance.

Vagal and sympathetic cardiac control generate different heart rate oscillations that can be quantified by the analyses of specific oscillatory frequency bands. While the cardiac vagal nerve tone has relatively high-frequency oscillations, mostly reflecting the respiratory frequency (0.25 Hz), sympathetic cardiac control reflects its heart rate influences in frequencies below 0.15 Hz (low-frequency HRV) [13–15]. Once dealing with the ratio between the two most significant oscillatory components of heart rate (LF/HF), specifically evident when short recording segments are taken into account, one has to keep in mind that the LF HRV comprises oscillations determined by the baroreflex control of heart rate. This is why the loss of oscillation power in the LF band carries the highest predictive value in HF patients [16], and the interpretation of the LF/HF ratio has to be understood properly in the contest of the decompensated heart.

Blood pressure changes estimate also allows quantification of cardiovascular autonomic control. Blood pressure oscillations are the result of complex interactions between cardiac and vascular neural regulation, mechanical influences of breathing, humoral and endothelial factors, large vessels compliance, and genetic imprinting.

Overall, frequency domain analyses of either HRV or blood pressure can provide valuable information on balance of ANS. These measurements may lack specificity, but they can be obtained in clinical practice and are not subject to interpreter's bias [17].

The ability of HRV and blood pressure fluctuations to mirror ANS control cardiovascular system is improved by using coherence models. The simplest ones address the relationship between spontaneous fluctuations in blood pressure and heart rate to assess baroreceptor sensitivity (BRS) and its modulation in daily life, either in the time or frequency domain [18–21].

Despite spontaneous variations in blood pressure and HRV clearly depend on autonomic mechanisms, they cannot be considered an immediate quantitative measurement of efferent SNA to the cardiovascular system. In variety of clinical situations including HF, indeed, low-frequency heart rate spectral power is minimally or totally unrelated to rates of NE spillover from the heart or sympathetic nerve firing detected by microneurography. At first glance such a discrepancy might lead to believe that HRV analyses are unspecific while they indeed properly describe the final consequence of unrestrained cardiac sympathetic drive: the cardiovascular system is totally dysregulated and operates on a metronome mode without short- or long-term oscillations. The simplest but most effective measure of impending HF is indeed the loss of circadian variations of a heart that is restless [22]. A critical aspect of HRV is that it is weakly correlated to left ventricular ejection fraction (LVEF), once more proving that autonomic responses are *not* the mere consequence of a loss of systolic function but they reflect mostly the balance between afferent information originating from the entire visceral organs

whose function is variably affected by the drop in cardiac output.

Cardiac innervation and function can be non-invasively assessed by using an isotope analogue of NE the ^{123}I-metaiodobenzylguanidine (MIBG): the myocardial isotope uptake can be measured by using semiquantitative analyses, namely, early heart-to-mediastinum ratio, late heart-to-mediastinum ratio, and myocardial washout [23].

Data from prospective studies and meta-analyses have shown that patients with decreased late heart-to-mediastinum ratio or increased myocardial ^{123}I-MIBG washout have a worse prognosis than those patients with normal semiquantitative myocardial ^{123}I-MIBG uptake [24].

Furthermore, regardless of LVEF, an increased incidence of sudden cardiac death has been found to occur in patients with ^{123}I-MIBG decreased uptake [25].

Moreover, in the ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) study, the ^{123}I-MIBG cardiac imaging provided additional independent prognostic information for risk-stratifying HF patients on top of the commonly used markers such as LVEF and B-type natriuretic peptide [26] highlighting the ANS-independent prognostication significance in the HF setting.

Sympathetic Innervation of the Kidney

The kidney is robustly innervated with both efferent adrenergic and somatic afferent neurons [27, 28] (Fig. 1). The efferent neurons terminate at multiple sites within the nephron and independently modulate tubular sodium reabsorption, renin secretion, and renal blood flow (RBF). Experimentally, sodium reabsorption is increased at very low sympathetic stimulation frequencies, while higher stimulating frequencies decrease RBF and raise renin secretion [29–31].

Thus, even mild sympathetic activation leads to sodium reabsorption and to plasma volume expansion. With enhancement of sympathetic activation, the angiotensin II (A II) expression increases, and this produces an increase in the renal sodium reabsorption. The combined vascular effects of NE, A II, and aldosterone drive vasoconstriction in the arterial compartment, and this is how efferent renal SNA produces simultaneously an increase in arterial pressure and blood volume and a decrease in RBF.

When a cardiovascular abnormality occurs, at the beginning, it triggers these compensatory mechanisms to counteract hypotension, due to a drop in volume flow. The natural response to these hemodynamic circumstances is fluid retention to restore pressure and volume flow. However, the abnormal reactive intensity of these responses builds up, over time, the conditions for unfavorable cardiac remodeling. Those mechanisms run, indeed, the maladaptive process linked to HF progression that, in turn, enhances the SNS activation and the neurohormonal cascade, increasing vascular congestion and worsening renal function. The excess of intravascular load, coupled with the renal filtration decline, further negatively affects heart and kidney function providing the pathway to CRS persistence and aggravation [32].

In addition, afferent fibers originating in the kidney reach the midbrain where they activate neural cardiovascular control centers [28]. The response of these afferent nervous fibers is activated by several factors including ischemia and adenosine release, both generated by intense vasoconstriction. The muscle SNA decline after removal of the native kidney in patients with end-stage renal disease (ESRD) and in renal transplant recipients [33–36] is confirmatory of this established relationship.

Another way the kidney can provide activation of SNA is the renin release by the macula densa that activates the angiotensin-aldosterone system leading to A II formation that can directly stimulate the central sympathetic drive [37].

The abnormal persistent activation of the afferent-efferent "sympathorenal axis" provides path to a generalized, sustained, self-perpetuating SNA cycle. However, it should be pointed out that many other reflexes and humoral substances, including natriuretic peptides (NP), can modify sympathetic activity, so that any contribution of the renal sympathetic afferent nerves to this self-perpetuating cycle can be modified by changes in activity of these other controllers [23].

The Sympathorenal Axis in Heart Failure

The muscle SNA and the overall NE spillover in the body are increased in patients with congestive HF. The renal contribution to these activations is prominent [12, 38]. Plasma NE has been known for more than three decades to be a strong predictor of outcomes in HF patients [39]. The paralleled efficacy of beta-blockers in decreasing mortality in HF patients, at any level of disease severity, is the most convincing evidence that excessive SNA is the main contributor to HF dismal prognosis [40].

However, the inhibition at central level of presynaptic NE release with moxonidine administration in HF subjects was associated with enhanced mortality, probably due to hypotension led by an inappropriate fall in plasma NE levels [41]. Excessive central sympathetic effect inhibition by bucindolol was suggested as contributing to the negative outcome of the BEST trial [42].

There is little doubt that renal NE spillover is, together with cardiac NE spillover, a major contributor to the total excess of sympathetic drive in HF patients [12]. Indeed, it has recently been shown that renal SNA, as measured by renal NE spillover, was highly predictive of outcomes despite concomitant therapy with neurohormonal inhibitor drugs [40]. In addition, in an experimental myocardial infarction model, renal sympathetic denervation was associated with improved outcomes [43]. The enhanced efferent sympathetic signaling to the kidney seen in HF presumably has the same effects it has in hypertension (enhanced sodium retention, decreased RBF, and activation of the renin angiotensin aldosteron system (RAAS)). These effects are even more harmful in HF because volume expansion and increased arterial pressure will aggravate myocardial loading conditions and, together with the direct actions of NE, A II, and aldosterone, worsen myocardial remodeling. The SNA-related sodium avidity and renal hemodynamic abnormalities may be especially deleterious in the CRS, because persistent congestion may itself contribute to further deterioration of renal function [32]. Kidney dysfunction often occurs during intensive treatment with loop diuretics. This event is not surprisingly because loop diuretics are known to further stimulate SNA either directly or through activation of the RAAS [44]. Augmentation of afferent signaling from the kidney may then contribute to perpetuate the global sympathetic overdrive in HF, completing the sympathorenal loop [40].

Consequences of Neurohormonal Axis Activation and Fluid Retention in the Circulatory System, in the Kidney Function, and in the Splanchnic Organs

Cardiac dysfunction runs immediate and progressive adverse changes in the setting of neurohormonal activation and in renal physiology.

In normal condition the 20% of cardiac stroke volume is delivered to the renal perfusion. The prominent marker of HF syndrome is the decreased cardiac output (CO) characterized by the arterial vasculature underfilling that promotes flow shunting to heart and brain circulation. The net effect is thereby the disproportionate decrease of renal perfusion.

One critical consequence of the greater imbalance in renal perfusion that occurs in HF patients is a result of neurohormonally mediated efferent arteriolar vasoconstriction and increased central venous pressure (CVP), both involved in the kidney strive to preserve urine output by increasing filtration fraction (FF) in face of the declining glomerular filtration fraction (GFR) (Fig. 1) [45]. In normal subjects FF is approximately 20%–25%; it increases above this value in HF and can rise above 50% when intra-abdominal pressure is abnormally raised by visceral congestion.

The increased FF in congestive HF raises the oncotic pressure in the peritubular capillaries (πPC) leading to augmented sodium and water reabsorption into the vasculature. When congestion occurs, both renal interstitial fluid hydrostatic pressure (PIF) and the peritubular capillaries hydrostatic pressure (PPC) increase in a disproportionate way because the kidney is an encapsulated organ. In contrast, the interstitial fluid oncotic pressure (πIF) drops because interstitial

proteins are removed by the increased lymph flow. This mechanism also favors net sodium and water reabsorption into the vasculature [46–53]. The overall pathophysiological process explains how increased FF itself augments sodium reabsorption, magnifying the activation of SNA and RAAS (Fig. 2).

Different transporters mediate active trespassing of sodium across the luminal side of proximal tubular cells. However, in the proximal tubules, a highly permeable epithelium can provide easy return of sodium to the lumen as passive Starling forces govern the net sodium reabsorption between the peritubular capillaries and renal interstitium.

The overall nephron function is profoundly influence by the abnormally high sodium reabsorption in the proximal portion of tubule. As active chloride transport requires ATP which is metabolically converted in adenosine, the macula densa senses the increased sodium chloride by the concentration of the metabolic end product (Fig. 2).

The macula densa releases adenosine that, in that specific contest, acts as vasoconstrictive agent on the afferent arteriole. This action protects the glomerulus from hyperfiltration injury and is known as tubule-glomerular feedback (TGF).

In congestive HF the increased sodium chloride reabsorption in the proximal tubule reduces

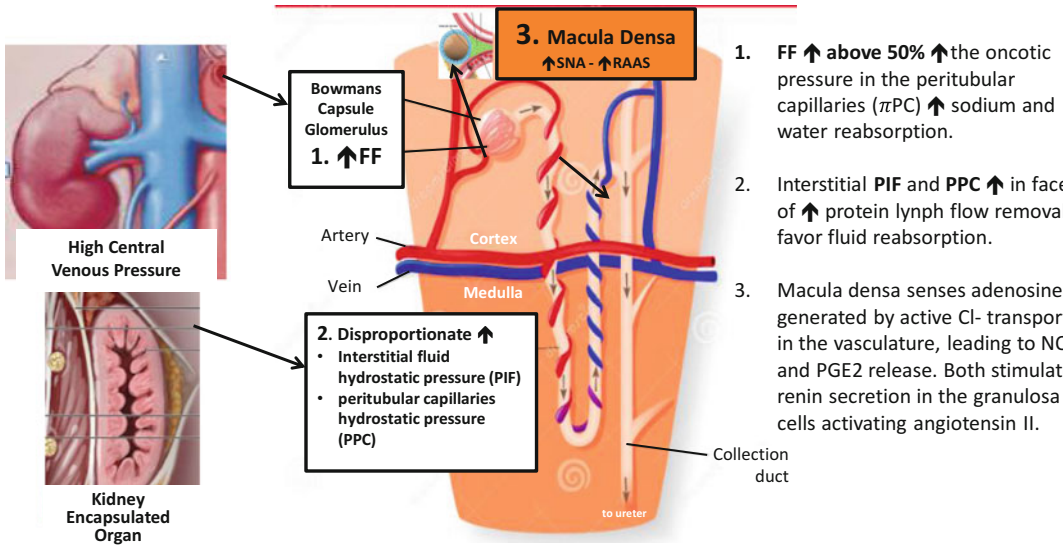

Fig. 2 The neurohormonal axis activation and fluid retention in the circulatory system, in kidney function, and in the splacnic organs. In HF, FF can rise above 50% when intra-abdominal pressure is abnormally raised by visceral congestion. The increased FF in congestive HF raises the oncotic pressure in the peritubular capillaries (πPC) leading to augmented sodium and water reabsorption into the vasculature. The interstitial fluid hydrostatic pressure (PIF) and the peritubular capillaries hydrostatic pressure (PPC) increase in a disproportionate way because the kidney is an encapsulated organ. In contrast, the interstitial fluid oncotic pressure (πIF) drops because interstitial proteins are removed by the increased lymph flow. This mechanism also favors net sodium and water reabsorption into the vasculature. Concomitantly the increased FF in itself augments sodium reabsorption, magnifying the activation of sympathetic drive and renin axis. In the proximal tubules the permeable epithelium can easy allow return of sodium to the lumen as passive Starling forces govern the net sodium reabsorption between the peritubular capillaries and renal interstitium. The overall nephron function is profoundly influenced by the abnormally high sodium reabsorption in the proximal portion of tubule. As active Cl^- transport requires ATP which is metabolically converted in adenosine, the macula densa senses the increased sodium chloride by the concentration of the metabolic end product. The increased NaCl reabsorption in the proximal tubule reduces Cl^- delivery and leads to low intracellular chloride levels in the macula densa. This effect stimulates NOS I and COX-2 activation and release of NO and PGE2. They both stimulate renin secretion in the granulosa cells of the afferent arteriole activating angiotensin II

chloride delivery and leads to low intracellular chloride levels in the macula densa.

This effect stimulates NOS I and COX-2 activation and release of NO and PGE2. Both are potent agents that stimulate renin secretion in the granulosa cells of the afferent arteriole activating angiotensin II. In this way, a vicious cycle of neurohormonal activation perpetuates by augmenting congestion.

It is also important to consider loop diuretics, which are the most widely used drugs in management of congestion, inhibit the Na+/K+/2Cl cotransporter in the thick portion of the ascending loop of Henle, further reducing macula densa uptake of sodium chloride and pushing up neurohormonal activation [45].

In the distal convoluted tubules and collecting ducts, the sodium occurs $\leq$10% of the sodium reabsorption of the total amount filtered by the glomerulus. In contrast to the portion of the nephron proximal to the macula densa, where net fractional sodium reabsorption is kept relatively constant under normal circumstances, distal fractional sodium reabsorption is depending on tubular flow rates and may vary significantly according to levels of aldosterone and arginine vasopressin [54–56]. Thus, it is the distal nephron function that determines the urinary sodium concentration and osmolality and, a prerequisite for the ability of the distal nephron to maintain a neutral sodium balance, is adequate sodium delivery.

In congestive HF, because of the increased fractional reabsorption in the proximal tubules and often the decreased GFR in nephron population, tubular flow might be low in the distal portion of the nephron despite systemic fluid excess. Moreover, the increased aldosterone and arginine vasopressin levels further stimulate reabsorption of the remaining fluid in the tubule.

Despite therapy with adequate doses of RAAS inhibitors, the decreased distal tubular flow mostly contributes to the aldosterone breakthrough leading to secondary hyperaldosteronism [57, 58].

Furthermore, an adaptive hypertrophy of distal tubular cells, leading to increased local sodium reabsorption and aldosterone secretion, is generated after prolonged exposure to loop diuretics. Indeed, investigational data address distal tubular cells; adaptation to loop diuretics can be significantly attenuated after administration of aldosterone antagonists or thiazide diuretics investigational data [57, 59].

From the above pathophysiological description, the cardiorenal interaction has a domino effect on the building up of visceral congestion running profound implications on splanchnic organs circulation and on reticular endothelial system [60].

In the splanchnic microcirculation, net filtration rate is governed by Starling forces relationship, $(PC-PIF)-(\pi C-\pi IF)$, which favors filtration throughout the entire capillary bed extension. When congestion generates higher capillary hydrostatic pressure, filtration pressure is higher [58]. In the low compliant interstitium, the excess of filtrated fluid is drained through the compensatory action of lymphatic capillaries, and only a slight increase in interstitial fluid volume remains inside. Splanchnic lymphatic drainage can increase as much as 20 times its normal value, indeed [61]. This is a prominent way the neurohormonal maladaptive response enhances congestion and interstitial edema [60].

Conclusion

The intravascular pressure/volume homeostasis is modulated by the regulatory action of the autonomic nervous system in order to preserve the function of both the heart and kidney.

Excessive sympathetic activation in HF initiates, maintains, and progressively enhances mutually detrimental interactions between the heart and the kidney which play key role in the progression of both HF and kidney diseases. Innovative non-pharmacological interventions that can favorably alter the cardiac and renal autonomic tone are currently being investigated.

The burning need to find effective treatment in cardiorenal syndrome is pushing research in many directions. Multiple clinical trials are currently

evaluating the safety and the efficacy of these therapeutic strategies, but it has to be noted the cardiorenal relationship is early involved by cardiac dysfunction; thus effective therapeutic strategy should target the kidney and heart since from the early beginning of cardiac and/or renal diseases.

References

1. May CN, Frithiof R, Hood SG, McAllen RM, McKinley MJ, Ramchandra R. Specific control of sympathetic nerve activity to the mammalian heart and kidney. Exp Physiol. 2009;95:34–40.
2. Morrison SF. Differential control of sympathetic outflow. Am J Physiol Regul Integr Comp Physiol. 2001;281:R683–98.
3. Watson AM, Mogulkoc R, McAllen RM, May CN. Stimulation of cardiac sympathetic nerve activity by central angiotensinergic mechanisms in conscious sheep. Am J Physiol Regul Integr Comp Physiol. 2004;286:R1051–6.
4. Frithiof R, Ramchandra R, Hood SG, May CN, Rundgren M. The hypothalamic paraventricular nucleus mediates sodium induced changes in cardiovascular and renal function in conscious sheep. Am J Physiol Regul Integr Comp Physiol. 2009;397: R185–93.
5. Ramchandra R, Hood SG, Watson AM, May CN. Responses of cardiac sympathetic nerve activity to changes in circulating volume differ in normal and heart failure sheep. Am J Physiol Regul Integr Comp Physiol. 2008;295:R719–26.
6. Sobotka PA, Krum H, Böhm M, Francis DP, Schlaich MP. The role of renal denervation in the treatment of heart failure. Curr Cardiol Rep. 2012;14:285–92.
7. Parati G, Esler M. The human sympathetic nervous system: its relevance in hypertension and heart failure. Eur Heart J. 2012;33:1058–66.
8. Macefield V, Wallin BG, Vallbo AB. The discharge behaviour of single vasoconstrictor motoneurones in human muscle nerves. J Physiol Lond. 1994; 481:799–809.
9. Lambert E, Straznicky N, Schlaich MP, et al. Differing patterns of sympathoexcitation in normal weight and obesity-related hypertension. Hypertension. 2007; 50:862–8.
10. Lambert G. The assessment of human sympathetic nervous system activity from measurements of norepinephrine turnover. Hypertension. 1988;11:3–20.
11. Friberg P, Meredith I, Jennings G, Lambert G, Fazio V, Esler M. Evidence of increased renal noradrenaline spillover rate during sodium restriction in man. Hypertension. 1990;16:121–30.
12. Hasking G, Esler M, Jennings G, Burton D, Johns J, Korner P. Norepinephrine spillover to plasma in congestive heart failure: evidence of increased overall and cardiorenal sympathetic nervous activity. Circulation. 1986;73:615–21.
13. Parati G, Saul JP, Di Rienzo M, Mancia G. Spectral analysis of blood pressure and heart rate variability in evaluating cardiovascular regulation. A critical appraisal. Hypertension. 1995;25:1276–86.
14. Saul JP, Berger RD, Albrecht P, Stein SP, Chen MH, Cohen RJ. Transfer function analysis of the circulation: unique insights into cardiovascular regulation. Am J Physiol Heart Circ Physiol. 1991;261: H1231–45.
15. Van de Borne P, Rahnama M, Mezzetti S, et al. Contrasting effects of phentolamine and nitroprusside on neural and cardiovascular variability. Am J Physiol Heart Circ Physiol. 2001;281:H559–65.
16. La Rovere MT, Pinna GD, Maestri R, Mortara A, Capomolla S, Febo O, Ferrari R, Franchini M, Gnemmi M, Opasich C, Riccardi PG, Traversi E, Cobelli F. Short-term heart rate variability strongly predicts sudden cardiac death in chronic heart failure patients. Circulation. 2003;107(4):565–70.. PMID: 12566367
17. Parati G, Mancia G, Di Rienzo M, Castiglioni P, Taylor JA, Studinger P. Point: counterpoint cardiovascular variability is/is not an index of autonomic control of circulation. J Appl Physiol. 2006;101:676–82.
18. Parati G, Di Rienzo M, Mancia G. How to measure baroreflex sensitivity: from the cardiovascular laboratory to daily life. J Hypertens. 2000;18:7–19.
19. Parati G, di Rienzo M, Bertinieri G, et al. Evaluation of the baroreceptor-heart rate reflex by 24-hour intra-arterial blood pressure monitoring in humans. Hypertension. 1988;12:214–22.
20. Pagani M, Somers V, Furlan R, et al. Changes in autonomic regulation induced by physical training in mild hypertension. Hypertension. 1988;12:600–10.
21. Robbe HW, Mulder LJ, Ruddel H, et al. Assessment of baroreceptor reflex sensitivity by means of spectral analysis. Hypertension. 1987;10:538–43.
22. Grassi M, Esler M. How to assess sympathetic activity in humans. J Hypertension. 1999;17:719–34.
23. Tripsodiakis F, Karayannis G, Giamouzis G, Skoularigis J, Louridas G, Butler J. The sympathetic nervous system in heart failure: physiology, pathophysiology and clinical implications. J Am Coll Cardiol. 2009;54:1747–62.
24. Verberne HJ, Brewster LM, Somsen GA, van Eck-Smit BL. Prognostic value of myocardial 123I-metaiodobenzylguanidine (MIBG) parameters in patients with heart failure: a systematic review. Eur Heart J. 2008;29:1147–59.
25. Tamaki S, Yamada T, Okuyama Y, et al. Cardiac iodine-123metaiodobenzylguanidine imaging predicts sudden cardiac death independently of left ventricular ejection fraction in patients with chronic heart failure and left ventricular systolic dysfunction: results from a comparative study with signal-averaged

electrocardiogram, heart rate variability, and QT dispersion. J Am Coll Cardiol. 2009;53:426–35.
26. Jacobson AF, Lombard J, Banerjee G, Camici PG. 123I-mIBG scintigraphy to predict risk for adverse cardiac outcomes in heart failure patients: design of two prospective multicenter international trials. J Nucl Cardiol. 2009;16:113–21.
27. DiBona GF, Kopp UC. Neural control of renal function. Physiol Rev. 1997;77:75–97.
28. DiBona GF. Neural control of the kidney: past, present, and future. Hypertension. 2003;41:621–4.
29. Bell-Reuss E, Trevino DL, Gottschalk CW. Effect of renal sympathetic nerve stimulation on proximal water and sodium reabsorption. J Clin Invest. 1976; 57:1104–7.
30. Zanchetti AS. Neural regulation of renin release: experimental evidence and clinical implications in arterial hypertension. Circulation. 1977;56:691–8.
31. Kirchheim H, Ehmke H, Persson P. Sympathetic modulation of renal hemodynamics, renin release and sodium excretion. Klin Wochenschr. 1989;67:858–64.
32. Shlipak MG, Massie BM. The clinical challenge of cardiorenal syndrome. Circulation. 2004;110:1514–7.
33. Katholi RE, Hageman GR, Whitlow PL, et al. Hemodynamic and afferent renal nerve responses to intrarenal adenosine in the dog. Hypertension. 1983;5:I149–54.
34. Campese VM, Kogosov E. Renal afferent denervation prevents hypertension in rats with chronic renal failure. Hypertension. 1995;25:878–82.
35. Hausberg M, Kosch M, Harmelink P, et al. Sympathetic nerve activity in end-stage renal disease. Circulation. 2002;106:1974–9.
36. Schlaich M, Krum H, Walton T, Lambert G, Sobotka P, Esler M. A novel catheter based approach to denervate the human kidney reduces blood pressure and muscle sympathetic nerve activity in a patient with end stage renal disease and hypertension. J Hypertension. 2009;27(Suppl 4):s437.
37. Zucker IH. Novel mechanisms of sympathetic regulation in chronic heart failure. Hypertension. 2006;48: 1005–11.
38. Petersson M, Friberg P, Eisenhofer G, Lambert G, Rundqvist B. Long-term outcome in relation to renal sympathetic activity in patients with chronic heart failure. Eur Heart J. 2005;26:906–13.
39. Cohn JN, Levine TB, Olivari MT, et al. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. N Engl J Med. 1984;311:819–23.
40. Goldsmith SR, Sobotka PA, Bart BA. The sympathorenal axis in hypertension and heart failure. J Cardiac Fail. 2010;16:369–73.
41. Cohn JN, Pfeffer MA, Rouleau J, et al. Adverse mortality effect of central sympathetic inhibition with sustained release moxonidine in patients with heart failure (MOXCON). Eur Journal Heart Fail. 2003;5:659–67.
42. Beta-Blocker Evaluation of Survival Trial Investigators, Eichhorn EJ, Domanski MJ, Krause-Steinrauf H, Bristow MR, Lavori PW. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. N Engl J Med. 2001;344(22):1659–67.
43. Nozawa T, Igawa A, Fujii N, et al. Effects of long-term renal sympathetic denervation on heart failure after myocardial infarction in rats. Heart Vessel. 2002; 16:51–6.
44. Francis GS, Siegel RM, Goldsmith SR, et al. Acute vasoconstrictor response to intravenous furosemide in patients with chronic congestive heart failure. Activation of the neurohumoral axis. Ann Intern Med. 1985;103:1–6.
45. Verbrugge FH, Dupont M, Steels P, et al. The kidney in congestive heart failure: are natriuresis, sodium, and diuretics really the good, the bad and the ugly? Eur J Heart Fail. 2014;16:133–42.
46. Gibson DG, Marshall JC, Lockey E. Assessment of proximal tubular sodium reabsorption during water diuresis in patients with heart disease. Br Heart J. 1970;32:399–405.
47. Lewy JE, Windhager EE. Peritubular control of proximal tubular fluid reabsorption in the rat kidney. Am J Phys. 1968;214:943–54.
48. Grandchamp A, Boulpaep EL. Pressure control of sodium reabsorption and intercellular backflux across proximal kidney tubule. J Clin Invest. 1974;54:69–82.
49. Gottschalk CW, Mylle M. Micropuncture study of pressures in proximal tubules and peritubular capillaries of the rat kidney and their relation to ureteral and renal venous pressures. Am J Phys. 1956; 185:430–9.
50. Burnett JCJ, Knox FG. Renal interstitial pressure and sodium excretion during renal vein constriction. Am J Phys. 1980;238:F279–82.
51. Haddy FJ, Scott J, Fleishman M, Emanuel D. Effect of change in renal venous pressure upon renal vascular resistance, urine and lymph flow rates. Am J Phys. 1958;195:97–110.
52. Lebrie SJ, Mayerson HS. Influence of elevated venous pressure on flow and composition of renal lymph. Am J Phys. 1960;198:1037–40.
53. Ott CE, Haas JA, Cuche JL, Knox FG. Effect of increased peritubule protein concentration on proximal tubule reabsorption in the presence and absence of extracellular volume expansion. J Clin Invest. 1975; 55:612–20.
54. Lote CJ, Snape BM. Collecting duct flow rate as a determinant of equilibration between urine and renal papilla in the rat in the presence of a maximal antidiuretic hormone concentration. J Physiol. 1977; 270:533–44.
55. Allen GG, Barratt LJ. Effect of aldosterone on the transepithelial potential difference of the rat distal tubule. Kidney Int. 1981;19:678–86.
56. Woodhall PB, Tisher CC. Response of the distal tubule and cortical collecting duct to vasopressin in the rat. J Clin Invest. 1973;52:3095–108.
57. Schrier RW. Aldosterone ‘escape’ vs ‘breakthrough’. Nat Rev Nephrol. 2010;6:61.

58. Tang WH, Vagelos RH, Yee YG, Benedict CR, Willson K, Liss CL, Fowler MB. Neurohormonal and clinical responses to high- versus low-dose enalapril therapy in chronic heart failure. J Am Coll Cardiol. 2002;39:70–8.
59. Kim GH. Long-term adaptation of renal ion transporters to chronic diuretic treatment. Am J Nephrol. 2004;24:595–605.
60. Verbrugge FH, Dupont M, Steels P, et al. Abdominal contributions to cardiorenal dysfunction in congestive heart failure. J Am Coll Cardiol. 2013;62:485–9559.
61. Aukland K, Reed RK. Interstitial-lymphatic mechanisms in the control of extracellular fluid volume. Physiol Rev. 1993;73:1–78.

4 Genetic Determinants Affecting the Relationship Between the Autonomic Nervous System and Sudden Death

Rachel M. A. ter Bekke and Paul G. A. Volders

Contents

Abstract

The autonomic nervous system with its sympathetic and parasympathetic limbs and its neurohormones (nor)epinephrine and acetylcholine is a well-recognized modulator of cardiac electrophysiology. Inherited or congenital inhomogeneities of cardiac autonomic innervation, sympathovagal imbalance, autonomic nervous system hyperactivity, autonomic conflict, and/or genetic variants of α- and β-adrenergic receptors can predispose even structurally normal hearts to life-threatening arrhythmias. Remodeling of the autonomic nervous system found in patients with epilepsy and sudden infant death syndrome can also predispose to sudden death. The overlap between small fiber neuropathy, cardiac

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*,
https://doi.org/10.1007/978-3-030-28008-6_6

conduction disease, and Brugada syndrome possibly via genomic modulation is briefly addressed. Alternatively, the heart itself may be intrinsically susceptible to variations in autonomic nervous function. Inherited arrhythmia syndromes like the long QT syndrome, catecholaminergic polymorphic ventricular tachycardia, and Brugada syndrome can lead to sudden death under conditions of altered autonomic nervous system tone. In this chapter we focus on the genetic determinants affecting the relationship between the autonomic nervous system and sudden death.

Keywords

Sudden cardiac death · Inherited arrhythmia syndromes · Takotsubo cardiomyopathy · Sudden unexplained death in epilepsy · Adrenergic receptors · Sudden infant death syndrome · Small fiber neuropathy

Introduction

Sudden cardiac death (SCD) remains an unnerving difficulty. It not only claims 20% of total mortality in the industrialized world but also imposes a devastating psychosocial impact on (the family of) the victims who are often in the prime of their lives [1]. There is a clear familial predisposition to SCD in specific conditions [2, 3, 4, 5]. These sudden and unexpected deaths are predominantly the result of ventricular fibrillation (VF), although the incidence of asystole is increasingly recognized [678]. The underlying pathophysiology is complex and multifactorial, but there is general consensus that a timely interaction is required between a transient trigger and a vulnerable substrate.

Sudden variations in autonomic tone, either swift augmentation of the sympathetic nervous system activity or altered vagal reflexes, confer important triggers of life-threatening arrhythmias in inherited [9, 10] and acquired cardiac diseases [11]. The peak incidence of SCD in the morning hours [12] during high sympathetic tone supports the concept of proarrhythmic potency of catecholaminergic influences. These zeniths are attenuated by anti-adrenergic therapies like β-adrenergic receptors blockers [13] and cardiac sympathetic denervation, which have reduced the burden of arrhythmia in a wide variety of arrhythmia syndromes [14]. Various functional and structural myocardial abnormalities may render the heart vulnerable to arrhythmogenic impact during autonomic fluctuations. As such, inherited genetic variation in cardiac ion channels but also acquired conditions like acute myocardial ischemia, fibrosis, ventricular dilatation, and electrolyte disturbances can increase myocardial vulnerability and set the stage for arrhythmias. Alternatively, certain deleterious variants in genes involved in the autonomic nervous system may create autonomic imbalance [15] and increase the ventricular susceptibility to autonomic triggers [16, 17]. In this chapter, neurocardiac interactions important for ventricular arrhythmogenesis are addressed first. In the second part, genetic variations implicated in neurocardiac electrophysiology and consequent ventricular tachyarrhythmia will be discussed.

Neurocardiac Interactions and Ventricular Arrhythmogenesis

Anatomy

Cardiac autonomic innervation comprises efferent and afferent neural pathways that intricately govern cardiac inotropy, chronotropy, dromotropy, and lusitropy on a beat-to-beat and longer-term basis via feedback loops between the intrinsic cardiac nervous system, extracardiac-intrathoracic ganglia, and higher brain centers (Fig. 1) [18]. The autonomic nervous system consists of sympathetic and parasympathetic fibers. The adrenal glands are largely responsible for the production of circulating epinephrine, only for a small amount of norepinephrine. Cardiac sympathetic afferent neurons ascend, in part, via the dorsal columns, spinothalamic and spinoreticular tracts to cortical terminals [19]. Efferent neural outflows to the heart are governed by central (preganglionic) and peripheral neuronal mediated

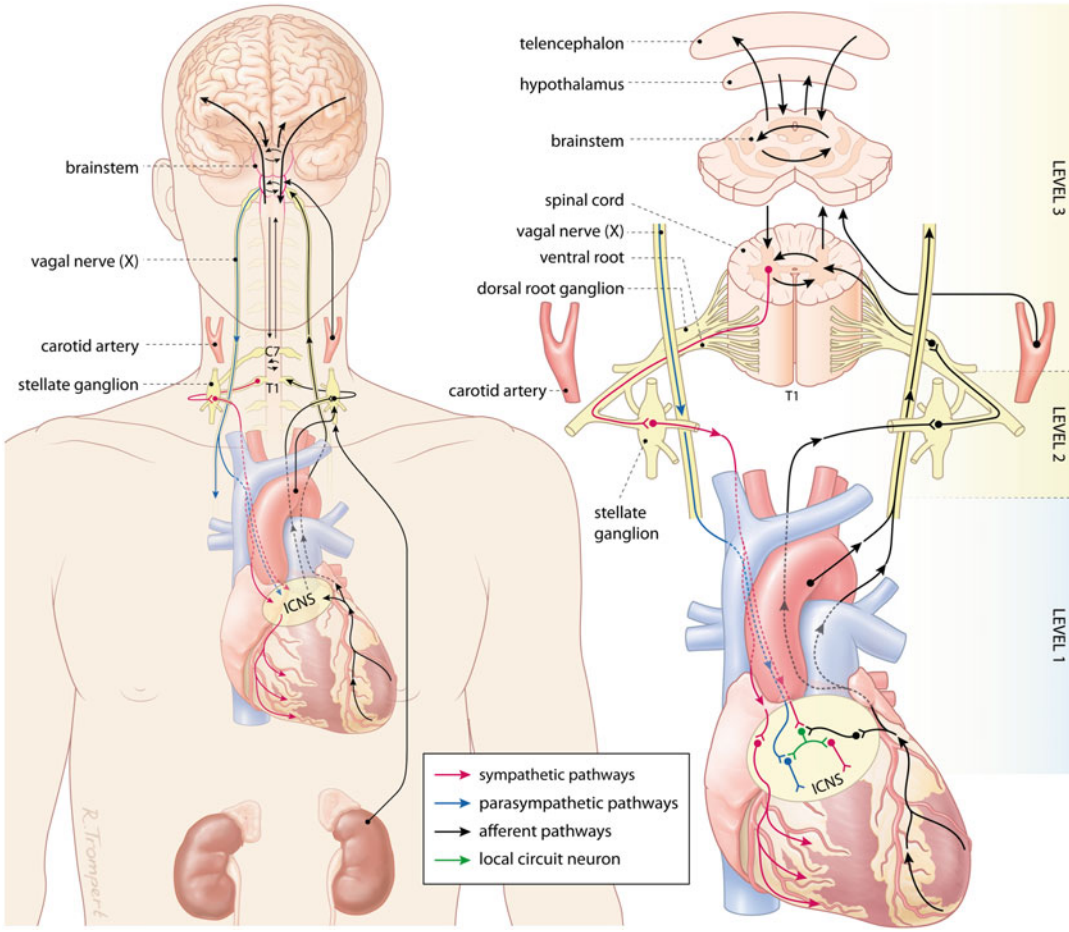

Fig. 1 Schematic illustration of the autonomic innervation of the heart. Various reflex loops exist at the cardiocardiac (level 1), intrathoracic (level 2), and spinal and brainstem region (level 3). The higher brain centers impose additional control. ICNS, intrinsic cardiac nervous system

(postganglionic) reflexes [18]. Cardiac sympathetic efferent preganglionic neurons descend through the intermediolateral column of the spinal cord [20] projecting axons to ganglia located in the neck and thorax (stellate ganglia) [21, 22]. Efferent postganglionic neurons from each stellate ganglion project to the atria and ventricles with laterality, but also substantial overlap [23]. Parasympathetic efferent preganglionic neurons in the medulla oblongata connect to postganglionic neurons in the atrial and ventricular ganglionated Plexi [24, 25]. Local circuit neurons in these intrinsic cardiac ganglia coordinate motor neural outputs to the heart [26] and can operate independently of the higher centers [27].

Physiology

Sympathetic cardiac outflow impacts on G-protein-coupled adrenergic receptors through the neurohormones norepinephrine and epinephrine. Catecholaminergic stimulation regulates heart rate and cardiac contractile and relaxation characteristics. The adrenergic receptors are divided in three subfamilies, α_{1}-, α_{2}-, and β-adrenergic receptors, with each containing three subtypes. β_1 (70–80%) [28]- and β_2-adrenergic receptors (20–30%) [29] are the dominant human cardiac subtypes. The β_1-adrenergic receptor is the predominant subtype in the (normal, healthy) myocardium, representing 75–80%

of total β-adrenergic receptor density, followed by β_2-adrenergic receptors, which comprise ±15–18% of total cardiomyocyte β-adrenergic receptors, and the remaining 2–3% are β3-adrenergic receptors (under normal conditions) [30]. The β_3-adrenergic receptor can act as a "fuse" against cardiac adrenergic overstimulation [31]. Stimulation of β-adrenergic receptors in ventricular myocytes activates the G_s-signaling cascade involving adenylyl cyclase, cyclic AMP, and protein kinase A (PKA) and PKA-dependent protein phosphorylation (Fig. 2), although functional and intermolecular interactions between the β-adrenergic receptor and the α_1-adrenergic receptor subtypes hint toward a more complex signalome regulation [32]. Protein complexes in myocytes that are phosphorylated by PKA include the L-type Ca^{2+} channel (I_{CaL}), Na^+ channel (I_{Na}), slowly activating delayed rectifier K^+ channel (I_{Ks}), ultra-rapid delayed rectifier K^+ channel (I_{Kur}), Na^+-K^+ ATP-ase (I_{NaK}), phospholamban, ryanodine receptor, and troponin I. Sustained β_1-adrenergic receptor stimulation results in PKA-independent Ca^{2+}-related activation of Ca^{2+}/calmodulin kinase II (CaMKII), which can evoke cardiac myocyte apoptosis and maladaptive remodeling [33]. The overall cellular effect of β-adrenergic receptor stimulation converges into shortening of the action potential duration [34] and larger Ca^{2+}-transient amplitudes with faster decay [35]. Stimulation of β_2-adrenergic receptors activates G_i proteins which, in turn, stimulates phosphoinositide 3-kinase and inhibits G_s-adenylyl cyclase-cAMP-PKA-mediated target-protein phosphorylation and positive inotropic and lusitropic effects [32, 36]. Specific functions of β_3 in relation to ion channel function I_{Ks} have been described for the human heart [37].

Although catecholamines regulate cardiac contractility mainly through the β-adrenergic receptors, the acute activation of α_1-adrenergic receptors also exerts a positive inotropic effect in the human heart [38]. Presynaptically, the α_2-adrenergic receptors have a critical role in regulating neurotransmitter release from sympathetic nerve endings [39]. The α_{2A}- and α_{2C}-subtypes inhibit transmitter release at high and lower stimulation frequencies, respectively [40].

Acetylcholine is the primordial parasympathetic neurotransmitter in the heart, although nitric oxide (NO) and vasoactive intestinal peptide are important cotransmitters (Fig. 2). Acetylcholine predominantly activates the muscarinic receptors M2 and M3 on cardiomyocytes and sympathetic nerve endings, operating mainly by antagonizing the cellular sympathetic effects. Besides muscarinic activation, vagal nerve stimulation also results in NO production through neuronal nitric oxide synthase (nNOS) activation [41, 42]. NO appears to modulate the parasympathetic effects on heart rate response and VF threshold [42, 43].

Role in Ventricular Arrhythmogenesis

Sympathetic nerve hyperactivity or adrenergic provocation can lower the threshold for ventricular tachyarrhythmias and provoke sudden cardiac death in susceptible hearts [44–47]. Indeed, spontaneous sympathetic nerve discharges from the left stellate ganglion precede VF in a canine model of SCD [48]. Sympatho-excitation impinges on ventricular electrophysiological properties by increasing cellular Ca^{2+} load and spontaneous Ca^{2+} release from the sarcoplasmic reticulum, which can exaggerate dispersion of refractoriness [49], facilitating triggered activity [50, 51] and reducing the VF threshold [52]. Especially the left sympathetic chain has a strong proarrhythmic potential [47, 53]. Besides a globally increased sympathetic activity, it is also recognized that nonuniform sympathetic cardiac innervation contributes considerably to electrical instability and ventricular arrhythmogenesis [15, 54, 55]. Such heterogenous innervation can be inherited [15, 54] or due to acquired cardiac diseases like myocardial infarction leading to excessive and dispersed regeneration of nerve sprouting [55]. Also, infarct-related local denervation supersensitivity to norepinephrine may increase arrhythmogenic susceptibility [56]. On the other hand, an increased susceptibility to ventricular tachyarrhythmias upon sympathetic triggering can be found in certain inherited arrhythmia syndromes like the long QT syndrome (LQTS; see below) [16] and catecholaminergic polymorphic

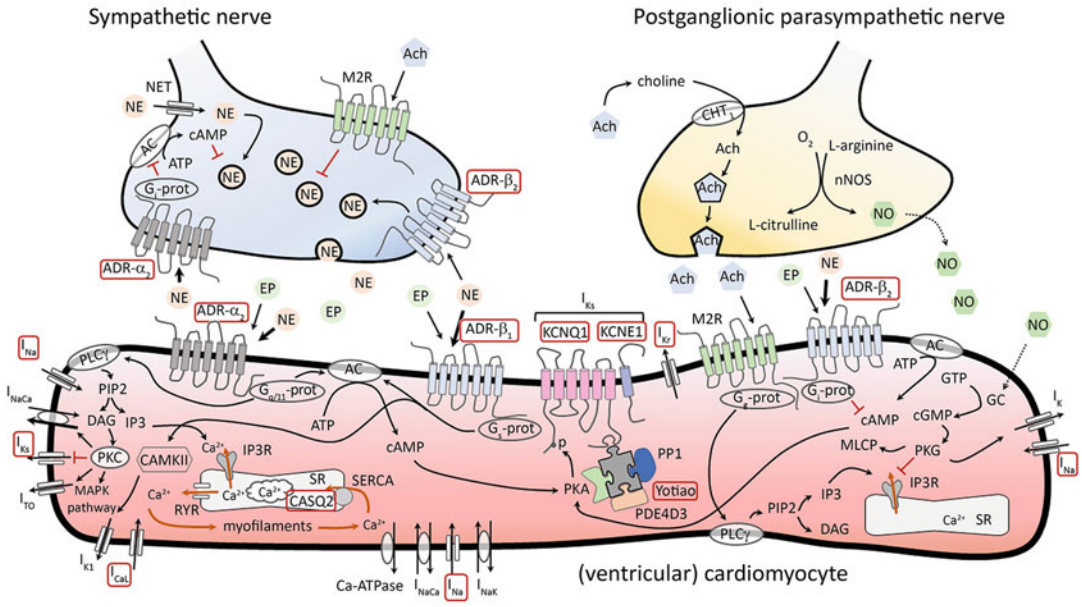

Fig. 2 Representation of molecular pathways involved in the sympathetic and postganglionic parasympathetic communication with the (ventricular) cardiomyocyte. Genetic determinants in genes/proteins affecting the relationship between autonomic nervous system and sudden cardiac death are framed in red. KCNQ1 encodes for the α subunit of I_{Ks}; KCNE1 for the axillary subunit of I_{Ks}. AC indicates adenylyl cyclase; Ach, acetylcholine; ADR-α1, α1-adrenergic receptor; ADR-α2, α2-adrenergic receptor; ADR-β1, β1-adrenergic receptor; ADR-β2, β2-adrenergic receptor; ATP, adenosine triphosphate; CaMKII, Ca^{2+}/calmodulin-dependent kinase II; cAMP, cyclic adenosine monophosphate; CASQ2, calsequestrin 2; cGMP, cyclic guanosine monophosphate; CHT1, choline transporter gene 1; DAG, diacylglycerol; EP, epinephrine; GTP, guanosine triphosphate; G_i prot, G_i protein; G_s prot, G_s protein; GC, guanylyl cyclase; $G_{q/11}$ prot, $G_{q/11}$ protein; I_{CaL}, L-type Ca^{2+} current; I_{K1}, inwardly rectifying K^+ current; I_{Kr}, rapidly activating delayed rectifier K^+ current; I_{Ks}, slowly activating delayed rectifier K^+ current; I_{Na}, voltage-dependent Na^+ current; I_{NaCa}, Na^+/Ca^{2+} exchange current; I_{NaK}, Na^+/K^+ pump current; IP3, inositol 1,4,5-trisphosphate; IP3R, inositol 1,4,5-trisphosphate receptor; I_{TO}, transient outward current; M2R, muscarinic M2 receptor; MAPK, mitogen-activated protein kinase; MLCP, myosin light chain phosphatase; NE, norepinephrine; NET, norepinephrine transporter; nNOS, neuronal nitric oxide synthase; NO, nitric oxide; PDE4D3, phosphodiesterase 4D3; PIP2, phosphatidylinositol 4,5-bisphosphate; PKA, protein kinase A; PKC, protein kinase C; PKG, protein kinase G; PLCγ, phosphoinositide-phospholipase C-γ; PP1, protein phosphatase 1; RYR, ryanodine receptor; SERCA, sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase; SR, sarcoplasmic reticulum; Yotiao, A-kinase anchoring protein

ventricular tachycardia (CPVT; see below) [57]. Allelic variants in LQTS-related genes can lead to a prolonged cardiac repolarization. The degree of repolarization prolongation can be assessed on a standard 12-lead electrocardiogram by measuring the QT interval. As the QT varies according to the preceding RR interval, it is mandatory to correct the QT for heart rate variations (QTc, heart rate corrected QT). In the LQTS, [^{123}I]-MIBG SPECT imaging unraveled anteroseptal reduced sympathetic innervation irrespective of the underlying genotype [58]. Patients with the LQTS demonstrate an increased susceptibility to torsades de pointes (TdP) arrhythmias, especially during sympathetic surges. Torsades de pointes, French for "twisting of the peaks," is a life-threatening polymorphic ventricular tachycardia (VT) with characteristic electrocardiographic features: periodic twisting of the QRS axis around the isoelectric baseline at high frequency (250–350 beats per minute). TdP arrhythmias are often preceded by short-long-short RR interval sequences, but are

sometimes fast-rate dependent (suggestive of sympathetic triggering).

Vagal nerve stimulation or strong vagal reflexes generally exert an anti-arrhythmic effect, reducing the spontaneous occurrence of ventricular tachycardia during coronary artery occlusion in conscious dogs [59, 60]. It prolongs the effective refractory period of canine ventricular cardiomyocytes via cholinergic muscarinic pathways [42, 61], increases the VF threshold via nNOS-mediated NO release [42], and augments the variability of the dominant VF frequency [62]. In clinical heart failure populations of the INOVATE-HF [63] and NECTAR-HF [64] trials, however, a protective role of a high vagal tone due to chronic right vagal nerve stimulation was not confirmed. Interestingly, dominant vagal activity is deemed pro-arrhythmic in the Brugada syndrome (see below) and a subset of long-QT1 patients. In the former, this is supported by the nocturnal incidence of VF[10] and the exaggerated reactivity of the parasympathetic nervous system involved in VF in the J-wave syndrome [65]. In long-QT type 1 patients, a higher baroreflex sensitivity and higher vagal reflexes, as determined by the phenylephrine method and by exercise stress testing, are implicated in increased risk for life-threatening arrhythmias [17, 66].

Intriguingly, and besides the classic "yin and yang" reciprocal autonomic inputs, specific conditions like cold-water immersion can provoke concomitant activation of sympathetic and parasympathetic drive. This so-called autonomic conflict imposes a pleiotropy of brady- and tachyarrhythmias including TdP arrhythmias in susceptible individuals [67]. The proarrhythmic consequences of dual autonomic activation appear to be larger in genetically susceptible hearts, given the strong association between swimming and sudden cardiac arrest in patients with the LQTS [16].This is corroborated by the proarrhythmic effect of reflex vagal activation during electrical stimulation of the left stellate ganglion in a canine drug-induced LQTS type 1 model [47].

Genetic Determinants of Autonomic Nervous System Remodeling

Altered Innervation

Cardiac sympathetic innervation during development is governed by chemoattractive and chemorepulsive factors. Nerve growth factor (NGF), a chemoattractive factor, stimulates sympathetic axon extension into the heart via the TrkA and p75 neurotrophic receptors in sympathetic neurons [68]. The infusion of NGF into the stellate ganglia promotes sympathetic nerve sprouting and increases the incidence of ventricular tachyarrhythmias and SCD in a canine model of myocardial infarction [69]. Thus far, no variants in the NGF gene have been identified, which are associated with increased VF susceptibility. Semaphorins (semaphorin-3A encoded by the *SEMA3A* gene), on the other hand, are typical chemorepulsive factors that guide neural connections [70]. *SEMA3A* is responsible for the epicardial-to-endocardial transmural gradient of sympathetic innervation. *SEMA3A*-deficient and *SEMA3A*-overexpressing mice demonstrate aberrant sympathetic innervation patterns that lead to a higher susceptibility to lethal arrhythmias and sudden death [71, 72]. Clinically, a non-synonymous polymorphism in exon 10 of the *SEMA3A* gene was enriched (I334V, rs138694505, chromosome 5) in a Japanese cohort of idiopathic VF patients [73]. The risk genotype G was present in 16% of idiopathic VF patients compared to 6% in controls.

Variants in Human Adrenergic Receptors

Various genetic variants residing in human α- and β-adrenergic receptor genes have been implicated in heart failure traits and β-adrenergic receptor blocker efficacy, where they can affect cardiac electrical stability and susceptibility to ventricular tachyarrhythmia (Fig. 3). First, the deletion/deletion genotype of the insertion/deletion

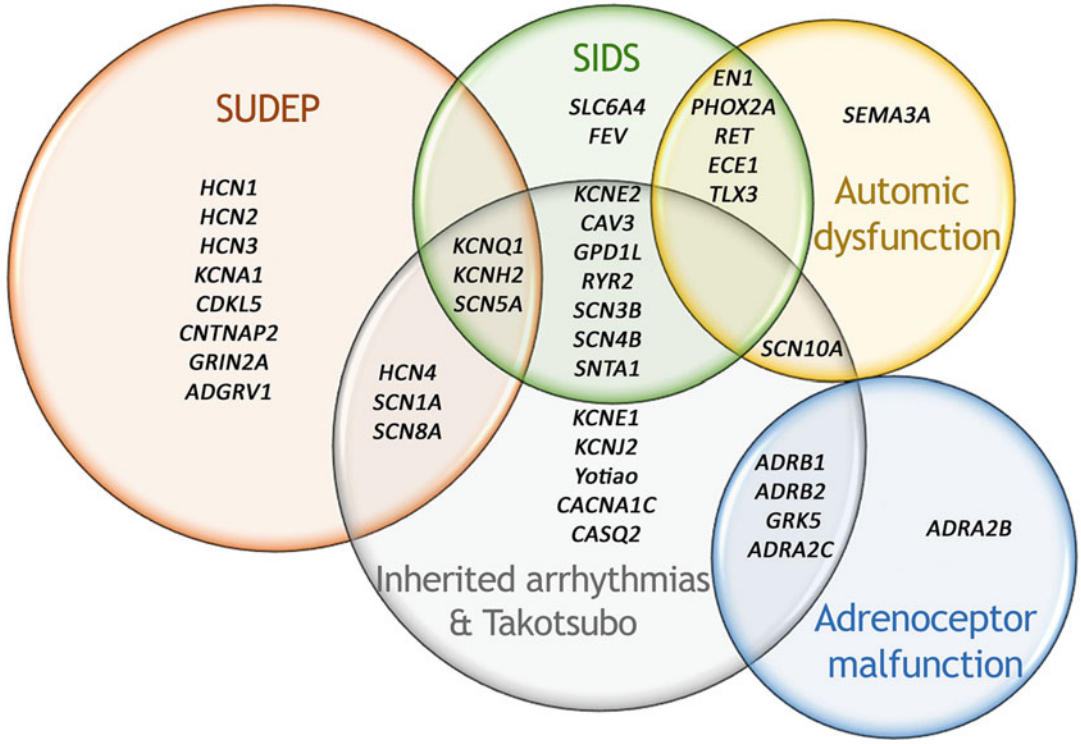

Fig. 3 Venn diagram demonstrating the overlapping phenotypes and currently known gene variants involved in the relationship between the autonomic nervous system and sudden death. SIDS indicates sudden infant death syndrome; SUDEP, sudden unexplained death in epilepsy

polymorphism in the α_{2B}-adrenergic receptor (*ADRA2B*, deletion of three glutamic acids at 301–303 from a glutamic acid repeat element in an acidic stretch of 18 amino acids: rs28365031, rs29000568, and rs4066772) confers an increased risk for fatal myocardial infarction and SCD in middle-aged white European men (allelic frequency 22%) [74]. Another 4-amino-acid deletion in the α_{2C}-adrenergic receptor gene (del322–325) promotes enhanced norepinephrine release from sympathetic nerve endings [75] and has been implicated with genotype-specific response to β-adrenergic receptor blocker therapy by bucindolol [76]. Nonsynonymous single nucleotide polymorphisms (SNPs) in β1 (*ADRB1*)- and β2 (*ADRB2*)-adrenergic receptor genes are also known for their ability to modulate arrhythmia risk: Ser49Gly (A145G, rs1801252) and Gly389Arg (G1165C, rs1801253; for *ADRB1*) and Arg16Gly (G46A, rs1042713) and Gln27Glu (G79C,T, rs1042714; for *ADRB2*). The β1-adrenergic receptor polymorphism Gly49 is associated with enhanced agonist-promoted receptor downregulation [77]. Heart failure patients carrying this *ADRB1*-Gly49 allele confer improved survival benefit when treated with β-adrenergic receptor blocker therapy [78] and demonstrate prominent reverse left-ventricular remodeling [79] compared to those with the normal genotype. However, the *ADRB1*-Gly49 allele also has been linked to adverse outcomes compared to homozygous *ADRB1*-Ser49 heart failure patients when treated with low-dose β-adrenergic receptor blockers, an effect that was obliterated at higher doses [80]. Another *ADRB1* polymorphism, Gly389, confers a significantly lower risk for ventricular tachyarrhythmias in patients with dilated cardiomyopathy [81, 82]. In univariate analysis, the odds ratio for VT in

patients carrying one or two copies of the Gly389 allele was 0.29 ([95% confidence interval, 0.13–0.64], $P = 0.002$), when compared with the Arg389 homozygotes. The *ADRB1*-Arg389Gly variant is located at the last transmembrane helix in the vicinity of the phosphorylation sites important for G-protein coupling and cell signaling. Additionally, heart failure patients with the Arg389 genotype had improved ventricular contractility and survival in a β-blocker evaluation of survival trial subcohort [83]. Transfected fibroblast studies have demonstrated that the homozygous *ADRB1*-Gly389 genotype reduces β-adrenergic receptor downstream signaling by 67% [81, 84]. No relevant associations were observed between the *ADRB1* SNPs and survival in patients with coronary artery disease [85] or acute coronary syndrome treated with β-adrenergic receptor blocker therapy [86]. With regard to *ADRB2* SNPs, the SNPs *ADRB2*-Gly16Arg and *ADRB2*-Gln27Glu were associated with higher mortality in patients with an acute coronary syndrome [86]. Likewise, homozygous *ADRB2*-Gln27 individuals had a higher risk for SCD than *ADRB2*-Glu27 carriers (hazard ratio, 1.56; 95% CI, 1.17 to 2.09) in the prospective Cardiovascular Health Study cohort [87]. Further evidence for the association between the *ADRB2*-Gln27 genotype and SCD was provided in a large prospective case-control series [88]. Functional experiments in transfected cells have demonstrated that *ADRB2* variants modify receptor downregulation and trafficking [89].

Altered Autonomic Nervous System in Neuronal Disease

Sudden Infant Death Syndrome

Altered autonomic nervous system remodeling characterized by immature cardiorespiratory autonomic control and failing arousal responsiveness from sleep can predispose to sudden death at young age [90]. The so-called sudden infant death syndrome (SIDS) alludes to sudden death of an infant younger than 1 year that remains unexplained despite extensive investigation, including autopsy, clinical history, and death scene examination. Familial studies show a five-fold increased SIDS risk for siblings, supporting a genetic etiology [91]. Indeed, in 5–10% of cases genetic determinants are implied [92], mostly constituting abnormalities in the development and function of medullary serotonin (5-HT) pathways [93]. Serotonin is a neurotransmitter which regulates autonomic cardiorespiratory function and circadian rhythms. Two functional polymorphisms in the serotonin transporter gene (*SLC6A4*, 5-HTT) are linked to SIDS risk: a promotor polymorphism (Japanese population) [94] and an intronic polymorphism (African-American population) [95]. Partly, these findings are replicated in African-American and Caucasian SIDS cases [96], but not in other cohorts [97, 98]. Furthermore, a rare intronic insertion mutation in the *FEV* gene, which plays a role in the development of 5-HT neurons, is found more commonly in (African-American) SIDS cases [99]. Other polymorphisms in genes that modulate the development of the autonomic nervous system like *PHOX2a*, *RET*, *ECE1*, *TLX3*, and *EN1* are also implicated [100]. Besides these neuronal developmental genetic determinants, it is recognized that SIDS victims had significantly longer QTc than non-SIDS fatal cases or controls [101]. Accordingly, genetic variants known in LQTS and CPVT have been linked to SIDS cases [102, 103]. These cardiac ion channel susceptibility genes are *CAV3* [104], *GPD1L* [105], *KCNQ1* [106], *KCNH2* [107], *SCN5A* [108, 109], *RYR2* [107], *KCNE2*, *SCN3B*, *SCN4B* [110], and *SNTA1* [111].

Sudden Unexpected Death in Epilepsy

Sudden unexpected death in epilepsy (SUDEP) is a sudden unexpected non-traumatic death of a person with epilepsy in the absence of autopsy findings deemed responsible for the cause of death. It accounts for 7.5–17% of mortality in epilepsy patients [112]. The pathophysiologic mechanisms underlying SUDEP are multifactorial, but it is currently believed that dysregulation of cardiorespiratory and cerebral function, as a consequence of recurrent seizures, can trigger SUDEP [113]. The most common cardiac feature is an ictal tachycardia that results from

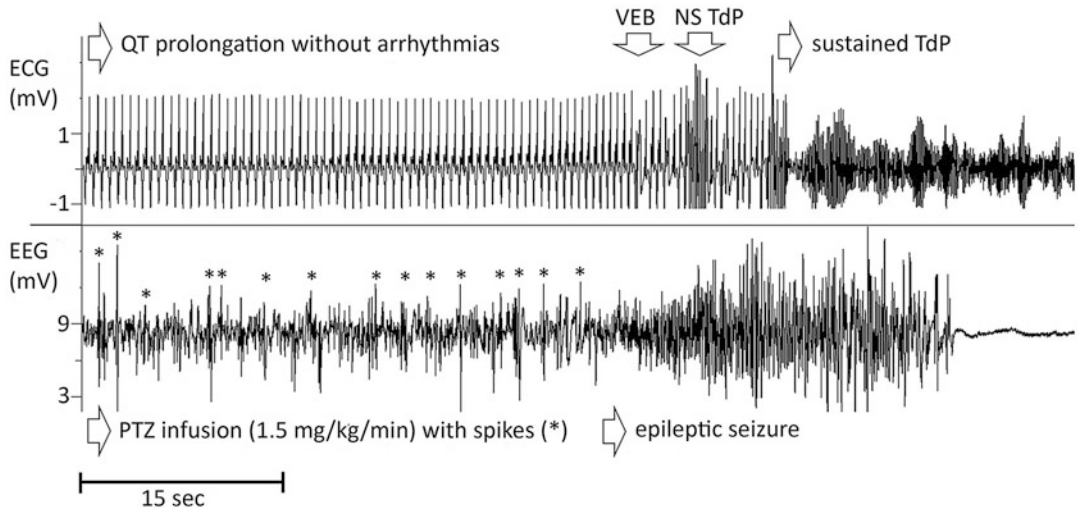

Fig. 4 Induction of torsades de pointes (TdP) in an anesthetized dog pretreated with the potent I_{Ks} blocker JNJ282 (0.5 mg/kg) [199] and the proconvulsant pentylenetetrazole (PTZ, 1.5 mg/kg/min) [200], leading to an epileptic seizure followed seconds later by the onset of ventricular ectopic beats (VEB), non-sustained (NS), and sustained arrhythmia. Spikes (∗) indicate proconvulsant risk. (Courtesy of H. van der Linde and D. Gallacher; from PhD thesis of H. van der Linde. Maastricht University, 2019)

sympathovagal imbalance and autonomic dysfunction due to recurrent epileptic seizures. Additionally, animal models of epilepsy show that chronic epilepsy can induce a secondary cardiac channelopathy [114]. Indeed, it is found that patients with long-standing epilepsy have longer QTc values than age-matched controls [115]. This is not confirmed by others [116], but this can derive from the occurrence of both lengthening [117] and shortening of ventricular repolarization [118] during the ictal period. One explanation may lie in the observation that chronic epilepsy patients can have cardiac sympathetic denervation [119].

Alternatively, there are various ion channels, co-expressed in the brain and the heart, that have been implicated in epilepsy and cardiac arrhythmias, for instance, the hyperpolarization-activated cyclic nucleotide-gated cation (HCN1–4) channels, which are involved in generating spontaneous rhythmic activity in cardiac pacemaker (I_f) and neuronal cells (I_h). In a large SUDEP cohort, six novel and three previously reported non-synonymous variants in *HCN1* ($n = 1$), *HCN2* ($n = 2$), *HCN3* ($n = 2$), and *HCN4* ($n = 4$) were identified [120]. Cardiac phenotypes of *HCN4* mutations encompass sinus node dysfunction, but also ventricular tachycardias [121]. As an example of a combined cardiac and neurologic phenotype, *HCN2* knockout mice were devoid of seizures and cardiac arrhythmias [122]. Another co-expressed gene, the *KCNA1* gene encoding the $K_v1.1$ channel, is implicated in epilepsy-related cardiac dysfunction, as $K_v1.1$ knockout mice demonstrate lethal asystole in the postictal period [123]. A different potassium channel, $K_v7.1$, encoded by the *KCNQ1* gene, is highly expressed in cardiac tissue and in the forebrain, the nucleus of the tractus solitarius, and the inner ear region [124]. It encodes for the α-subunit of the slowly activating delayed rectifier potassium (I_{Ks}) channel, and loss-of-function mutations in this gene mostly manifest as LQTS1 [125]. An association between *KCNQ1* mutations, LQTS1, and epilepsy was first demonstrated in a mouse model [124]. Canine studies during pharmacological I_{Ks} block demonstrated TdP arrhythmias to occur immediately after pentylenetetrazole-induced seizures (Fig. 4). Later, a comprehensive genetic analysis using next-generation sequencing technology identified rare genetic variants in the *KCNQ1* (but also in *CDKL5*, *CNTNAP2*, *GRIN2A,* and

ADGRV1) gene in pedigrees with cardiac conduction disorder and SUDEP [112]. A third potassium channel, $K_v11.1$, encoded by the *KCNH2* gene and generating the rapidly activating delayed-rectifier potassium current (I_{Kr}), is also highly co-expressed in the heart and the hippocampus. Loss-of-function *KCNH2* mutations confer the LQTS2 phenotype. Several case reports have identified *KCNH2* mutations that underlie QTc prolongation and recurrent seizure episodes [120, 126, 127]. Indeed, LQTS1 and LQTS2 patients more frequently have abnormal electrical cerebral activity compared to healthy controls [128]. Finally, various sodium channels are involved, for example, $Na_V1.1$ (encoded by the *SCN1A* gene) which is co-expressed in the brain (hippocampus) and the heart (ventricular t-tubules and sinoatrial node). Loss-of-function mutations in this *SCN1A* gene are implicated in up to 90% of Dravet syndrome [129], a syndrome of severe myoclonic epilepsy in infancy and high risk of SUDEP. Epileptic rats show enhanced cardiomyocyte expression of $Na_V1.1$ resulting in an increased late component of I_{Na} (I_{NaL}) and prolonged action potential duration [130]. Another (predominant cardiac) sodium channel, $Na_V1.5$, is encoded by the *SCN5A* gene. Mutations in this gene have been primarily linked to LQTS3, Brugada syndrome, and cardiac conduction defects. However, some reports describe the copresence of epilepsy and Brugada syndrome [131]. *SCN5A* mutations have also been associated with isolated epilepsy [120, 132]. Besides *SCN1A* and *SCN5A*, *SCN8A* encodes another sodium channel subunit implicated in SUDEP, i.e., the $Na_V1.6$ channel that is expressed in the nodes of Ranvier in motor neurons [133]. A de novo missense mutation in *SCN8A* (c.5302A > G; rs202151337) with a gain-of-function effect was identified in infantile epileptic encephalopathy and SUDEP [133]. Indeed, gain-of-function *SCN8A*-mutant mice demonstrate a prolonged ventricular action potential duration, altered cellular Ca^{2+} handling, delayed afterdepolarizations, and an increased susceptibility to ventricular arrhythmias during catecholaminergic surges [134].

Small Fiber Neuropathy

Mutations in the *SCN10A* gene encoding the α-subunit of $Na_V1.8$ have been implicated in small fiber neuropathy [135]. This neuronal Na^+ channel is mainly expressed in dorsal root ganglion neurons and peripheral nerve axons. RNA sequencing to evaluate the *SCN10A* expression in human heart showed extremely low transcript values, and the genotype-*SCN5A* expression correlations next to the physiological profiles of *SCN10A* knockout mice suggest its neglectable physiological impact on the heart [136]. Nevertheless, variants in *SCN10A* have been described in cardiac conduction disease and Brugada syndrome [137, 138]. This may result from the genomic modulation of functional variants in *SCN10A* on the transcription of *SCN5A*, a pivotal gene for cardiac conduction [136]. Rare variants in the *SCN10A* gene are not deemed responsible for a significant proportion of *SCN5A* mutation-negative Brugada syndrome patients, although a common SNP *SCN10A*-Val1073 (rs6795970) is strongly associated with Brugada syndrome [139].

Genetic Determinants of Inherited Arrhythmia Syndromes Susceptible to Autonomic Nervous System Triggering

The inherited arrhythmia syndromes represent a specific group of genetic diseases that affect ion channel subunits or ion channel-related proteins of the heart. These syndromes often share clinical presentations, including increased susceptibility to ventricular tachyarrhythmia and sudden cardiac arrest in the absence of structural abnormalities. The prevalence of inherited arrhythmia syndromes like LQTS, Brugada syndrome, and CPVT is estimated to be ~1:2,500 individuals [140]. Despite mounting insights into the mechanistic underpinnings of these syndromes, it remains challenging to accurately predict arrhythmia risk in affected individuals. Brisk alterations in autonomic tone during strenuous exercise and auditory stimuli or while asleep can precipitate arrhythmias.

Long QT Syndrome

LQTS is characterized by QT interval prolongation and the increased risk for developing TdP, potentially leading to SCD. Hitherto, mutations in 15 genes encoding cardiac ion channels or related proteins have been recognized. Most patients harbor genetic variants in the *KCNQ1* (30–35%, LQTS type 1), *KCNH2* (25–30%, LQTS type 2), and *SCN5A* (5–10%, LQTS type 3) genes. Mutations in the *KCNQ1* gene (LQTS1) generally result in a reduction of the adrenergic-sensitive I_{Ks} that fails to adequately shorten ventricular repolarization during increased sympathetic tone. Consequently, arrhythmia risk for LQTS1 patients is increased during instances with elevated sympathetic activity, such as during exercise [141]. A lower heart rate and a "relatively low" baroreflex sensitivity exert a protective role in LQTS1 patients (p.(Ala341Val)) [66]. In this founder population, individuals with a concurrent *ADRA2C*-del322–325 polymorphism or *ADRB1*-Arg389 homozygosity were more likely to have baroreflex-sensitivity values above the upper tertile (45 versus 8%, $P < 0.05$) and thus exhibit increased autonomic reactivity [66]. On the other hand, it is demonstrated that higher vagal responses after exercise constituted a higher arrhythmic risk in LQTS1 [17]. The role of autonomic nervous system variation in LQTS becomes even more complex when considering the heart rate variability analyses that demonstrated the protective influence of higher sympathetic control of the QT interval and reduced vagal control of the heart rate [142]. Asymptomatic LQTS1 mutation carriers are postulated to adapt their QT more swiftly to heart rate changes, for reasons that may lie in a more homogeneous ventricular repolarization prolongation during reduced vagal control of heart rate. Other groups have found heterogeneous sympathetic nerve sprouting [58] and enhanced posterolateral synaptic catecholamine concentration in patients with LQTS [143]. Moreover, as mentioned in the introduction of this chapter, cold-water swimming, a powerful co-activator of sympathetic and parasympathetic neurocardiac drive, is a feared trigger of deadly arrhythmias in patients with LQTS1 [47, 144]. LQTS2 patients have an impaired I_{Kr} leading to a prolonged QT interval. The risk of LQTS2-related arrhythmias is highest during physical exercise, auditory stimuli, or startling events [16]. In line with these observations, β-adrenergic receptor blockade is most effective in LQTS1 and (to a lesser extent) in LQTS2 [145, 146]. LQTS3 patients with a genetically increased late I_{Na} are generally at greatest arrhythmic risk during rest when sympathetic activity is expected to be low [16]. Despite this, it appears that particularly female LQTS3 patients treated with β-adrenergic receptor blockade are protected from cardiac events including syncope, aborted cardiac arrest, or LQTS-related SCD [147]. Interestingly, sympathetically related cardiac arrhythmias including TdP were found in a large founder population segregating the deletion of phenylalanine at position 1617 of the *SCN5A* gene [148]. These data allude to more complex autonomic susceptibility toward arrhythmias beyond the underlying genotype only. The striking antiarrhythmic properties of left cardiac sympathetic denervation for symptomatic LQTS patients support the arrhythmogenic proclivity of augmented sympathetic tone [149]. In case of a persistent arrhythmia burden, subsequent bilateral stellectomy may be beneficial.

Catecholaminergic Polymorphic Ventricular Tachycardia

CPVT is an inherited arrhythmia syndrome, mostly due to mutations in the *RYR2* gene (encoding the ryanodine receptor) and with an autosomal dominant inheritance pattern [150]. In rare cases, autosomal recessive mutations in the *CASQ2* gene (encoding calsequestrin 2) [151] or the triadin gene account for CPVT. Recently, compound heterozygosity has been described for mutations in *CASQ2* [152]. CPVT is characterized by abnormal Ca^{2+} handling due to a lowered threshold for release (*RYR2*) or insufficient Ca^{2+} storage capacity (*CASQ2*) [153]. β-Adrenergic stimulation further increases Ca^{2+} accumulation in the sarcoplasmic reticulum leading to regenerative Ca^{2+} release, delayed afterdepolarizations, ventricular

arrhythmias, and SCD. Patients with CPVT have normal baseline ECGs but develop bidirectional or polymorphic VT during stress or exercise in the absence of structural abnormalities. Cases of apparently idiopathic VF who were identified as carriers of *RYR2* mutations have also been described [154]. β-Adrenergic receptor blockers, flecainide, and left cardiac sympathetic denervation are the mainstay therapies in CPVT [155, 156]. Interestingly, leaky ryanodine channels in a mutant mice model led to a combined neurocardiac phenotype of spontaneous generalized tonic-clonic seizures and (independently occurring) ventricular arrhythmias [157].

Brugada Syndrome

Patients with the Brugada syndrome have a mutation in the *SCN5A* gene in ±25% of cases. The functional consequence is a loss of function of I_{Na}, which reflects on the ECG as an incomplete right bundle branch block with coved or saddleback-type ST-segment elevation and with T-wave negativity in the right precordial leads. Brugada patients are at risk of ventricular tachycardia, VF, and SCD. These arrhythmic events occur more frequently during sleep or at night [10]. Low sympathetic activity, high parasympathetic activity, bradycardia, increased transient outward current (I_{to}), and elevated body temperature predispose to arrhythmogenic deterioration [158]. Patients may have abnormal cardiac sympathetic innervation [159] and increased presynaptic catecholamine recycling [58], altering the sympathovagal balance. Moreover, reduced levels of norepinephrine were found in cardiac biopsies from Brugada patients [160], despite normal β-adrenergic receptor density [58]. A modulatory role for the vagal limb was suggested as exaggerated parasympathetic reactivity during baroreflex sensitivity testing predisposed to VF [65]. Finally, a specific *SCN5A* mutation located in a (β-adrenergic-dependent) PKA phosphorylation site showed impaired I_{Na} upregulation during catecholaminergic stimulation, next to an anticipated reduced basal I_{Na} [161]. Again, these data suggest a complex, potentially genotype-dependent susceptibility to arrhythmias during autonomic nervous system variations.

Takotsubo Cardiomyopathy

Acute stress-induced (takotsubo) cardiomyopathy exhibits a dramatic clinical presentation mimicking acute myocardial infarction with ventricular ballooning, and it is triggered by intense physical or emotional stress. If treated adequately, patients usually recover, although a mortality of 3–5% is recognized, mostly attributed to ventricular tachyarrhythmias, heart failure, cardiac rupture, or thromboembolic sequelae [162]. It has been suggested that exaggerated sympathetic stimulation results in a cardiotoxic discharge of circulating catecholamines (epinephrine, norepinephrine, and dopamine) [163]. However, other investigations could not confirm these findings [164]. It is therefore not clear if catecholamines are causative, a bystander phenomenon, or the result of takotsubo cardiomyopathy. A potential genetic predisposition for its development is likely as there are several reports of familial cases [165, 166], because it recurs in 5–10% of patients [167], and it is sometimes concomitant with rare genetic– syndromes [168, 169]. Animal models hint toward a role for the involvement of apically expressed β_2-adrenergic receptors [170]. Hitherto, small genetic studies focusing on polymorphisms of *ADRA2C* and *ADRB1* [171] failed to identify significant causative variants, although Vriz et al. [172] found that the *ADRB1*-Arg389 homozygous and *ARDB2*-Gln27Glu polymorphism were more prevalent in patients with takotsubo cardiomyopathy. In another study, a different distribution of the *GRK5*-L41Q polymorphism (rs17098707) was found [173]. Whole-exome sequencing for genes involved in catecholaminergic signaling identified malignant variants in 55 candidate genes and suggested a polygenic inheritance pattern [174]. A recent genome-wide analysis in takotsubo syndrome [175], however, did not show genome-wide significant signals, but was underpowered.

Sudden Cardiac Death in General Population

The contribution of rare genetic syndromes to the total burden of SCD in the general population is low, accounting for fewer than 5% of deaths [176]. Rare private mutations in ion channel and other arrhythmia genes increase the risks in families, which may contribute to SCD risk in the general population [177]. On the other hand, there is considerable interest in understanding the role of common genetic variation in SCD risk, but, despite major efforts, common variants in candidate arrhythmia genes could not be associated with SCD in the general population [178]. Common variants are expected to confer only a small increase in SCD risk individually, since they would otherwise be subject to strong negative selection. Rare variants or SNPs related to increased SCD risk reside in genes that regulate cardiac conduction [179–182] and repolarization [183, 184], but also in genes that modulate the sympathetic nervous system [74, 81, 86–88]. Other SCD-related genes implicated are related to thrombosis/atherogenesis [185], fatty acid metabolism [186], and the renin-angiotensin-aldosterone system [187], but fall outside of the scope of this chapter.

The *SCN5A*-Ser1102Tyr polymorphism is one of the first SNPs that was linked to SCD susceptibility [183]. It is present in 13% of African-American patients and increases the risk of SCD in this population [179, 183]. Also, it was found that *SCN5A* variants and mutations are associated with risk of SCD in Caucasian women [188]. In this study, a similar association was lacking in the male population. Another study investigated SNPs in a large population of SCD cases and identified two intronic variants, one in *KCNQ1* (rs2283222) and one in *SCN5A* (rs11720524) gene linked to arrhythmic death [184]. The homozygous CC genotype of this *SCN5A* rs11720524 was significantly associated with SCD in patients with chronic ischemic heart disease [189]. Likewise, the association of rs11720524 to patients with VF during a first ST-segment elevation infarction (GEVAMI cohort) was identified [190]. A different SNP in *SCN5A* (rs41312391) was found to be linked to increased risk of SCD in a Finnish population (risk allele A) [191]. This SNP and rs11708996, both on the *SCN5A* gene, however, were not associated with VF in the GEVAMI cohort [190]. The first genome-wide association study for ST-segment elevation myocardial infarction patients with VF before primary percutaneous coronary intervention (AGNES study) reported a significant association with VF at chromosome 21q21 (rs2824292), a locus harboring the *CXADR* gene [192]. This important signal could not be detected in the GEVAMI study [190] nor in a small case-control study [193]. Potential explanations could be altered gene-gene or gene-environment interactions or the lack of a homogenous phenotype. Finally, a meta-analysis of genome-wide association studies on predisposition of SCD including SCD cases and controls found a strong signal for SCD susceptibility at a locus on chromosome 2q24.2 (rs4665058, near the *BAZ2B* gene) [194]. However, this SNP was not associated with VF in the AGNES and GEVAMI cohorts [190, 192]. The common SNPs associated with SCD or VF all have small effect sizes on arrhythmia risk, which renders them unsuitable for clinical decision-making.

Various common variants in genes encoding proteins relevant for functioning of the autonomic nervous system have been associated with increased SCD risk. As has been described above, a genetic predisposition toward increased mortality (often in the setting of heart failure or acute ischemic heart disease) has been linked to polymorphisms residing in the *ADRA2B* [74], *ADRB1* [81], and *ADRB2* genes [86]. Besides altered adrenergic receptor activity, it was found that allelic variation in the *GNAS* gene encoding the downstream signaling of the stimulatory G-protein alpha-subunit ($G_{\alpha s}$) was associated with an increased arrhythmia risk in an ICD population [195]. Of the two *GNAS* SNPs (rs7121, rs12481583), one, rs7121 (c.393C > T), was subsequently replicated in a community-based population of SCD cases [195]. Others identified a genome-wide signal in the intronic region of the *RAB3GAP1* gene at rs6730157 on chromosome

2q21 in 948 SCD cases with underlying coronary artery disease [196]. *RAB3GAP1* encodes the catalytic subunit of the RabGTPase-activating protein that is involved in calcium-mediated hormone and neurotransmitter exocytosis. Interestingly, a protein similar to human RAB3GAP1 interacts with intracellular domains of *SCN10A* in the dorsal root ganglia [197].

Studies that incorporate the cumulative effect of different SNPs, as well as the influence of the "exposome" defined as the lifelong environmental influence that acts on the genetic substrate, have not yet been performed, and they represent the challenge for future advances. Perhaps a combined weighed genetic risk score such as developed by the CARDIoGRAMplusC4D consortium (GRSCAD) [198] for coronary artery disease could shed light on this problem. Both retrospective and prospective data demonstrated a strong association between the GRSCAD and occurrence of SCD.

Conclusion

The integrity of the neurocardiac axis is of paramount importance to maintain electrical and hemodynamic homeostasis in patients. Genetic determinants at different levels of this axis may render the heart more susceptible to autonomic tone variation or cause a primary inhomogeneous autonomic efferent output to provoke an arrhythmogenic response. The increasing availability of genetic testing pave the way to a deeper understanding of these genetic underpinnings that connect autonomics and sudden death.

References

1. Albert CM, Chae CU, Grodstein F, Rose LM, Rexrode KM, Ruskin JN, Stampfer MJ, Manson JE. Prospective study of sudden cardiac death among women in the United States. Circulation. 2003;107:2096–101.
2. Friedlander Y, Siscovick DS, Weinmann S, Austin MA, Psaty BM, Lemaitre RN, Arbogast P, Raghunathan TE, Cobb LA. Family history as a risk factor for primary cardiac arrest. Circulation. 1998;97:155–60.
3. Jouven X, Desnos M, Guerot C, Ducimetière P. Predicting sudden death in the population: the Paris Prospective Study I. Circulation. 1999;99:1978–183.
4. Dekker LR, Bezzina CR, Henriques JP, Tanck MW, Koch KT, Alings MW, Arnold AE, de Boer MJ, Gorgels AP, Michels HR, Verkerk A, Verheugt FW, Zijlstra F, Wilde AA. Familial sudden death is an important risk factor for primary ventricular fibrillation: a case-control study in acute myocardial infarction patients. Circulation. 2006;114:1140–5.
5. Kaikkonen KS, Kortelainen ML, Linna E, Huikuri HV. Family history and the risk of sudden cardiac death as a manifestation of an acute coronary event. Circulation. 2006;114:1462–7.
6. Callans DJ. Out-of-hospital cardiac arrest–the solution is shocking. N Engl J Med. 2004;351:632–4.
7. Deo R, Albert CM. Epidemiology and genetics of sudden cardiac death. Circulation. 2012;125:620–37.
8. Hulleman M, Berdowski J, de Groot JR, van Dessel PF, Borleffs CJ, Blom MT, Bardai A, de Cock CC, Tan HL, Tijssen JG, Koster RW. Implantable cardioverter-defibrillators have reduced the incidence of resuscitation for out-of-hospital cardiac arrest caused by lethal arrhythmias. Circulation. 2012;126:815–21.
9. Schwartz PJ, Priori SG. Sympathetic nervous system and cardiac arrhythmias. In: Zipes DP, Jalife J, editors. Cardiac electrophysiology from cell to bedside. Philadelphia: WB Saunders; 1990. p. 330–43.
10. Matsuo K, Kurita T, Inagaki M, Kakishita M, Aihara N, Shimizu W, Taguchi A, Suyama K, Kamakura S, Shimomura K. The circadian pattern of the development of ventricular fibrillation in patients with Brugada syndrome. Eur Heart J. 1999;20:465–70.
11. Schwartz PJ, La Rovere MT, Vanoli E. Autonomic nervous system and sudden cardiac death. Experimental basis and clinical observations for post-myocardial infarction risk stratification. Circulation. 1992;85:I77–91.
12. Muller JE, Ludmer PL, Willich SN, Tofler GH, Aylmer G, Klangos I, Stone PH. Circadian variation in the frequency of sudden cardiac death. Circulation. 1987;75:131–8.
13. Peters RW. Propranolol and the morning increase in sudden cardiac death: (the beta-blocker heart attack trial experience). Am J Cardiol. 1990;66:57G–9G.
14. Schwartz PJ. Cardiac sympathetic denervation to prevent life-threatening arrhythmias. Nat Rev Cardiol. 2014;11:346–53.
15. Moïse NS, Gilmour RF Jr, Riccio ML. An animal model of spontaneous arrhythmic death. J Cardiovasc Electrophysiol. 1997;8:98–103.
16. Schwartz PJ, Priori SG, Spazzolini C, Moss AJ, Vincent GM, Napolitano C, Denjoy I, Guicheney P, Breithardt G, Keating MT, Towbin JA, Beggs AH, Brink P, Wilde AA, Toivonen L, Zareba W, Robinson JL, Timothy KW, Corfield V,

Wattanasirichaigoon D, Corbett C, Haverkamp W, Schulze-Bahr E, Lehmann MH, Schwartz K, Coumel P, Bloise R. Genotype-phenotype correlation in the long-QT syndrome: gene-specific triggers for life-threatening arrhythmias. Circulation. 2001;103:89–95.

17. Crotti L, Spazzolini C, Porretta AP, Dagradi F, Taravelli E, Petracci B, Vicentini A, Pedrazzini M, La Rovere MT, Vanoli E, Goosen A, Heradien M, George AL Jr, Brink PA, Schwartz PJ. Vagal reflexes following an exercise stress test: a simple clinical tool for gene-specific risk stratification in the long QT syndrome. J Am Coll Cardiol. 2012;60:2515–24.
18. Ardell JL, Andresen MC, Armour JA, Billman GE, Chen PS, Foreman RD, Herring N, O'Leary DS, Sabbah HN, Schultz HD, Sunagawa K, Zucker IH. Translational neurocardiology: preclinical models and cardioneural integrative aspects. J Physiol. 2016;594:3877–909.
19. Foreman RD. Mechanisms of cardiac pain. Annu Rev Physiol. 1999;61:143–67.
20. Guyenet PG. The sympathetic control of blood pressure. Nat Rev Neurosci. 2006;7:335–46.
21. Norris JE, Foreman RD, Wurster RK. Responses of the canine heart to stimulation of the first five ventral thoracic roots. Am J Phys. 1974;227:9–12.
22. Norris JE, Lippincott D, Wurster RD. Responses of canine endocardium to stimulation of the upper thoracic roots. Am J Phys. 1977;233:H655–9.
23. Vaseghi M, Zhou W, Shi J, Ajijola OA, Hadaya J, Shivkumar K, Mahajan A. Sympathetic innervation of the anterior left ventricular wall by the right and left stellate ganglia. Heart Rhythm. 2012;9:1303–9.
24. Pauza DH, Skripka V, Pauziene N, Stropus R. Morphology, distribution, and variability of the epicardiac neural ganglionated subplexuses in the human heart. Anat Rec. 2000;259:353–82.
25. Ulphani JS, Cain JH, Inderyas F, Gordon D, Gikas PV, Shade G, Mayor D, Arora R, Kadish AH, Goldberger JJ. Quantitative analysis of parasympathetic innervation of the porcine heart. Heart Rhythm. 2010;7:1113–9.
26. Armour JA. Potential clinical relevance of the 'little brain' on the mammalian heart. Exp Physiol. 2008;93:165–76.
27. Ardell JL, Butler CK, Smith FM, Hopkins DA, Armour JA. Activity of in vivo atrial and ventricular neurons in chronically decentralized canine hearts. Am J Phys. 1991;260:H713–21.
28. Lands AM, Arnold A, McAuliff JP, Luduena FP, Brown TG Jr. Differentiation of receptor systems activated by sympathomimetic amines. Nature. 1967;214:597–8.
29. Brodde OE. Beta 1- and beta 2-adrenoceptors in the human heart: properties, function, and alterations in chronic heart failure. Pharmacol Rev. 1991;43:203–42.
30. Brodde OE. Beta-adrenoceptors in cardiac disease. Pharmacol Ther. 1993;60:405–30.
31. Rozec B, Erfanian M, Laurent K, Trochu JN, Gauthier C. Nebivolol, a vasodilating selective beta (1)-blocker, is a beta(3)-adrenoceptor agonist in the nonfailing transplanted human heart. J Am Coll Cardiol. 2009;53:1532–8.
32. Xiao RP, Zhu W, Zheng M, Cao C, Zhang Y, Lakatta EG, Han Q. Subtype-specific α1- and β-adrenoceptor signaling in the heart. Trends Pharmacol Sci. 2006;27:330–7.
33. Wang W, Zhu W, Wang S, Yang D, Crow MT, Xiao RP, Cheng H. Sustained beta1-adrenergic stimulation modulates cardiac contractility by Ca2+/calmodulin kinase signaling pathway. Circ Res. 2004;95:798–806.
34. Volders PG, Stengl M, van Opstal JM, Gerlach U, Spatjens RL, Beekman JD, Sipido KR, Vos MA. Probing the contribution of I_{Ks} to canine ventricular repolarization: key role for ß-adrenergic receptor stimulation. Circulation. 2003;107:2753–60.
35. Heijman J, Volders PG, Westra RL, Rudy Y. Local control of beta-adrenergic stimulation: effects on ventricular myocyte electrophysiology and Ca(2+)-transient. J Mol Cell Cardiol. 2011;50:863–71.
36. Xiao RP, Zhu W, Zheng M, Chakir K, Bond R, Lakatta EG, Cheng H. Subtype-specific beta-adrenoceptor signaling pathways in the heart and their potential clinical implications. Trends Pharmacol Sci. 2004;25:358–65.
37. Kathöfer S, Röckl K, Zhang W, Thomas D, Katus H, Kiehn J, Kreye V, Schoels W, Karle C. Human beta(3)-adrenoreceptors couple to KvLQT1/MinK potassium channels in Xenopus oocytes via protein kinase C phosphorylation of the KvLQT1 protein. Naunyn Schmiedeberg's Arch Pharmacol. 2003;368:119–26.
38. Li K, He H, Li C, Sirois P, Rouleau JL. Myocardial alpha1-adrenoceptor: inotropic effect and physiologic and pathologic implications. Life Sci. 1997;60:1305–18.
39. Starke K, Gothert M, Kilbinger H. Modulation of neurotransmitter release by presynaptic autoreceptors. Physiol Rev. 1989;69:864–989.
40. Hein L, Altman JD, Kobilka BK. Two functionally distinct alpha2-adrenergic receptors regulate sympathetic neurotransmission. Nature. 1999;402:181–4.
41. Brack KE, Patel VH, Coote JH, Ng GA. Nitric oxide mediates the vagal protective effect on ventricular fibrillation via effects on action potential duration restitution in the rabbit heart. J Physiol. 2007;583:695–704.
42. Brack KE, Patel VH, Mantravardi R, Coote JH, Ng GA. Direct evidence of nitric oxide release from neuronal nitric oxide synthase activation in the left ventricle as a result of cervical vagus nerve stimulation. J Physiol. 2009;587:3045–54.
43. Herring N, Golding S, Paterson DJ. Pre-synaptic NO-cGMP pathway modulates vagal control of heart rate in isolated adult Guinea pig atria. J Mol Cell Cardiol. 2000;32:1795–804.

44. Schwartz PJ, Snebold NG, Brown AM. Effects of unilateral cardiac sympathetic denervation on the ventricular fibrillation threshold. Am J Cardiol. 1976;37:1034–40.
45. Gallacher DJ, Van de Water A, van der Linde H, Hermans AN, Lu HR, Towart R, Volders PG. In vivo mechanisms precipitating torsades de pointes in a canine model of drug-induced long-QT1 syndrome. Cardiovasc Res. 2007;76:247–56.
46. Doytchinova A, Patel J, Zhou S, Chen LS, Lin H, Shen C, Everett TH, Lin SF, Chen PS. Subcutaneous nerve activity and spontaneous ventricular arrhythmias in ambulatory dogs. Heart Rhythm. 2015;12: 612–20.
47. ter Bekke RMA, Moers AME, de Jong MMJ, Johnson DM, Schwartz PJ, Vanoli E, Volders PGA. Proarrhythmic proclivity of left-stellate ganglion stimulation in a canine model of drug-induced long-QT syndrome type 1. Int J Cardiol. 2019;286:66–72.
48. Zhou S, Jung BC, Tan AY, Trang VQ, Gholmieh G, Han SW, Lin SF, Fishbein MC, Chen PS, Chen LS. Spontaneous stellate ganglion nerve activity and ventricular arrhythmia in a canine model of sudden death. Heart Rhythm. 2008;5:131–9.
49. Opthof T, Misier AR, Coronel R, Vermeulen JT, Verberne HJ, Frank RG, Moulijn AC, van Capelle FJ, Janse MJ. Dispersion of refractoriness in canine ventricular myocardium. Effects of sympathetic stimulation. Circ Res. 1991;68:1204–15.
50. Volders PG, Vos MA, Szabo B, Sipido KR, de Groot SH, Gorgels AP, Wellens HJ, Lazzara R. Progress in the understanding of cardiac early afterdepolarizations and torsades de pointes: time to revise current concepts. Cardiovasc Res. 2000;46:376–92.
51. Myles RC, Wang L, Kang C, Bers DM, Ripplinger CM. Local beta-adrenergic stimulation overcomes source-sink mismatch to generate focal arrhythmia. Circ Res. 2012;110:1454–64.
52. Ng GA, Brack KE, Patel VH, Coote JH. Autonomic modulation of electrical restitution, alternans and ventricular fibrillation initiation in the isolated heart. Cardiovasc Res. 2007;73:750–60.
53. Schwartz PJ, Stone HL, Brown AM. Effects of unilateral stellate ganglion blockade on the arrhythmias associated with coronary occlusion. Am Heart J. 1976;92:589–99.
54. Dae MW, Lee RJ, Ursell PC, Chin MC, Stillson CA, Moïse NS. Heterogeneous sympathetic innervation in German shepherd dogs with inherited ventricular arrhythmia and sudden cardiac death. Circulation. 1997;96:1337–42.
55. Cao JM, Fishbein MC, Han JB, Lai WW, Lai AC, Wu TJ, Czer L, Wolf PL, Denton TA, Shintaku IP, Chen PS, Chen LS. Relationship between regional cardiac hyperinnervation and ventricular arrhythmia. Circulation. 2000;101:1960–9.
56. Inoue H, Zipes DP. Results of sympathetic denervation in the canine heart: supersensitivity that may be arrhythmogenic. Circulation. 1987;75:877–87.
57. Reid DS, Tynan M, Braidwood L, Fitzgerald GR. Bidirectional tachycardia in a child. A study using His bundle electrography. Br Heart J. 1975;37: 339–44.
58. Kies P, Paul M, Gerss J, Stegger L, Mönnig G, Schober O, Wichter T, Schäfers M, Schulze-Bahr E. Impaired cardiac sympathetic innervation in symptomatic patients with long QT syndrome. Eur J Nucl Med Mol Imaging. 2011;38:1899–907.
59. Schwartz PJ, Vanoli E, Stramba-Badiale M, De Ferrari GM, Billman GE, Foreman RD. Autonomic mechanisms and sudden death. New insights from analysis of baroreceptor reflexes in conscious dogs with and without a myocardial infarction. Circulation. 1988;78:969–79.
60. De Ferrari GM, Vanoli E, Stramba-Badiale M, Hull SS Jr, Foreman RD, Schwartz PJ. Vagal reflexes and survival during acute myocardial ischemia in conscious dogs with healed myocardial infarction. Am J Phys. 1991;261:H63–9.
61. Martins JB, Zipes DP. Effects of sympathetic and vagal nerves on recovery properties of the endocardium and epicardium of the canine left ventricle. Circ Res. 1980;46:100–10.
62. Naggar I, Nakase K, Lazar J, Salciccioli L, Selesnick I, Stewart M. Vagal control of cardiac electrical activity and wall motion during ventricular fibrillation in large animals. Auton Neurosci. 2014;183:12–22.
63. Gold MR, Van Veldhuisen DJ, Hauptman PJ, Borggrefe M, Kubo SH, Lieberman RA, Milasinovic G, Berman BJ, Djordjevic S, Neelagaru S, Schwartz PJ, Starling RC, Mann DL. Vagus nerve stimulation for the treatment of heart failure: the INOVATE-HF trial. J Am Coll Cardiol. 2016;68:149–58.
64. Zannad F, De Ferrari GM, Tuinenburg AE, Wright D, Brugada J, Butter C, Klein H, Stolen C, Meyer S, Stein KM, Ramuzat A, Schubert B, Daum D, Neuzil P, Botman C, Castel MA, D'Onofrio A, Solomon SD, Wold N, Ruble SB. Chronic vagal stimulation for the treatment of low ejection fraction heart failure: results of the NEural Cardiac TherApy foR Heart Failure (NECTAR-HF) randomized controlled trial. Eur Heart J. 2015;36:425–33.
65. Shinohara T, Kondo H, Otsubo T, Fukui A, Yufu K, Nakagawa M, Takahashi N. Exaggerated reactivity of parasympathetic nerves is involved in ventricular fibrillation in J-wave syndrome. J Cardiovasc Electrophysiol. 2017;28:321–6.
66. Schwartz PJ, Vanoli E, Crotti L, Spazzolini C, Ferrandi C, Goosen A, Hedley P, Heradien M, Bacchini S, Turco A, La Rovere MT, Bartoli A, George AL Jr, Brink PA. Neural control of heart rate is an arrhythmia risk modifier in long QT syndrome. J Am Coll Cardiol. 2008;51:920–9.
67. Shattock MJ, Tipton MJ. 'Autonomic conflict': a different way to die during cold water immersion? J Physiol. 2012;590:3219–30.
68. Lorentz CU, Alston EN, Belcik T, Lindner JR, Giraud GD, Habecker BA. Heterogeneous ventricular

sympathetic innervation, altered beta-adrenergic receptor expression, and rhythm instability in mice lacking the p75 neurotrophin receptor. Am J Physiol Heart Circ Physiol. 2010;298:H1652–60.
69. Cao JM, Chen LS, KenKnight BH, Ohara T, Lee MH, Tsai J, Lai WW, Karagueuzian HS, Wolf PL, Fishbein MC, Chen PS. Nerve sprouting and sudden cardiac death. Circ Res. 2000;86: 816–21.
70. Tanelian DL, Barry MA, Johnston SA, Le T, Smith GM. Semaphorin III can repulse and inhibit adult sensory afferents in vivo. Nat Med. 1997;3: 1398–401.
71. Ieda M, Kanazawa H, Kimura K, Hattori F, Ieda Y, Taniguchi M, Lee JK, Matsumura K, Tomita Y, Miyoshi S, Shimoda K, Makino S, Sano M, Kodama I, Ogawa S, Fukuda K. *Sema3a* maintains normal heart rhythm through sympathetic innervation patterning. Nat Med. 2007;13:604–12.
72. Kimura K, Ieda M, Fukuda K. Development, maturation, and transdifferentiation of cardiac sympathetic nerves. Circ Res. 2012;110:325–36.
73. Nakano Y, Chayama K, Ochi H, Toshishige M, Hayashida Y, Miki D, Hayes CN, Suzuki H, Tokuyama T, Oda N, Suenari K, Uchimura-Makita Y, Kajihara K, Sairaku A, Motoda C, Fujiwara M, Watanabe Y, Yoshida Y, Ohkubo K, Watanabe I, Nogami A, Hasegawa K, Watanabe H, Endo N, Aiba T, Shimizu W, Ohno S, Horie M, Arihiro K, Tashiro S, Makita N, Kihara Y. A nonsynonymous polymorphism in semaphorin 3A as a risk factor for human unexplained cardiac arrest with documented ventricular fibrillation. PLoS Genet. 2013;9: e1003364.
74. Snapir A, Mikkelsson J, Perola M, Penttila A, Scheinin M, Karhunen PJ. Variation in the alpha2B-adrenoceptor gene as a risk factor for prehospital fatal myocardial infarction and sudden cardiac death. J Am Coll Cardiol. 2003;41:190–4.
75. Small KM, Wagoner LE, Levin AM, Kardia SL, Liggett SB. Synergistic polymorphisms of beta1- and alpha2C-adrenergic receptors and the risk of congestive heart failure. N Engl J Med. 2002;347:1135–42.
76. O'Connor CM, Fiuzat M, Carson PE, Anand IS, Plehn JF, Gottlieb SS, Silver MA, Lindenfeld J, Miller AB, White M, Walsh R, Nelson P, Medway A, Davis G, Robertson AD, Port JD, Carr J, Murphy GA, Lazzeroni LC, Abraham WT, Liggett SB, Bristow MR. Combinatorial pharmacogenetic interactions of bucindolol and beta1, alpha2C adrenergic receptor polymorphisms. PLoS One. 2012;7: e44324.
77. Levin MC, Marullo S, Muntaner O, Andersson B, Magnusson Y. The myocardium-protective Gly-49 variant of the beta 1-adrenergic receptor exhibits constitutive activity and increased desensitization and down-regulation. J Biol Chem. 2002;277: 30429–3035.
78. Börjesson M, Magnusson Y, Hjalmarson A, Andersson B. A novel polymorphism in the gene coding for the beta(1)-adrenergic receptor associated with survival in patients with heart failure. Eur Heart J. 2000;21:1853–8.
79. Terra SG, Hamilton KK, Pauly DF, Lee CR, Patterson JH, Adams KF, Schofield RS, Belgado BS, Hill JA, Aranda JM, Yarandi HN, Johnson JA. Beta1-adrenergic receptor polymorphisms and left ventricular remodeling changes in response to beta-blocker therapy. Pharmacogenet Genomics. 2005;15:227–34.
80. Magnusson Y, Levin MC, Eggertsen R, Nyström E, Mobini R, Schaufelberger M, Andersson B. Ser49Gly of beta1-adrenergic receptor is associated with effective beta-blocker dose in dilated cardiomyopathy. Clin Pharmacol Ther. 2005;78: 221–31.
81. Iwai C, Akita H, Shiga N, Takai E, Miyamoto Y, Shimizu M, Kawai H, Takarada A, Kajiya T, Yokoyama M. Suppressive effect of the Gly389 allele of the beta1-adrenergic receptor gene on the occurrence of ventricular tachycardia in dilated cardiomyopathy. Circ J. 2002;66:723–8.
82. Biolo A, Clausell N, Santos KG, Salvaro R, Ashton-Prolla P, Borges A, Rohde LE. Impact of beta1-adrenergic receptor polymorphisms on susceptibility to heart failure, arrhythmogenesis, prognosis, and response to beta-blocker therapy. Am J Cardiol. 2008;102:726–32.
83. Liggett SB, Mialet-Perez J, Thaneemit-Chen S, Weber SA, Greene SM, Hodne D, Nelson B, Morrison J, Domanski MJ, Wagoner LE, Abraham WT, Anderson JL, Carlquist JF, Krause-Steinrauf HJ, Lazzeroni LC, Port JD, Lavori PW, Bristow MR. A polymorphism within a conserved beta(1)-adrenergic receptor motif alters cardiac function and beta-blocker response in human heart failure. Proc Natl Acad Sci U S A. 2006;103:11288–93.
84. Mason DA, Moore JD, Green SA, Liggett SB. A gain-of-function polymorphism in a G-protein coupling domain of the human beta1-adrenergic receptor. J Biol Chem. 1999;274:12670–4.
85. Tseng ZH, Aouizerat BE, Pawlikowska L, Vittinghoff E, Lin F, Whiteman D, Poon A, Herrington D, Howard TD, Varosy PD, Hulley SB, Malloy M, Kane J, Kwok PY, Olgin JE. Common beta-adrenergic receptor polymorphisms are not associated with risk of sudden cardiac death in patients with coronary artery disease. Heart Rhythm. 2008;5:814–21.
86. Lanfear DE, Jones PG, Marsh S, Cresci S, McLeod HL, Spertus JA. Beta2-adrenergic receptor genotype and survival among patients receiving beta-blocker therapy after an acute coronary syndrome. JAMA. 2005;294:1526–33.
87. Sotoodehnia N, Siscovick DS, Vatta M, Psaty BM, Tracy RP, Towbin JA, Lemaitre RN, Rea TD, Durda JP, Chang JM, Lumley TS, Kuller LH, Burke GL, Heckbert SR. Beta2-adrenergic receptor

genetic variants and risk of sudden cardiac death. Circulation. 2006;113:1842–8.
88. Gavin MC, Newton-Cheh C, Gaziano JM, Cook NR, VanDenburgh M, Albert CM. A common variant in the beta2-adrenergic receptor and risk of sudden cardiac death. Heart Rhythm. 2011;8:704–10.
89. Green SA, Turki J, Innis M, Liggett SB. Amino-terminal polymorphisms of the human beta 2-adrenergic receptor impart distinct agonist-promoted regulatory properties. Biochemistry. 1994;33:9414–9.
90. Moon RY, Horne RS, Hauck FR. Sudden infant death syndrome. Lancet. 2007;370:1578–87.
91. Guntheroth WG, Lohmann R, Spiers PS. Risk of sudden infant death syndrome in subsequent siblings. J Pediatr. 1990;116:520–4.
92. Tester DJ, Ackerman MJ. Sudden infant death syndrome: how significant are the cardiac channelopathies? Cardiovasc Res. 2005;67:388–96.
93. Paterson DS, Trachtenberg FL, Thompson EG, Belliveau RA, Beggs AH, Darnall R, Chadwick AE, Krous HF, Kinney HC. Multiple serotonergic brainstem abnormalities in sudden infant death syndrome. JAMA. 2006;296:2124–32.
94. Narita N, Narita M, Takashima S, Nakayama M, Nagai T, Okado N. Serotonin transporter gene variation is a risk factor for sudden infant death syndrome in the Japanese population. Pediatrics. 2001;107:690–2.
95. Weese-Mayer DE, Zhou L, Berry-Kravis EM, Maher BS, Silvestri JM, Marazita ML. Association of the serotonin transporter gene with sudden infant death syndrome: a haplotype analysis. Am J Med Genet A. 2003;122A:238–45.
96. Weese-Mayer DE, Berry-Kravis EM, Maher BS, Silvestri JM, Curran ME, Marazita ML. Sudden infant death syndrome: association with a promoter polymorphism of the serotonin transporter gene. Am J Med Genet A. 2003;117A:268–74.
97. Haas C, Braun J, Bar W, Bartsch C. No association of serotonin transporter gene variation with sudden infant death syndrome (SIDS) in Caucasians. Leg Med (Tokyo). 2009;11(Suppl 1):S210–2.
98. Paterson DS, Rivera KD, Broadbelt KG, Trachtenberg FL, Belliveau RA, Holm IA, Haas EA, Stanley C, Krous HF, Kinney HC, Markianos K. Lack of association of the serotonin transporter polymorphism with the sudden infant death syndrome in the San Diego Dataset. Pediatr Res. 2010;68:409–13.
99. Rand CM, Berry-Kravis EM, Zhou L, Fan W, Weese-Mayer DE. Sudden infant death syndrome: rare mutation in the serotonin system FEV gene. Pediatr Res. 2007;62:180–2.
100. Weese-Mayer DE, Berry-Kravis EM, Zhou L, Maher BS, Curran ME, Silvestri JM, Marazita ML. Sudden infant death syndrome: case-control frequency differences at genes pertinent to early autonomic nervous system embryologic development. Pediatr Res. 2004;56:391–5.
101. Schwartz PJ, Stramba-Badiale M, Segantini A, Austoni P, Bosi G, Giorgetti R, Grancini F, Marni ED, Perticone F, Rosti D, Salice P. Prolongation of the QT interval and the sudden infant death syndrome. N Engl J Med. 1998;338:1709–14.
102. Wilders R. Cardiac ion channelopathies and the sudden infant death syndrome. ISRN Cardiol. 2012;2012:846171.
103. Van Norstrand DW, Ackerman MJ. Sudden infant death syndrome: do ion channels play a role? Heart Rhythm. 2009;6:272–8.
104. Cronk LB, Ye B, Kaku T, Tester DJ, Vatta M, Makielski JC, Ackerman MJ. Novel mechanism for sudden infant death syndrome: persistent late sodium current secondary to mutations in caveolin-3. Heart Rhythm. 2007;4:161–6.
105. Van Norstrand DW, Valdivia CR, Tester DJ, Ueda K, London B, Makielski JC, Ackerman MJ. Molecular and functional characterization of novel glycerol-3-phosphate dehydrogenase 1 like gene (GPD1-L) mutations in sudden infant death syndrome. Circulation. 2007;116:2253–9.
106. Rhodes TE, Abraham RL, Welch RC, Vanoye CG, Crotti L, Arnestad M, Insolia R, Pedrazzini M, Ferrandi C, Vege A, Rognum T, Roden DM, Schwartz PJ, George AL Jr. Cardiac potassium channel dysfunction in sudden infant death syndrome. J Mol Cell Cardiol. 2008;44:571–81.
107. Tester DJ, Dura M, Carturan E, Reiken S, Wronska A, Marks AR, Ackerman MJ. A mechanism for sudden infant death syndrome (SIDS): stress-induced leak via ryanodine receptors. Heart Rhythm. 2007;4:733–9.
108. Arnestad M, Crotti L, Rognum TO, Insolia R, Pedrazzini M, Ferrandi C, Vege A, Wang DW, Rhodes TE, George AL Jr, Schwartz PJ. Prevalence of long-QT syndrome gene variants in sudden infant death syndrome. Circulation. 2007;115:361–7.
109. Ackerman MJ, Siu BL, Sturner WQ, Tester DJ, Valdivia CR, Makielski JC, Towbin JA. Postmortem molecular analysis of SCN5A defects in sudden infant death syndrome. JAMA. 2001;286:2264–9.
110. Tan BH, Pundi KN, Van Norstrand DW, Valdivia CR, Tester DJ, Medeiros-Domingo A, Makielski JC, Ackerman MJ. Sudden infant death syndrome-associated mutations in the sodium channel beta subunits. Heart Rhythm. 2010;7:771–8.
111. Cheng J, Van Norstrand DW, Medeiros-Domingo A, Valdivia C, Tan BH, Ye B, Kroboth S, Vatta M, Tester DJ, January CT, Makielski JC, Ackerman MJ. Alpha1-syntrophin mutations identified in sudden infant death syndrome cause an increase in late cardiac sodium current. Circ Arrhythm Electrophysiol. 2009;2:667–76.
112. Coll M, Striano P, Ferrer-Costa C, Campuzano O, Mates J, Del Olmo B, Iglesias A, Perez-Serra A, Mademont I, Pico F, Oliva A, Brugada R. Targeted next-generation sequencing provides novel clues for associated epilepsy and cardiac conduction disorder/SUDEP. PLoS One. 2017;12:e0189618.

113. Ravindran K, Powell KL, Todaro M, O'Brien TJ. The pathophysiology of cardiac dysfunction in epilepsy. Epilepsy Res. 2016;127:19–29.
114. Powell KL, Jones NC, Kennard JT, Ng C, Urmaliya V, Lau S, Tran A, Zheng T, Ozturk E, Dezsi G, Megatia I, Delbridge LM, Pinault D, Reid CA, White PJ, O'Brien TJ. HCN channelopathy and cardiac electrophysiologic dysfunction in genetic and acquired rat epilepsy models. Epilepsia. 2014;55:609–20.
115. Neufeld G, Lazar JM, Chari G, Kamran H, Akajagbor E, Salciccioli L, Kassotis J, Stewart M. Cardiac repolarization indices in epilepsy patients. Cardiology. 2009;114:255–60.
116. Krishnan V, Krishnamurthy KB. Interictal 12-lead electrocardiography in patients with epilepsy. Epilepsy Behav. 2013;29:240–6.
117. Brotherstone R, Blackhall B, McLellan A. Lengthening of corrected QT during epileptic seizures. Epilepsia. 2010;51:221–32.
118. Surges R, Thijs RD, Tan HL, Sander JW. Sudden unexpected death in epilepsy: risk factors and potential pathomechanisms. Nat Rev Neurol. 2009;5:492–504.
119. Druschky A, Hilz MJ, Hopp P, Platsch G, Radespiel-Troger M, Druschky K, Kuwert T, Stefan H, Neundorfer B. Interictal cardiac autonomic dysfunction in temporal lobe epilepsy demonstrated by [(123)I]metaiodobenzylguanidine-SPECT. Brain. 2001;124:2372–82.
120. Tu E, Bagnall RD, Duflou J, Semsarian C. Post-mortem review and genetic analysis of sudden unexpected death in epilepsy (SUDEP) cases. Brain Pathol. 2011;21:201–8.
121. Ueda K, Nakamura K, Hayashi T, Inagaki N, Takahashi M, Arimura T, Morita H, Higashiuesato Y, Hirano Y, Yasunami M, Takishita S, Yamashina A, Ohe T, Sunamori M, Hiraoka M, Kimura A. Functional characterization of a trafficking-defective HCN4 mutation, D553N, associated with cardiac arrhythmia. J Biol Chem. 2004;279:27194–8.
122. Ludwig A, Budde T, Stieber J, Moosmang S, Wahl C, Holthoff K, Langebartels A, Wotjak C, Munsch T, Zong X, Feil S, Feil R, Lancel M, Chien KR, Konnerth A, Pape HC, Biel M, Hofmann F. Absence epilepsy and sinus dysrhythmia in mice lacking the pacemaker channel HCN2. EMBO J. 2003;22:216–24.
123. Moore BM, Jerry Jou C, Tatalovic M, Kaufman ES, Kline DD, Kunze DL. The Kv1.1 null mouse, a model of sudden unexpected death in epilepsy (SUDEP). Epilepsia. 2014;55:1808–16.
124. Goldman AM, Glasscock E, Yoo J, Chen TT, Klassen TL, Noebels JL. Arrhythmia in heart and brain: KCNQ1 mutations link epilepsy and sudden unexplained death. Sci Transl Med. 2009;1:2ra6.
125. Goldenberg I, Moss AJ. Long QT syndrome. J Am Coll Cardiol. 2008;51:2291–300.
126. Zamorano-Leon JJ, Yanez R, Jaime G, Rodriguez-Sierra P, Calatrava-Ledrado L, Alvarez-Granada RR, Mateos-Caceres PJ, Macaya C, Lopez-Farre AJ. KCNH2 gene mutation: a potential link between epilepsy and long QT-2 syndrome. J Neurogenet. 2012;26:382–6.
127. Partemi S, Cestele S, Pezzella M, Campuzano O, Paravidino R, Pascali VL, Zara F, Tassinari CA, Striano S, Oliva A, Brugada R, Mantegazza M, Striano P. Loss-of-function KCNH2 mutation in a family with long QT syndrome, epilepsy, and sudden death. Epilepsia. 2013;54:e112–6.
128. Haugaa KH, Vestervik TT, Andersson S, Amlie JP, Jorum E, Gjerstad L, Tauboll E. Abnormal electroencephalograms in patients with long QT syndrome. Heart Rhythm. 2013;10:1877–83.
129. Jansen FE, Sadleir LG, Harkin LA, Vadlamudi L, McMahon JM, Mulley JC, Scheffer IE, Berkovic SF. Severe myoclonic epilepsy of infancy (Dravet syndrome): recognition and diagnosis in adults. Neurology. 2006;67:2224–6.
130. Biet M, Morin N, Lessard-Beaudoin M, Graham RK, Duss S, Gagne J, Sanon NT, Carmant L, Dumaine R. Prolongation of action potential duration and QT interval during epilepsy linked to increased contribution of neuronal sodium channels to cardiac late Na+ current: potential mechanism for sudden death in epilepsy. Circ Arrhythm Electrophysiol. 2015;8:912–20.
131. Parisi P, Oliva A, Coll Vidal M, Partemi S, Campuzano O, Iglesias A, Pisani D, Pascali VL, Paolino MC, Villa MP, Zara F, Tassinari CA, Striano P, Brugada R. Coexistence of epilepsy and Brugada syndrome in a family with SCN5A mutation. Epilepsy Res. 2013;105:415–8.
132. Aurlien D, Leren TP, Tauboll E, Gjerstad L. New SCN5A mutation in a SUDEP victim with idiopathic epilepsy. Seizure. 2009;18:158–60.
133. Veeramah KR, O'Brien JE, Meisler MH, Cheng X, Dib-Hajj SD, Waxman SG, Talwar D, Girirajan S, Eichler EE, Restifo LL, Erickson RP, Hammer MF. De novo pathogenic SCN8A mutation identified by whole-genome sequencing of a family quartet affected by infantile epileptic encephalopathy and SUDEP. Am J Hum Genet. 2012;90:502–10.
134. Frasier CR, Wagnon JL, Bao YO, McVeigh LG, Lopez-Santiago LF, Meisler MH, Isom LL. Cardiac arrhythmia in a mouse model of sodium channel SCN8A epileptic encephalopathy. Proc Natl Acad Sci U S A. 2016;113:12838–43.
135. Faber CG, Lauria G, Merkies IS, Cheng X, Han C, Ahn HS, Persson AK, Hoeijmakers JG, Gerrits MM, Pierro T, Lombardi R, Kapetis D, Dib-Hajj SD, Waxman SG. Gain-of-function Nav1.8 mutations in painful neuropathy. Proc Natl Acad Sci U S A. 2012;109:19444–9.
136. van den Boogaard M, Smemo S, Burnicka-Turek O, Arnolds DE, van de Werken HJ, Klous P, McKean D, Muehlschlegel JD, Moosmann J, Toka O, Yang XH, Koopmann TT, Adriaens ME, Bezzina CR, de Laat W, Seidman C, Seidman JG, Christoffels VM,

Nobrega MA, Barnett P, Moskowitz IP. A common genetic variant within SCN10A modulates cardiac SCN5A expression. J Clin Invest. 2014;124: 1844–52.

137. Bezzina CR, Barc J, Mizusawa Y, Remme CA, Gourraud JB, Simonet F, Verkerk AO, Schwartz PJ, Crotti L, Dagradi F, Guicheney P, Fressart V, Leenhardt A, Antzelevitch C, Bartkowiak S, Borggrefe M, Schimpf R, Schulze-Bahr E, Zumhagen S, Behr ER, Bastiaenen R, Tfelt-Hansen J, Olesen MS, Kääb S, Beckmann BM, Weeke P, Watanabe H, Endo N, Minamino T, Horie M, Ohno S, Hasegawa K, Makita N, Nogami A, Shimizu W, Aiba T, Froguel P, Balkau B, Lantieri O, Torchio M, Wiese C, Weber D, Wolswinkel R, Coronel R, Boukens BJ, Bézieau S, Charpentier E, Chatel S, Despres A, Gros F, Kyndt F, Lecointe S, Lindenbaum P, Portero V, Violleau J, Gessler M, Tan HL, Roden DM, Christoffels VM, Le Marec H, Wilde AA, Probst V, Schott JJ, Dina C, Redon R. Common variants at SCN5A-SCN10A and HEY2 are associated with Brugada syndrome, a rare disease with high risk of sudden cardiac death. Nat Genet. 2013;45:1044–9.
138. Hu D, Barajas-Martinez H, Pfeiffer R, Dezi F, Pfeiffer J, Buch T, Betzenhauser MJ, Belardinelli L, Kahlig KM, Rajamani S, DeAntonio HJ, Myerburg RJ, Ito H, Deshmukh P, Marieb M, Nam GB, Bhatia A, Hasdemir C, Haissaguerre M, Veltmann C, Schimpf R, Borggrefe M, Viskin S, Antzelevitch C. Mutations in SCN10A are responsible for a large fraction of cases of Brugada syndrome. J Am Coll Cardiol. 2014;64:66–79.
139. Behr ER, Savio-Galimberti E, Barc J, Holst AG, Petropoulou E, Prins BP, Jabbari J, Torchio M, Berthet M, Mizusawa Y, Yang T, Nannenberg EA, Dagradi F, Weeke P, Bastiaenan R, Ackerman MJ, Haunso S, Leenhardt A, Kaab S, Probst V, Redon R, Sharma S, Wilde A, Tfelt-Hansen J, Schwartz P, Roden DM, Bezzina CR, Olesen M, Darbar D, Guicheney P. Role of common and rare variants in SCN10A: results from the Brugada syndrome QRS locus gene discovery collaborative study. Cardiovasc Res. 2015;106:520–9.
140. Kaltman JR, Thompson PD, Lantos J, Berul CI, Botkin J, Cohen JT, Cook NR, Corrado D, Drezner J, Frick KD, Goldman S, Hlatky M, Kannankeril PJ, Leslie L, Priori S, Saul JP, Shapiro-Mendoza CK, Siscovick D, Vetter VL, Boineau R, Burns KM, Friedman RA. Screening for sudden cardiac death in the young: report from a national heart, lung, and blood institute working group. Circulation. 2011;123:1911–8.
141. Moss AJ, Shimizu W, Wilde AA, Towbin JA, Zareba W, Robinson JL, Qi M, Vincent GM, Ackerman MJ, Kaufman ES, Hofman N, Seth R, Kamakura S, Miyamoto Y, Goldenberg I, Andrews ML, McNitt S. Clinical aspects of type-1 long-QT syndrome by location, coding type, and biophysical function of mutations involving the KCNQ1 gene. Circulation. 2007;115:2481–9.
142. Porta A, Girardengo G, Bari V, George AL Jr, Brink PA, Goosen A, Crotti L, Schwartz PJ. Autonomic control of heart rate and QT interval variability influences arrhythmic risk in long QT syndrome type 1. J Am Coll Cardiol. 2015;65:367–74.
143. Zumhagen S, Vrachimis A, Stegger L, Kies P, Wenning C, Ernsting M, Muller J, Seebohm G, Paul M, Schafers K, Stallmeyer B, Schafers M, Schulze-Bahr E. Impact of presynaptic sympathetic imbalance in long-QT syndrome by positron emission tomography. Heart. 2018;104:332–9.
144. Ackerman MJ, Tester DJ, Porter CJ. Swimming, a gene-specific arrhythmogenic trigger for inherited long QT syndrome. Mayo Clin Proc. 1999;74:1088–94.
145. Shimizu W, Antzelevitch C. Differential effects of beta-adrenergic agonists and antagonists in LQT1, LQT2 and LQT3 models of the long QT syndrome. J Am Coll Cardiol. 2000;35:778–86.
146. Priori SG, Napolitano C, Schwartz PJ, Grillo M, Bloise R, Ronchetti E, Moncalvo C, Tulipani C, Veia A, Bottelli G, Nastoli J. Association of long QT syndrome loci and cardiac events among patients treated with beta-blockers. JAMA. 2004;292:1341–4.
147. Wilde AA, Moss AJ, Kaufman ES, Shimizu W, Peterson DR, Benhorin J, Lopes C, Towbin JA, Spazzolini C, Crotti L, Zareba W, Goldenberg I, Kanters JK, Robinson JL, Qi M, Hofman N, Tester DJ, Bezzina CR, Alders M, Aiba T, Kamakura S, Miyamoto Y, Andrews ML, McNitt S, Polonsky B, Schwartz PJ, Ackerman MJ. Clinical aspects of type 3 long-QT syndrome: an international multicenter study. Circulation. 2016;134:872–82.
148. ter Bekke RMA, Isaacs A, Barysenka A, Hoos MB, Jongbloed JDH, Hoorntje JCA, Patelski ASM, Helderman-van den Enden A, van den Wijngaard A, Stoll M, Volders PGA. Heritability in a SCN5A-mutation founder population with increased female susceptibility to non-nocturnal ventricular tachyarrhythmia and sudden cardiac death. Heart Rhythm. 2017;14:1873–81.
149. Moss AJ, McDonald J. Unilateral cervicothoracic sympathetic ganglionectomy for the treatment of long QT interval syndrome. N Engl J Med. 1971;285:903–4.
150. Behere SP, Weindling SN. Catecholaminergic polymorphic ventricular tachycardia: an exciting new era. Ann Pediatr Cardiol. 2016;9:137–46.
151. Lahat H, Pras E, Olender T, Avidan N, Ben-Asher E, Man O, Levy-Nissenbaum E, Khoury A, Lorber A, Goldman B, Lancet D, Eldar M. A missense mutation in a highly conserved region of *CASQ2* is associated with autosomal recessive catecholamine-induced polymorphic ventricular tachycardia in Bedouin families from Israel. Am J Hum Genet. 2001;69:1378–84.
152. Josephs K, Patel K, Janson CM, Montagna C, McDonald TV. Compound heterozygous CASQ2 mutations and long-term course of catecholaminergic

polymorphic ventricular tachycardia. Mol Genet Genomic Med. 2017;5:788–94.
153. Priori SG, Chen SR. Inherited dysfunction of sarcoplasmic reticulum Ca2+ handling and arrhythmogenesis. Circ Res. 2011;108:871–83.
154. Paech C, Gebauer RA, Karstedt J, Marschall C, Bollmann A, Husser D. Ryanodine receptor mutations presenting as idiopathic ventricular fibrillation: a report on two novel familial compound mutations, c.6224T>C and c.13781A>G, with the clinical presentation of idiopathic ventricular fibrillation. Pediatr Cardiol. 2014;35:1437–41.
155. van der Werf C, Zwinderman AH, Wilde AA. Therapeutic approach for patients with catecholaminergic polymorphic ventricular tachycardia: state of the art and future developments. Europace. 2012;14:175–83.
156. Watanabe H, Chopra N, Laver D, Hwang HS, Davies SS, Roach DE, Duff HJ, Roden DM, Wilde AA, Knollmann BC. Flecainide prevents catecholaminergic polymorphic ventricular tachycardia in mice and humans. Nat Med. 2009;15:380–3.
157. Lehnart SE, Mongillo M, Bellinger A, Lindegger N, Chen BX, Hsueh W, Reiken S, Wronska A, Drew LJ, Ward CW, Lederer WJ, Kass RS, Morley G, Marks AR. Leaky Ca2+ release channel/ryanodine receptor 2 causes seizures and sudden cardiac death in mice. J Clin Invest. 2008;118:2230–45.
158. Morita H, Zipes DP, Wu J. Brugada syndrome: insights of ST elevation, arrhythmogenicity, and risk stratification from experimental observations. Heart Rhythm. 2009;6:S34–43.
159. Wichter T, Matheja P, Eckardt L, Kies P, Schafers K, Schulze-Bahr E, Haverkamp W, Borggrefe M, Schober O, Breithardt G, Schafers M. Cardiac autonomic dysfunction in Brugada syndrome. Circulation. 2002;105:702–6.
160. Paul M, Meyborg M, Boknik P, Gergs U, Schmitz W, Breithardt G, Wichter T, Neumann J. Autonomic dysfunction in patients with Brugada syndrome: further biochemical evidence of altered signaling pathways. Pacing Clin Electrophysiol. 2011;34:1147–53.
161. Aiba T, Farinelli F, Kostecki G, Hesketh GG, Edwards D, Biswas S, Tung L, Tomaselli GF. A mutation causing Brugada syndrome identifies a mechanism for altered autonomic and oxidant regulation of cardiac sodium currents. Circ Cardiovasc Genet. 2014;7:249–56.
162. Sharkey SW, Windenburg DC, Lesser JR, Maron MS, Hauser RG, Lesser JN, Haas TS, Hodges JS, Maron BJ. Natural history and expansive clinical profile of stress (tako-tsubo) cardiomyopathy. J Am Coll Cardiol. 2010;55:333–41.
163. Wittstein IS, Thiemann DR, Lima JA, Baughman KL, Schulman SP, Gerstenblith G, Wu KC, Rade JJ, Bivalacqua TJ, Champion HC. Neurohumoral features of myocardial stunning due to sudden emotional stress. N Engl J Med. 2005;352:539–48.
164. Madhavan M, Borlaug BA, Lerman A, Rihal CS, Prasad A. Stress hormone and circulating biomarker profile of apical ballooning syndrome (Takotsubo cardiomyopathy): insights into the clinical significance of B-type natriuretic peptide and troponin levels. Heart. 2009;95:1436–41.
165. Pison L, De Vusser P, Mullens W. Apical ballooning in relatives. Heart. 2004;90:e67.
166. Kumar G, Holmes DR Jr, Prasad A. "Familial" apical ballooning syndrome (Takotsubo cardiomyopathy). Int J Cardiol. 2010;144:444–5.
167. Templin C, Ghadri JR, Diekmann J, Napp LC, Bataiosu DR, Jaguszewski M, Cammann VL, Sarcon A, Geyer V, Neumann CA, Seifert B, Hellermann J, Schwyzer M, Eisenhardt K, Jenewein J, Franke J, Katus HA, Burgdorf C, Schunkert H, Moeller C, Thiele H, Bauersachs J, Tschope C, Schultheiss HP, Laney CA, Rajan L, Michels G, Pfister R, Ukena C, Bohm M, Erbel R, Cuneo A, Kuck KH, Jacobshagen C, Hasenfuss G, Karakas M, Koenig W, Rottbauer W, Said SM, Braun-Dullaeus RC, Cuculi F, Banning A, Fischer TA, Vasankari T, Airaksinen KE, Fijalkowski M, Rynkiewicz A, Pawlak M, Opolski G, Dworakowski R, MacCarthy P, Kaiser C, Osswald S, Galiuto L, Crea F, Dichtl W, Franz WM, Empen K, Felix SB, Delmas C, Lairez O, Erne P, Bax JJ, Ford I, Ruschitzka F, Prasad A, Luscher TF. Clinical features and outcomes of Takotsubo (stress) cardiomyopathy. N Engl J Med. 2015;373:929–38.
168. Kushiro T, Saito F, Kusama J, Takahashi H, Imazeki T, Tani S, Kikuchi S, Imai S, Matsudaira K, Watanabe I, Hino T, Sato Y, Nakayama T, Nagao K, Kanmatsuse K. Takotsubo-shaped cardiomyopathy with type I CD36 deficiency. Heart Vessel. 2005;20:123–5.
169. Limongelli G, D'Alessandro R, Masarone D, Maddaloni V, Vriz O, Minisini R, Citro R, Calabro P, Russo MG, Calabro R, Pacileo G, Bossone E, Elliott PM. Takotsubo cardiomyopathy: do the genetics matter? Heart Fail Clin. 2013;9:207–16.
170. Lyon AR, Rees PS, Prasad S, Poole-Wilson PA, Harding SE. Stress (Takotsubo) cardiomyopathy–a novel pathophysiological hypothesis to explain catecholamine-induced acute myocardial stunning. Nat Clin Pract Cardiovasc Med. 2008;5:22–9.
171. Sharkey SW, Maron BJ, Nelson P, Parpart M, Maron MS, Bristow MR. Adrenergic receptor polymorphisms in patients with stress (tako-tsubo) cardiomyopathy. J Cardiol. 2009;53:53–7.
172. Vriz O, Minisini R, Citro R, Guerra V, Zito C, De Luca G, Pavan D, Pirisi M, Limongelli G, Bossone E. Analysis of beta1 and beta2-adrenergic receptors polymorphism in patients with apical ballooning cardiomyopathy. Acta Cardiol. 2011;66:787–90.
173. Spinelli L, Trimarco V, Di Marino S, Marino M, Iaccarino G, Trimarco B. L41Q polymorphism of the G protein coupled receptor kinase 5 is associated with left ventricular apical ballooning syndrome. Eur J Heart Fail. 2010;12:13–6.

174. Goodloe AH, Evans JM, Middha S, Prasad A, Olson TM. Characterizing genetic variation of adrenergic signalling pathways in Takotsubo (stress) cardiomyopathy exomes. Eur J Heart Fail. 2014;16: 942–9.
175. Eitel I, Moeller C, Munz M, Stiermaier T, Meitinger T, Thiele H, Erdmann J. Genome-wide association study in takotsubo syndrome – preliminary results and future directions. Int J Cardiol. 2017;236: 335–9.
176. Noseworthy PA, Newton-Cheh C. Genetic determinants of sudden cardiac death. Circulation. 2008;118: 1854–63.
177. Milano A, Blom MT, Lodder EM, van Hoeijen DA, Barc J, Koopmann TT, Bardai A, Beekman L, Lichtner P, van den Berg MP, Wilde AA, Bezzina CR, Tan HL. Sudden cardiac arrest and rare genetic variants in the community. Circ Cardiovasc Genet. 2016;9:147–53.
178. Ashar FN, Mitchell RN, Albert CM, Newton-Cheh C, Brody JA, Müller-Nurasyid M, Moes A, Meitinger T, Mak A, Huikuri H, Junttila MJ, Goyette P, Pulit SL, Pazoki R, Tanck MW, Blom MT, Zhao X, Havulinna AS, Jabbari R, Glinge C, Tragante V, Escher SA, Chakravarti A, Ehret G, Coresh J, Li M, Prineas RJ, Franco OH, Kwok PY, Lumley T, Dumas F, McKnight B, Rotter JI, Lemaitre RN, Heckbert SR, O'Donnell CJ, Hwang SJ, Tardif JC, VanDenburgh M, Uitterlinden AG, Hofman A, Stricker BHC, de Bakker PIW, Franks PW, Jansson JH, Asselbergs FW, Halushka MK, Maleszewski JJ, Tfelt-Hansen J, Engstrom T, Salomaa V, Virmani R, Kolodgie F, AAM W, Tan HL, Bezzina CR, Eijgelsheim M, Rioux JD, Jouven X, Kaab S, Psaty BM, Siscovick DS, Arking DE, Sotoodehnia N. A comprehensive evaluation of the genetic architecture of sudden cardiac arrest. Eur Heart J. 2018;39:3961–9.
179. Burke A, Creighton W, Mont E, Li L, Hogan S, Kutys R, Fowler D, Virmani R. Role of SCN5A Y1102 polymorphism in sudden cardiac death in blacks. Circulation. 2005;112:798–802.
180. Marsman RF, Bezzina CR, Freiberg F, Verkerk AO, Adriaens ME, Podliesna S, Chen C, Purfurst B, Spallek B, Koopmann TT, Baczko I, Dos Remedios CG, George AL Jr, Bishopric NH, Lodder EM, de Bakker JM, Fischer R, Coronel R, Wilde AA, Gotthardt M, Remme CA. Coxsackie and adenovirus receptor is a modifier of cardiac conduction and arrhythmia vulnerability in the setting of myocardial ischemia. J Am Coll Cardiol. 2014;63: 549–59.
181. Stecker EC, Sono M, Wallace E, Gunson K, Jui J, Chugh SS. Allelic variants of SCN5A and risk of sudden cardiac arrest in patients with coronary artery disease. Heart Rhythm. 2006;3:697–700.
182. Westaway SK, Reinier K, Huertas-Vazquez A, Evanado A, Teodorescu C, Navarro J, Sinner MF, Gunson K, Jui J, Spooner P, Kääb S, Chugh SS. Common variants in CASQ2, GPD1L, and NOS1AP are significantly associated with risk of sudden death in patients with coronary artery disease. Circ Cardiovasc Genet. 2011;4:397–402.
183. Splawski I, Timothy KW, Tateyama M, Clancy CE, Malhotra A, Beggs AH, Cappuccio FP, Sagnella GA, Kass RS, Keating MT. Variant of SCN5A sodium channel implicated in risk of cardiac arrhythmia. Science. 2002;297:1333–6.
184. Albert CM, MacRae CA, Chasman DI, VanDenburgh M, Buring JE, Manson JE, Cook NR, Newton-Cheh C. Common variants in cardiac ion channel genes are associated with sudden cardiac death. Circ Arrhythm Electrophysiol. 2010;3:222–9.
185. Mikkelsson J, Perola M, Laippala P, Penttila A, Karhunen PJ. Glycoprotein IIIa Pl(A1/A2) polymorphism and sudden cardiac death. J Am Coll Cardiol. 2000;36:1317–23.
186. Lemaitre RN, Johnson CO, Hesselson S, Sotoodehnia N, McKnight B, Sitlani CM, Rea TD, King IB, Kwok PY, Mak A, Li G, Brody J, Larson E, Mozaffarian D, Psaty BM, Huertas-Vazquez A, Tardif JC, Albert CM, Lyytikainen LP, Arking DE, Kääb S, Huikuri HV, Krijthe BP, Eijgelsheim M, Wang YA, Reinier K, Lehtimaki T, Pulit SL, Brugada R, Muller-Nurasyid M, Newton-Cheh CH, Karhunen PJ, Stricker BH, Goyette P, Rotter JI, Chugh SS, Chakravarti A, Jouven X, Siscovick DS. Common variation in fatty acid metabolic genes and risk of incident sudden cardiac arrest. Heart Rhythm. 2014;11:471–7.
187. Sotoodehnia N, Li G, Johnson CO, Lemaitre RN, Rice KM, Rea TD, Siscovick DS. Genetic variation in angiotensin-converting enzyme-related pathways associated with sudden cardiac arrest risk. Heart Rhythm. 2009;6:1306–14.
188. Albert CM, Nam EG, Rimm EB, Jin HW, Hajjar RJ, Hunter DJ, MacRae CA, Ellinor PT. Cardiac sodium channel gene variants and sudden cardiac death in women. Circulation. 2008;117:16–23.
189. Marcsa B, Denes R, Voros K, Racz G, Sasvari-Szekely M, Ronai Z, Toro K, Keszler G. A common polymorphism of the human cardiac sodium channel alpha subunit (SCN5A) gene is associated with sudden cardiac death in chronic ischemic heart disease. PLoS One. 2015;10:e0132137.
190. Jabbari R, Glinge C, Jabbari J, Risgaard B, Winkel BG, Terkelsen CJ, Tilsted HH, Jensen LO, Hougaard M, Haunso S, Engstrom T, Albert CM, Tfelt-Hansen J. A common variant in SCN5A and the risk of ventricular fibrillation caused by first ST-segment elevation myocardial infarction. PLoS One. 2017;12:e0170193.
191. Lahtinen AM, Noseworthy PA, Havulinna AS, Jula A, Karhunen PJ, Kettunen J, Perola M, Kontula K, Newton-Cheh C, Salomaa V. Common genetic variants associated with sudden cardiac death: the FinSCDgen study. PLoS One. 2012;7:e41675.
192. Bezzina CR, Pazoki R, Bardai A, Marsman RF, de Jong J, Blom MT, Scicluna BP, Jukema JW, Bindraban NR, Lichtner P, Pfeufer A, Bishopric NH, Roden DM, Meitinger T, Chugh SS, Myerburg RJ, Jouven X, Kääb S, Dekker LRC, Tan HL,

Tanck MWT, Wilde AAM. Genome-wide association study identifies a susceptibility locus at 21q21 for ventricular fibrillation in acute myocardial infarction. Nat Genet. 2010;42:688–91.

193. Bugert P, Elmas E, Stach K, Weiss C, Kalsch T, Dobrev D, Borggrefe M. No evidence for an association between the rs2824292 variant at chromosome 21q21 and ventricular fibrillation during acute myocardial infarction in a German population. Clin Chem Lab Med. 2011;49:1237–9.
194. Arking DE, Junttila MJ, Goyette P, Huertas-Vazquez A, Eijgelsheim M, Blom MT, Newton-Cheh C, Reinier K, Teodorescu C, Uy-Evanado A, Carter-Monroe N, Kaikkonen KS, Kortelainen ML, Boucher G, Lagacé C, Moes A, Zhao X, Kolodgie F, Rivadeneira F, Hofman A, Witteman JC, Uitterlinden AG, Marsman RF, Pazoki R, Bardai A, Koster RW, Dehghan A, Hwang SJ, Bhatnagar P, Post W, Hilton G, Prineas RJ, Li M, Köttgen A, Ehret G, Boerwinkle E, Coresh J, Kao WH, Psaty BM, Tomaselli GF, Sotoodehnia N, Siscovick DS, Burke GL, Marbán E, Spooner PM, Cupples LA, Jui J, Gunson K, Kesäniemi YA, Wilde AA, Tardif JC, O'Donnell CJ, Bezzina CR, Virmani R, Stricker BH, Tan HL, Albert CM, Chakravarti A, Rioux JD, Huikuri HV, Chugh SS. Identification of a sudden cardiac death susceptibility locus at 2q24.2 through genome-wide association in European ancestry individuals. PLoS Genet. 2011;7:e1002158.
195. Wieneke H, Svendsen JH, Lande J, Spencker S, Martinez JG, Strohmer B, Toivonen L, Le Marec H, Garcia-Fernandez FJ, Corrado D, Huertas-Vazquez A, Uy-Evanado A, Rusinaru C, Reinier K, Foldesi C, Hulak W, Chugh SS, Siffert W. Polymorphisms in the GNAS gene as predictors of ventricular tachyarrhythmias and sudden cardiac death: results from the DISCOVERY trial and Oregon Sudden Unexpected Death Study. J Am Heart Assoc. 2016;5:e003905.
196. Huertas-Vazquez A, Nelson CP, Guo X, Reinier K, Uy-Evanado A, Teodorescu C, Ayala J, Jerger K, Chugh H, WTCCC, Braund PS, Deloukas P, Hall AS, Balmforth AJ, Jones M, Taylor KD, Pulit SL, Newton-Cheh C, Gunson K, Jui J, Rotter JI, Albert CM, Samani NJ, Chugh SS. Novel loci associated with increased risk of sudden cardiac death in the context of coronary artery disease. PLoS One. 2013;8:e59905.
197. Malik-Hall M, Poon WY, Baker MD, Wood JN, Okuse K. Sensory neuron proteins interact with the intracellular domains of sodium channel NaV1.8. Brain Res Mol Brain Res. 2003;110:298–304.
198. Hernesniemi JA, Lyytikäinen LP, Oksala N, Seppälä I, Kleber ME, Mononen N, März W, Mikkelsson J, Pessi T, Louhelainen AM, Martiskainen M, Nikus K, Klopp N, Waldenberger M, Illig T, Kähönen M, Laaksonen R, Karhunen PJ, Lehtimäki T. Predicting sudden cardiac death using common genetic risk variants for coronary artery disease. Eur Heart J. 2015;36:1669–75.
199. Chadha PS, Zunke F, Davis AJ, Jepps TA, Linders JT, Schwake M, Towart R, Greenwood IA. Pharmacological dissection of K(v)7.1 channels in systemic and pulmonary arteries. Br J Pharmacol. 2012;166:1377–87.
200. van der Linde HJ, Van Deuren B, Somers Y, Teisman A, Drinkenburg WH, Gallacher DJ. EEG in the FEAB model: measurement of electroencephalographical burst suppression and seizure liability in safety pharmacology. J Pharmacol Toxicol Methods. 2011;63:96–101.

Cognitive Decline in Elderly Patients with Hypertensive Heart Disease

5

Role of Atrial Fibrillation

Ilaria Liguori, Francesco Curcio, Pasquale Abete, and Gianluca Testa

Contents

Abstract

The elderly population is increasing worldwide together with the incidence and prevalence of cardiovascular diseases, including hypertension, coronary artery disease, atrial fibrillation, and chronic heart failure. In particular, aging is considered a risk factor for the development of hypertension, due to functional and structural changes induced in blood vessels (e.g., endothelial dysfunction and vascular remodeling), which widely overlap the functional and structural changes induced by hypertension. At the same time, both hypertension and aging predispose to the development of other

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*,
https://doi.org/10.1007/978-3-030-28008-6_8

cardiovascular diseases, in particular, atrial fibrillation and heart failure, but also of neurocognitive disorders. However, the pathophysiological mechanisms underlying the relationship between increased blood pressure and cognitive impairment are not fully understood. This chapter aims to analyze the role of atrial fibrillation in the development of cognitive decline in elderly patients with hypertensive heart disease, underlining the role of atrial fibrillation in determining both these conditions and suggesting the hypothesis of a heart-brain continuum among hypertensive heart disease, atrial fibrillation, and cognitive impairment.

Keywords

Hypertension · Atrial fibrillation · Cognitive impairment · Dementia · Elderly

Introduction

The elderly population is rapidly increasing worldwide, with people aged over 65 years expected to grow in 2050 from 8% to 16.1%, corresponding to about 1.5 billion individuals [1]. Several studies have shown an important relationship between aging and cardiovascular diseases (CVDs), including hypertension, coronary artery disease (CAD), atrial fibrillation (AF), and chronic heart failure (HF), which are frequently found in the elderly and whose prevalences are expected to grow together with geriatric population [2]. In particular, advanced age is considered a major non-modifiable risk factor in the development of hypertension, due to functional and structural changes induced in blood vessels, including endothelial dysfunction and vascular remodeling, which widely overlap the functional and structural changes of the "vascular phenotype" of hypertension [3]. Thus, if aging contributes to the development of hypertension, the joint contributions of hypertension and aging are well-established risk factors for the development of other CVDs, including AF and HF, but also of cognitive impairment and dementia [4]. However, the pathophysiological mechanisms underlying the relationship between increased blood pressure (BP) and cognitive dysfunction are controversial and not completely understood [5]. In this chapter we analyze the role of AF in the development of cognitive decline in elderly patients with hypertensive heart disease (HHD), pointing out the possible linking role of AF between these two conditions, and we hypothesize a heart-brain continuum among HHD, AF, and cognitive impairment.

Hypertension and Hypertensive Heart Disease in the Elderly

Hypertension in the Elderly: Prevalence and Characteristics

Hypertension is a condition characterized by high BP. According to the new 2017 American Heart Association and American College of Cardiology guidelines for hypertension in the adults, normal BP is set at $<$120/80 mmHg, and stage 1 hypertension is set at BP levels above 130/80 mmHg rather than 140/90 mmHg, as in the 2018 European Society of Cardiology (ESC) guidelines, and this difference is due to the recent adaptation of the American guidelines to the result of the Systolic blood PRessure INtervention Trial (SPRINT) study [6]. However, defining BP targets in the geriatric population is very difficult because of elderly susceptibility to adverse outcomes deriving from the excessive BP lowering such as falls, fractures, and cognitive impairment [7].

The prevalence of hypertension increases with age, from 7.5% among adults aged 18–39 to 33.2% among those aged 40–59 and 63.1% among those aged 60 and over in both men and women [8]. In fact, of all the risk factors contributing to hypertension, such as genetics, obesity, dyslipidemia, sedentary lifestyle, and diabetes, advancing age is the most important [3].

Hypertension is a major risk factor for cardiovascular morbidity and mortality: over the range of 115/75 to 185/115 mmHg, each 20/10 mmHg

increase in BP doubles the risk of myocardial ischemia and stroke in individuals aged from 40 to 90 years [9].

Hypertension in the elderly has peculiar characteristics. First of all, hypertension is mainly systolic, a condition known as isolated systolic hypertension, whose prevalence in people aged 80 and more is higher than 90% [1]. Moreover, in the elderly BP control rates are lower than in young people (34.3% vs. 39.8%), especially in women [10]. In fact, in the Framingham Heart Study population, only 23% of women versus 38% of men aged 80 years or more had BP values <140/90 mmHg [11].

Aging and Hypertensive Heart Disease

Vascular aging is characterized by endothelial dysfunction and increased vascular wall thickening both associated with arterial stiffness [3]. Endothelial dysfunction can be defined as the progressive impairment of endothelium-dependent vascular dilation leading to an increased vascular tone [12]. This is due to a decreased production and bioavailability of nitric oxide and to an increased production of reactive oxygen species [13]. Endothelial dysfunction is involved in age-related arterial stiffening in the elderly both in healthy subjects and in patients with hypertension [12]. Although the arterial tone is regulated by endothelial function, arterial relaxation is influenced by the content of elastin, collagen, and smooth muscle in the vessel wall [14]. In particular, aging is accompanied by arterial wall remodeling, especially in the aorta, characterized by intimal thickening due to vascular smooth muscle cell hypertrophy, increased collagen content, and fragmentation of elastic lamellae in the tunica media with secondary fibrosis and calcification, leading to loss of elasticity and then to arterial stiffening [1]. The reduction in aorta's compliance during systole and in its elastic recoil during diastole is responsible for an increase in systolic BP and a decrease in diastolic BP, which is observed both in normotensive and in old hypertensive subjects, i.e. the abovementioned phenomenon of isolated systolic hypertension [15]. This age-related vascular remodeling closely resembles the vascular alterations induced by hypertension, so that hypertension accelerates and worsens age-related vascular dysfunction and aging may impact on the severity of vascular damage in hypertension, indicating close interactions between biological aging and BP elevation. Thus, hypertension can be considered a condition of aging, and both are risk factors for the development of HHD [16].

The term HHD refers to a set of cardiac functional and structural adaptations to a lifetime of increased BP load. The main characteristics of HHD are left ventricular hypertrophy (LVH), left ventricular diastolic dysfunction, and, if inadequately treated, their clinical manifestations including arrhythmias (e.g., AF) and symptomatic HF [9, 17].

The pathogenesis of HHD involves a progressive transition from hypertension to LVH to diastolic dysfunction with preserved systolic function, usually expressed by ejection fraction (EF). If not treated, this condition might lead to ventricular dilation and HF with reduced ejection fraction (HFrEF) [9].

Myocardial compensatory response to chronically increased load (either preload or afterload), as for any other muscle, is hypertrophy. In particular, myocardial remodeling to a predominant volume overload (increased preload) consists of eccentric hypertrophy, while myocardial remodeling to a predominant pressure overload (increased afterload) consists of concentric hypertrophy [18]. These cardiac compensatory responses can be explained by the Laplace's law: $T = P \cdot r/2 \cdot h$, stating that LV wall stress (T), which is a major determinant of myocardial oxygen demand, is directly related to LV pressure (P) and radius (r) and inversely related to LV wall thickness (h) [19].

According to this law, cardiac volume overload is expressed by an increased chamber radius which is associated with an improved LV wall stress. In order to normalize LV wall stress, cardiac compensatory response is a remodeling of LV thickness, characterized by a lengthening of cardiomyocytes due to the addition of new sarcomeres in series, resulting in a structural pattern

known as eccentric hypertrophy [19]. Therefore, LV eccentric hypertrophy is characterized by increased end-diastolic volume and preserved ventricular systolic function, according to the Frank-Starling law. However, with the persistence of volume overload, further ventricular dilation becomes maladaptive and leads to HFrEF. Eccentric hypertrophy may occur in response to physical conditioning (the so-called *athlete's* heart), in response to chronic volume overload (chronic kidney disease, anemia, or obesity), or during diseases causing ventricular dilation [9].

Conversely, according to the Laplace's law, cardiac pressure overload, as occurs in HHD, is expressed by an increased LV pressure which is associated with an improved LV wall stress. In order to normalize LV wall stress, cardiac compensatory response is an increased LV thickness, characterized by a reduction in the number but an increase in the width of cardiomyocytes caused by the parallel addition of new sarcomeres and to a higher deposition of collagen (fibrosis) [19]. This LV thickening results in an increase in cardiac mass at the expense of chamber radius and consequently of LV volume and compliance [1]. This structural pattern is known as concentric hypertrophy. LVH preserves LV systolic function but has long-term negative consequences, because it predisposes to the development of left ventricular diastolic dysfunction and HF with preserved ejection fraction (HFpEF) [20].

In summary, cardiac compensatory response to chronic overload is hypertrophy. Volume overload leads to eccentric hypertrophy, while pressure overload leads to concentric hypertrophy. Eccentric hypertrophy is mainly characterized by an increase in LV volume leading to HFrEF. Concentric hypertrophy is characterized by an increase in LV mass leading to HFpEF.

Left ventricular diastolic dysfunction refers to an impaired left ventricular diastolic filling and is a strong predictor of CVDs, especially AF and HF. Left ventricular diastolic dysfunction is more prevalent in the elderly population, and among the risk factors for left ventricular diastolic dysfunction, hypertension has been reported as the most important in community-dwelling elderly subjects. More in detail, hypertension, leading to LVH and stiffening, reduces LV chamber volume and compliance inducing an impaired LV diastolic filling, in which the chamber filling is slow or incomplete in the absence of increased diastolic filling pressure [21]. Consequently, the reduction in early diastolic LV filling is counteracted by an increased filling in late diastole due to a more vigorous left atrial (LA) contraction, which is followed by increased LA pressure and consequently by LA hypertrophy and dilation [22]. These mechanisms explain the echocardiographic pattern of HHD, which is observed also in the aging heart, characterized by a reduction of E/A ratio, where E corresponds to the early diastolic filling and A to the late diastolic filling due to atrial contraction [23, 24].

The end stage of HHD usually is associated with both pressure and myocardial volume overload, resulting in dilated cardiomyopathy with both diastolic and systolic dysfunction [18]. According to the pathophysiologic impact of hypertension on the heart, HHD can be divided into four degrees of increasing severity:

I. Isolated left ventricular diastolic dysfunction with no LVH
II. Left ventricular diastolic dysfunction with concentric LVH
III. Clinical HF (dyspnea and pulmonary edema) with preserved EF (HFpEF)
IV. Dilated cardiomyopathy with HF and reduced EF (HFrEF) [25]

Several studies support the evidence that hypertensive patients with concentric LVH commonly develop dilated cardiac failure and suggest the pivotal role of myocardial infarction in this phenomenon [17]. Indeed, LVH is associated with an increased risk of CAD, including myocardial infarction [26]. Although the mechanisms linking LVH and myocardial ischemia are mainly unknown, hypertension is associated with coronary atherosclerosis leading to a reduced coronary reserve, and, in turn, LVH is associated with an increased myocardial oxygen demand [21]. In fact, concentric LVH mainly progresses to dilated cardiac failure with reduced systolic function due to intercurrent myocardial infarction; on the contrary, the progression of concentric LVH to dilated

cardiac failure in the absence of an interval myocardial infarction is not common [17].

On the contrary, a recent systematic review of literature has shown that hypertension is the most common and strong risk factor for the development of symptomatic HFpEF, which is a syndrome characterized by signs and symptoms of HF in a contest of normal EF and altered diastolic function [27]. The progression from left ventricular diastolic dysfunction with concentric LVH to HFpEF might be explained by the direct transmission of the elevated ventricular filling pressures to the pulmonary capillaries, which are believed to contribute to increasing dyspnea, right heart overload, exercise intolerance, and pulmonary edema [9]. However, several studies have investigated the mechanisms underlying the transition from HHD to HFpEF, showing a multifactorial pathophysiology, involving not only the cardiac structural remodeling (i.e., LVH, diastolic dysfunction, LA dilatation, vascular stiffening, etc.) but also systemic endothelial inflammation and fibrosis [28].

Therefore, both hypertension and aging, inducing a similar variety of cardiovascular structural and functional changes, predispose to the development of HHD and its clinical consequences.

From Hypertensive Heart Disease to Atrial Fibrillation

Atrial Fibrillation in the Elderly: Prevalence and Characteristics

AF has become one of the most important public health problems due to population aging. The incidence of AF ranges between 0.21 and 0.41 per 1000 person/years, and the global prevalence of AF is almost 2% of the general population [29]. The prevalence of AF varies with age and sex. AF is more common in men than in women (1.1% vs. 0.8%) [30], and its prevalence increases together with age, from 0.12% to 0.16% of those younger than 49 years to 3.7%–4.2% in those aged 60–70 years and 10%–17% in those aged 80 years or older [29].

AF in elderly patients is frequently asymptomatic (silent or subclinical AF), and the diagnosis is often made incidentally during a cardiological checkup. In fact, in the elderly ventricular rate seems to be better controlled because of their inactivity and/or the concomitant presence of atrioventricular nodal disease. For these reasons, they are less likely to report palpitations, and AF often presents with fatigue, stroke, worsening HF, and/or angina. Those presenting with syncope often have concurrent sinus and atrioventricular nodal disease [31].

Several risk factors have been shown to be associated with the development of AF. In the Framingham Heart Study, age, diabetes mellitus, hypertension, HF, CAD, and valve diseases were shown to be independent risk factors for AF in both sexes [32]. In fact, AF is frequently diagnosed in patients with concomitant CVDs, primarily hypertension, followed by HF, CAD, and valvular heart disease, for paroxysmal, persistent, and permanent AF [33]. These data confirm that aging and hypertension are the primary risk factors for the development of AF.

The Development of Atrial Fibrillation in Hypertensive Heart Disease

Age-related changes in LA predispose to the development of AF [34]. In particular, aging is associated with several electro-anatomical LA alterations: fatty infiltration, collagen, and amyloid deposition in LA wall; decreased number of atrial myocytes, pacemaker cells, and conduction tissue replaced by fibrosis; increased LA size, pressure, and volume; cytosolic Ca^{2+} overload because of enhanced sodium/calcium exchanger; and upregulation of atrial-specific ultra-rapid delayed rectifier potassium currents resulting in a shortening of action potential duration and a decreased refractory period [31]. These structural and electrical changes make the LA more susceptible to AF.

Along with aging, also untreated or suboptimally treated hypertension predisposes to the development of AF. Cardiac response to chronic pressure overload is characterized by LVH and fibrosis, leading to a reduction in LV compliance and consequently an increase in LV stiffness and

filling pressure and a decrease in coronary flow reserve and an increased activation of the autonomic nervous system (ANS) and of the renin-angiotensin-aldosterone system (RAAS) [35]. These LV changes negatively affect LA, whose remodeling takes place at three different levels: electrical, contractile, and structural [36].

Electrical remodeling consists of a shortening of atrial refractoriness. When the wavelength of the atrial impulse is short, small regions of atrial conduction block may be development sites for multiple small reentry circuits, increasing not only the vulnerability for AF but also the stability of AF itself [37]. The main ionic mechanism underlying this arrhythmogenic process is the marked reduction in L-type Ca^{2+} current, explaining the shortening of the atrial action potential and the loss of the physiological rate adaptation of the duration of the action potential [38].

Contractile remodeling consists of a loss of atrial contractility, and it is strictly dependent on atrial electrical remodeling [36]. The reduction in L-type Ca^{2+} current leads to a decrease in intracellular Ca^{2+} concentration which may be responsible for the loss of contractility. Impaired atrial contraction leading to stasis of blood, primarily in the LA appendage, may promote the development of blood clots, promoting thromboembolic events, in particular stroke, which is the most dangerous clinical consequence of AF [37]. Finally, atrial contractile remodeling is also associated with increased compliance of atrial wall which may enhance atrial dilatation and promote the persistence of AF [35].

Structural remodeling includes proliferation and differentiation of fibroblasts into myofibroblasts, enhanced connective tissue deposition and fibrosis, and increase in atrial cell size and signs of irreversible intracellular changes (e.g., disruption of mitochondrial cristae, fragmentation of sarcoplasmic reticulum, abnormal secondary lysosomes, cytosolic blebs, lipid droplets) leading to cell death (myolysis) [36]. Myolysis probably contributes to the impairment of atrial contractility, and fibrosis could explain intra-atrial conduction disturbances and the susceptibility for AF [37].

In summary, electrical, contractile, and structural atrial changes are dependent on each other. In fact, the reduction in L-type Ca^{2+} current primarily causes a shortening in atrial refractoriness contributing to the development of reentry circuits and so to AF onset. At the same time, this process leads to a loss of atrial contractility promoting atrial dilation and AF onset and persistence. However, atrial electrical and contractile remodeling are sustained by structural changes, in particular myolysis, which promotes atrial dilation and fibrosis and which contributes to atrial electrical disturbance and AF development [37].

Together with atrial remodeling, in the genesis of AF, is also important the role of ANS and RAAS activation.

ANS is involved in BP regulation, but it also significantly influences atrial electrophysiological characteristics, especially in patients with structural heart disease, such as HHD [35]. Hypertension-induced ANS activation has an important role in the dynamics of AF occurrence and maintenance because it induces the release of acetylcholine and catecholamines, which may consequently stimulate fast ectopic impulses able to trigger paroxysmal AF [39].

RAAS activation and HHD are closely linked, as shown by the fact that high circulating levels of angiotensin II (AT-II) are seen in hypertensive patients and that RAAS inhibition has a significant therapeutic effect on BP control [40]. In particular, hypertension-induced atrial dilation and myocyte stretch are responsible for increased expression of tissue angiotensin-converting enzyme in the atria and consequently an increased concentration of AT-II, which promotes AF onset and maintenance [41]. AT-II exerts its arrhythmogenic effects through several mechanisms: AT-II directly affects ion channel structure, function, and distribution (especially calcium and potassium channels) and stimulates transcription of proteins that promote cellular proliferation and differentiation, leading to myocyte hypertrophy [35]. Another component of RAAS, aldosterone, plays a pivotal role in the development of AF through local effects on atrial myocardium and interstitium, promoting fibrosis and atrial remodeling through induction of fibroblast proliferation and differentiation and upregulation of matrix metalloproteinases activity [42]. The interdependence and positive feedback

between the ANS and RAAS in HHD support the importance of these two biohumoral systems in the development of AF [35].

From Atrial Fibrillation to Cognitive Decline

Cognitive Decline in the Elderly: Prevalence and Characteristics

Cognitive impairment is a broad term that generally describes a decline in cognitive functions: complex attention, executive functioning, learning and memory, language, visuospatial function, and social cognition, which play a pivotal role in controlling the consciousness of situation, needs, and goals [43]. Neurocognitive disorders include major neurocognitive disorder, which corresponds to dementia, and mild cognitive impairment (MCI), which is a state intermediate between normal cognition and dementia, with essentially preserved functional abilities [44]. Diagnostic criteria for neurocognitive disorders according to the fifth edition of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) are shown in Table 1 [45]. In particular, dementia is diagnosed when one or (usually) more cognitive domains are impaired, negatively affecting the subject's activities of daily living. The diagnosis of MCI is made when there is modest impairment in one or more cognitive domains, but the subject's activities of daily living are still preserved; the impairment must represent a decline from a previously higher level and should be documented both by history and/or by objective assessment. Further, for both the diagnosis, the cognitive deficits must not occur exclusively in the context of a delirium or be better explained by another mental disorder [45].

The incidence of neurocognitive disorders increases steadily until age 85 or 90 years but then continues to increase less rapidly. The annual incidence of neurocognitive disorders ranges from

Table 1 Neurocognitive disorders as diagnosed in DSM-5 [45]

Diagnostic criteria	Major neurocognitive disorder/dementia	MCI
A	Significant cognitive decline in one or more cognitive domains based on: Concern about significant decline expressed by the individual or reliable informant or observed by the clinician Substantial impairment documented by objective cognitive assessment	Modest cognitive decline in one or more cognitive domains based on: Concern about mild decline expressed by the individual or reliable informant or observed by the clinician Modest impairment documented by objective cognitive assessment
B	Interference with independence in everyday activities	No interference with independence in everyday activities, although these activities may require more time and effort, accommodation, or compensatory strategies
C	Not exclusively during delirium	
D	Not better explained by another mental disorder	
E	Specify one or more causal subtypes caused by: Alzheimer's disease Cerebrovascular disease (vascular neurocognitive disorder) Frontotemporal lobar degeneration (frontotemporal neurocognitive disorder) Dementia with Lewy bodies (neurocognitive disorder with Lewy bodies) Parkinson's disease Huntington disease Traumatic brain injury Human immunodeficiency virus infection Prion disease Another medical condition Multiple causes	

Legend: *MCI* mild cognitive impairment

0.1% at age 60–64 years to 8.6% at age 95 years, and it is similar in men and women. Prevalence of dementia increases exponentially with increasing age and doubles every 5 years after age 65 years; in fact, in those aged 65 years and older, prevalence is 5% to 10%, and it is higher in women than in men [44].

Neurocognitive disorders, especially dementia, have high costs in both social and economic terms. In particular, dementia is a leading cause of death, disability, and institutionalization [46]; family caregivers experience increased emotional stress, depression, and health problems; healthcare system costs for the management of patients with dementia are high and progressively growing together with the life expectancy of the worldwide population [47].

After excluding reversible causes of dementia, the most common subtypes of dementia to be seen in the elderly population are Alzheimer's disease (AD), vascular dementia, dementia with Lewy bodies (DLB), and frontotemporal dementia (FTD), which account for 90% of all cases [2].

The AD is the most common neurodegenerative disorder, characterized by progressive loss of temporoparietal bilateral synapses and neurons, accumulation of amyloid plaques, neurofibrillary tangles, and prominent cholinergic deficits. The onset of symptoms is typically between the eighth and ninth decades of life, but early-onset forms of the disease may arise in the fifth decade [44]. Average life expectancy is about 10 years after the onset of dementia, but is widely influenced by the age of onset, the severity of cognitive impairment, and the presence of comorbid diseases [48].

Vascular dementia or vascular neurocognitive disorder, frequently referred to as atherosclerotic dementia, multi-infarct dementia, and vascular cognitive impairment, is the second most prevalent cause of dementia in the elderly, primarily due to cerebrovascular diseases, and frequently presented in combination with AD (mixed dementia) [44]. To diagnose the vascular neurocognitive disorder, cognitive impairment should be temporally related to neuroimaging evidence of cerebrovascular disease and/or a clear history of stroke or transient ischemic attacks [2]. It can involve both large and small vessels, and the site of the lesions is more important than their extension. The variability of the lesions' location explains the variability of the clinical presentation and its progression over time [49]. Cognitive decline usually involves the domains of complex attention and executive functions, but also gait disturbance, urinary symptoms, and personality or mood changes (especially the so-called vascular depression) are common [45]. The progression of the neurocognitive decline can show an acute stepwise pattern, a more gradual pattern, or can be fluctuating or rapid in its course [44].

DLB is the second most common neurodegenerative type of dementia after AD, and it is primarily characterized by alpha-synuclein misfolding and aggregation within the Lewy bodies, which are also found in Parkinson's disease. It is typically diagnosed between the sixth and ninth decades, and the average survival is 5 to 7 years [45]. DLB's cognitive deficits mainly involve the domains of attention, visuospatial functioning, and executive functioning [50]. Cognitive decline is frequently associated with visual hallucinations and parkinsonism, but, unlike dementia of Parkinson's disease, cognitive impairment precedes the onset of parkinsonism. Suggestive features of DLB include rapid eye movement sleep behavior disorder and high neuroleptic sensitivity [44].

FTD is the third most common degenerative type of dementia in the elderly and is characterized by frontal and temporal lobes' atrophy and inclusions of hyperphosphorylated tau or ubiquitin protein [44]. It is typically diagnosed in the sixth decade and is a common cause of early-onset dementia. The average survival is 6 to 10 years after symptom onset and 3 to 4 years after diagnosis [45]. The clinical subtypes of FTD correspond with specific areas of brain atrophy and include behavioral and three language variants [51]. The behavioral variant is mainly characterized by changes in personality and behavior (e.g., loss of interest in personal affairs and responsibilities, social withdrawal, loss of awareness of personal hygiene, and socially disinhibited behavior) [44]. The three language variants include the semantic type (fluent aphasia, intact syntax and prosody, and sometimes loss of empathy and rigid behaviors), progressive nonfluent aphasia, and the logopenic subtype [51].

Table 2 Protective and risk factors for neurocognitive disorders [44]

Risk factors	Protective factors
Age and sex (women)	High education level
Race	Bilingualism
Genetics	Cognitively stimulating activities
Head injury	Drugs: NSAIDs Statins
Apolipoprotein E polymorphism	
Lifestyle and environmental factors: Heavy consumption of alcohol Environmental and occupational exposures (e.g., pesticides) Smoking	Lifestyle factors: Moderate alcohol consumption Mediterranean diet High physical activity
Psychiatric disorders: Depression Late-life anxiety Post-traumatic stress disorder Traits of harm avoidance and lesser sense of purpose	
Cardiovascular diseases: Hypertension CAD HF AF Hypercholesterolemia Obesity Diabetes mellitus Inflammation Obstructive sleep apnea syndrome Stroke	

Legend: *NSAIDs* nonsteroidal anti-inflammatory drugs, *CAD* coronary artery disease, *HF* chronic heart failure, *AF* atrial fibrillation

Risk and protective factors for neurocognitive disorders are shown in Table 2. Among the risk factors for neurocognitive disorders, the most important are demographic and medical ones. In particular, advancing age is not only the strongest risk factor for dementia but also the only risk factor identified after the eighth decade of life [44]. CVDs, including hypertension, CAD, and HF, are recognized risk factors for both vascular and degenerative dementia, especially AD [2]. Although the etiology of cognitive impairment in CVDs remains unknown, the mechanisms mainly involved in this relationship seem to be embolic stroke and/or chronic cerebral hypoperfusion [52]. Since the prevalence, but not the incidence, of dementia is higher in women than in men, probably this phenomenon may be due to a longer life expectancy and to the higher cardiovascular morbidity in women population [44].

From Atrial Fibrillation to Cognitive Decline

Physiological aging induces important changes in cognitive function, brain structure, and susceptibility to ischemia [53, 54]. Several studies have shown that aging is associated with a linear decline of fluid abilities (e.g., processing speed) and a linear increase in crystallized abilities (e.g., vocabulary). Together with processing speed, also sensory perception declines with age. In particular, auditory acuity begins to decline after age 30, and up to 70% of subjects aged 80 have a measurable hearing loss, negatively affecting speech discrimination and sound localization [55]. Aging is also characterized by a decline in attention, executive cognitive functions, and working and prospective memory, while procedural memories are preserved [53]. These cognitive impairments may be explained by many age-related structural changes occurring in the brain, such as atrophy due not to neuronal loss (no more than 10%) but to neuronal structural changes (e.g., decreased number and length of dendrites and axons, loss of dendritic spines, increased axonal segmental demyelination) and loss of synapses [56, 57]. Thus, aging alone is associated with a physiological decline in cognitive functions.

In addition to aging, several observational studies have also demonstrated the association of AF to cognitive decline and dementia, but the mechanisms underlying this causal relationship remain unclear because of the shared risk factor, especially aging and hypertension [58]. However, AF may increase the risk and accelerate the onset of cognitive decline through different possible mechanisms such as cerebral hypoperfusion,

systemic inflammation, cerebral small vessel disease (SVD), genetic factors, and as a consequence of AF ablation [58, 59].

A hypothetical mechanism at the basis of the relationship between AF and cognitive impairment is the cerebral hypoperfusion [58]. AF reduces cardiac output and may lead to chronic cerebral hypoperfusion, with consequent chronic hypoxic injury, which may reduce the clearance and promote the accumulation of amyloid-beta peptides in cerebral vessels, thus leading to cerebral amyloid angiopathy [2, 59]. The high prevalence of neurocognitive impairment and dementia in patients with AF and HF further supports this potential effect of cerebral hypoperfusion [60]. In particular, in subjects with AF, ventricular rate response (VRR) seems to play a critical role in the development of dementia in cognitively impaired elderly subjects. A study conducted on 358 cognitively impaired elderly subjects (MMSE <24) with and without AF stratified in low/high (<50/>90) and moderate (>50/<90 bpm) VRR and followed for a follow-up of 10 years showed that low/high VRR (<50/>90 bpm) was predictive of dementia in the presence but not in the absence of AF, as shown in Fig. 1 [61]. These data support the hypothesis that the reduction of cardiac output, secondary to an altered VRR induced by AF, could contribute to cerebral hypoperfusion and consequently to the increased incidence of dementia in cognitively impaired elderly subjects with AF [2].

Several studies have suggested the role of systemic inflammation in the pathophysiology of AF and, in turn, the role of AF in worsening the inflammatory response [58]. Furthermore, increased markers of inflammation have been linked to cognitive impairment in patients with AF. Since AF is associated with a chronic systemic inflammation status and prothrombotic environment, patients with AF may be more susceptible to cerebral microvascular changes, leading to cognitive decline and dementia [62]. Moreover, systemic inflammation is associated with hypercoagulation, endothelial dysfunction, and increased platelet activation, worsening AF-related thromboembolism [59]. In fact, high levels of high-sensitivity C-reactive protein are associated with worse executive functioning and more microvascular damage in the white matter and an elevated risk of all dementia subtypes independently of cardiovascular risk factors and related diseases [63].

The term SVD refers to a variety of pathological processes, including silent subcortical infarcts,

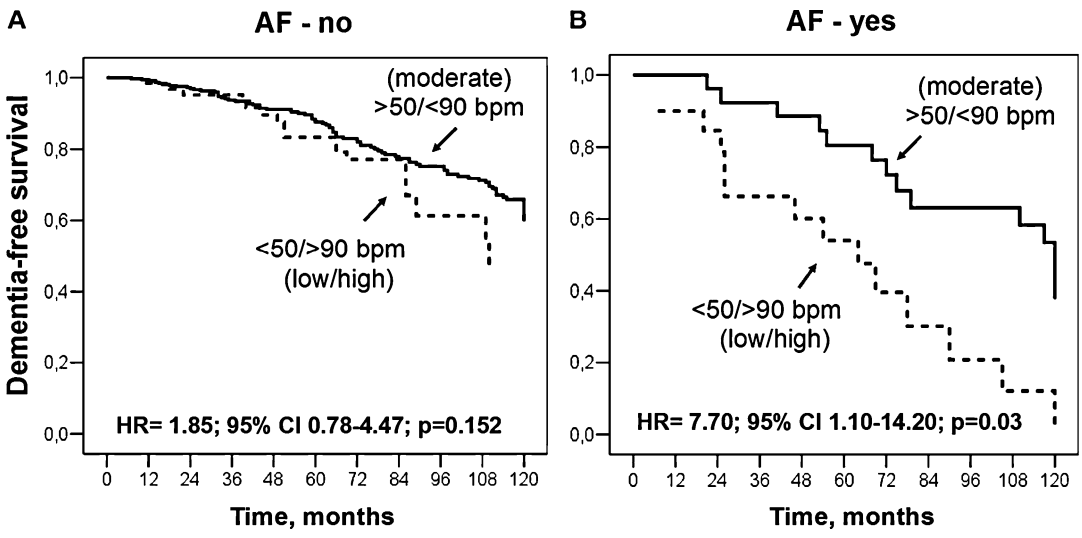

Fig. 1 Cox regression analysis of cumulative dementia in cognitively impaired elderly subjects stratified for the absence (**a**) and the presence (**b**) of chronic atrial fibrillation stratified in low/high (<50/>90 bpm) and moderate (>50/<90 bpm) ventricular rate response (adapted from [61]) (Legend: *AF* atrial fibrillation, *HR* hazard ratio, *CI* confidence interval)

lacunes, white matter hyperintensities (WMHs), brain atrophy, and cerebral microbleeds (CMBs), which affect small arteries, arterioles, venules, and capillaries of the brain [64, 65]. SVD is the leading cause of cognitive decline in the elderly, and it seems to play a pivotal role in the association between AF and cognitive decline [59]. Several studies have demonstrated the presence of silent ischemic brain lesions due to microembolism in 90% of patients with AF, associated with two- to threefold increased risk of both symptomatic stroke and dementia [66]. The detection of WMHs in patients with AF may be explained by the fact that brain ischemia, resulting from the low cardiac output and cerebral hypoperfusion, may lead to WMHs and that chronic silent cerebral ischemic lesions could also convert into WMHs [59]. SVD also includes brain atrophy, which is associated with cognitive decline. AF may cause brain atrophy through several mechanisms: hypoperfusion of gray matter, systemic inflammation, chronic microembolisms, and CMBs [67]. The occurrence of CMBs increases with advancing age, is more prevalent among AF patients, and is associated with faster cognitive decline and high risk of dementia [59]. In fact, aging, inducing cerebral amyloid angiopathy, negatively affects small cerebral vessels making them more susceptible to microbleeds. This phenomenon is worsened by the use of anticoagulant drugs, whose main adverse effects are CMBs and subsequent intracranial hemorrhages [68].

The association between genetic factors and cognitive decline in patients with AF is still under investigation [58]. A recent study compared 112 Caucasian patients with AF and dementia with matched control subjects with AF and normal cognitive function, testing genetic variants known to be associated with AF (PITX2 locus and ZFHX3 locus) or AD (apolipoprotein E ε4 allele). The results of the study showed that the AF-related gene PITX2 was significantly associated with dementia [69], but more studies are needed to confirm these results and identify other genetic factors involved in predisposing AF patients to neurocognitive disorders.

AF catheter ablation increases the risk of microemboli and cognitive impairment in the periprocedural period, as shown by the high incidence of silent cerebral ischemia and of ischemic strokes detected using magnetic resonance after AF ablation [70]. However, although the acute increased incidence of ischemic events, AF ablation seems to reduce the long-term risk for dementia, which becomes similar to those of patients without AF [71, 72]. The mechanisms underlying this protective effect of AF ablation from cognitive decline are poorly understood; thus more studies are needed to confirm and explain this association [58].

Hypertensive Heart Disease, Atrial Fibrillation, and Cognitive Decline: A Heart-Brain Continuum Hypothesis

Figure 2 depicts our hypothesis of a heart-brain continuum from HHD to cognitive decline, showing the linking role of AF between these two pathologies and underlining the role of cardiovascular aging in the development of all these pathologies. Indeed, since aging is a physiological condition necessarily present in the elderly, taking into account cardiovascular and cerebrovascular age-related changes is necessary for understanding the pathophysiological mechanisms underlying HHD, AF, and cognitive decline.

Aging is a well-known risk factor for both cardiovascular and cerebrovascular diseases, especially hypertension, AF, and cognitive decline. In particular, aging is responsible for endothelial dysfunction and vascular remodeling, leading, respectively, to vasoconstriction and arterial stiffening, both predisposing to the development of high BP. LV responses to the increased afterload due to chronic hypertension are LVH and fibrosis, which are associated with a lower LV compliance leading to increased LV filling pressure and reduced LV early diastolic filling, respectively, and associated with an increase in LA pressure and contraction. The rise in LA pressure and contraction is followed by LA dilation and hypertrophy, also affected by aging, which represent the structural substrate predisposing to the atrial electrophysiological disturbances involved in the development and persistence of AF. This latter, through VRR impairment, reduces cardiac output

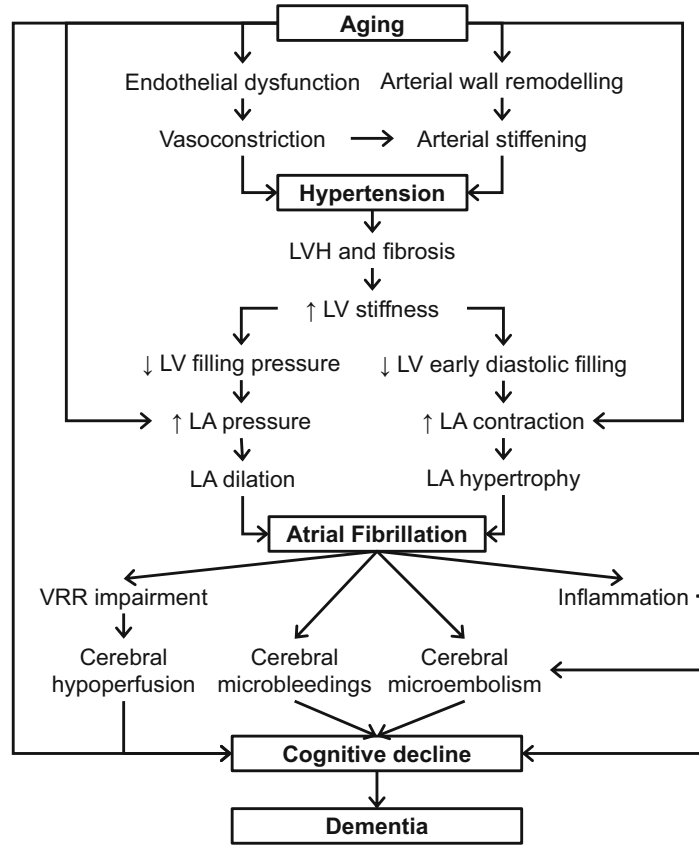

Fig. 2 Hypertensive heart disease, atrial fibrillation, and cognitive decline: a heart-brain continuum hypothesis. See text for explanation. (Legend: *LVH* left ventricular hypertrophy, *LV* left ventricular, *LA* left atrial, *VRR* ventricular rate response)

leading to cerebral hypoperfusion. Moreover, AF is associated with a systemic inflammation state leading to hypercoagulability and platelet activation, which worsens AF-related cerebral microembolism, and to endothelial dysfunction, further contributing to CMBs also due to anticoagulant drugs. Finally, the overlap of AF-induced cerebral hypoperfusion, microembolism, and microbleedings to the normal age-related cerebral functional and structural changes is responsible for the development of cognitive impairment and its consequent worsening in dementia.

Conclusions

The prevalence of CVDs, especially hypertension and AF, is increasing worldwide together with the elderly population. In particular, aging is associated with a variety of cardiac and vascular changes which predisposes to the development of hypertension and consequently of HHD. Both hypertension and aging increase the risk of development of neurocognitive disorders, but the mechanisms underlying the association between HHD and cognitive decline are not completely understood. Since the prevalence of AF is higher in hypertensive elderly patients as well as neurocognitive disorders are more prevalent in AF patients, AF could be the missing link between these two geriatric pathologies, suggesting the hypothesis of a heart-brain continuum among HHD, AF, and cognitive decline.

In the last decades, this intriguing field of research is progressively becoming the object of several studies aimed to clarify the role of each in the development of the others.

References

1. Virdis A, Bruno RM, Fritsch Neves M, Bernini G, Taddei S, Ghiadoni L. Hypertension in the elderly: an evidence-based review. Curr Pharm Des. 2011;17:3020–31.
2. Abete P, Della-Morte D, Gargiulo G, Basile C, Langellotto A, Galizia G, Testa G, Canonico V, Bonaduce D, Cacciatore F. Cognitive impairment and cardiovascular diseases in the elderly. A heart–brain continuum hypothesis. Ageing Res Rev. 2014;18:41–52.
3. Harvey A, Montezano AC, Touyz RM. Vascular biology of ageing—implications in hypertension. J Mol Cell Cardiol. 2015;83:112–21.
4. Santos CY, Snyder PJ, Wu W-C, Zhang M, Echeverria A, Alber J. Pathophysiologic relationship between Alzheimer's disease, cerebrovascular disease, and cardiovascular risk: a review and synthesis. Alzheimers Dement Diagn Assess Dis Monit. 2017;7:69–87.
5. Tadic M, Cuspidi C, Hering D. Hypertension and cognitive dysfunction in elderly: blood pressure management for this global burden. BMC Cardiovasc Disord. 2016;16:208. https://doi.org/10.1186/s12872-016-0386-0.
6. Spiering W, Burnier M, Clement DL, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension. J Hypertens. 2018;36:89.
7. Russo G, Liguori I, Aran L, et al. Impact of SPRINT results on hypertension guidelines: implications for "frail" elderly patients. J Hum Hypertens. 2018;32:633–8.
8. Fryar CD, Zhang G. Hypertension prevalence and control among adults: United States, 2015–2016. NCHS Data Brief. 2017;289:1–8.
9. Izzo JL, Gradman AH. Mechanisms and management of hypertensive heart disease: from left ventricular hypertrophy to heart failure. Med Clin North Am. 2004;88:1257–71.
10. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics—2011 update: a report from the American Heart Association. Circulation. 2011;123:e18. https://doi.org/10.1161/CIR.0b013e3182009701.
11. Franklin SS, Gustin W, Wong ND, Larson MG, Weber MA, Kannel WB, Levy D. Hemodynamic patterns of age-related changes in blood pressure. The Framingham heart study. Circulation. 1997;96:308–15.
12. Higashi Y, Kihara Y, Noma K. Endothelial dysfunction and hypertension in aging. Hypertens Res. 2012;35:1039–47.
13. Collins C, Tzima E. Hemodynamic forces in endothelial dysfunction and vascular aging. Exp Gerontol. 2011;46:185–8.
14. Veerasamy M, Ford GA, Neely D, Bagnall A, MacGowan G, Das R, Kunadian V. Association of Aging, arterial stiffness, and cardiovascular disease: a review. Cardiol Rev. 2014;22:223–32.
15. McEniery CM, McDonnell BJ, So A, et al. Aortic calcification is associated with aortic stiffness and isolated systolic hypertension in healthy individuals. Hypertension. 2009;53:524–31.
16. Harvey A, Montezano AC, Lopes RA, Rios F, Touyz RM. Vascular fibrosis in aging and hypertension: molecular mechanisms and clinical implications. Can J Cardiol. 2016;32:659–68.
17. Drazner MH. The progression of hypertensive heart disease. Circulation. 2011;123:327–34.
18. Messerli FH, Rimoldi SF, Bangalore S. The transition from hypertension to heart failure. JACC Heart Fail. 2017;5:543–51.
19. Nadruz W. Myocardial remodeling in hypertension. J Hum Hypertens. 2015;29:1–6.
20. Lip G. Hypertensive heart disease. A complex syndrome or a hypertensive "cardiomyopathy"? Eur Heart J. 2000;21:1653–65.
21. Nadruz W, Shah AM, Solomon SD. Diastolic dysfunction and hypertension. Med Clin North Am. 2017;101:7–17.
22. Gaasch WH, Zile MR. Left ventricular diastolic dysfunction and diastolic heart failure. Annu Rev Med. 2004;55:373–94.
23. Lakatta EG, Levy D. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: part II: the aging heart in health: links to heart disease. Circulation. 2003;107:346–54.
24. Mitter SS, Shah SJ, Thomas JD. A test in context. J Am Coll Cardiol. 2017;69:1451–64.
25. Iriarte M, Murga N, Sagastagoitia D, Morillas M, Boveda J, Molinero E, Etxebeste J, Salcedo A, Rodriguez E, Ormaetxe JM. Classification of hypertensive cardiomyopathy. Eur Heart J. 1993;14(Suppl J):95–101.
26. Vlasseros I, Katsi V, Vyssoulis G, Pylarinos I, Richter D, Gialernios T, Souretis G, Tousoulis D, Stefanadis C, Kallikazaros I. Aggravation of left ventricular diastolic dysfunction in hypertensives with coronary artery disease. Hypertens Res. 2013;36:885–8.
27. Tsioufis C, Georgiopoulos G, Oikonomou D, Thomopoulos C, Katsiki N, Kasiakogias A, Chrysochoou C, Konstantinidis D, Kalos T, Tousoulis D. Hypertension and heart failure with preserved ejection fraction: connecting the dots. Curr Vasc Pharmacol. 2017;16:15. https://doi.org/10.2174/1570161115666170414120532.
28. Teo LYL, Chan LL, Lam CSP. Heart failure with preserved ejection fraction in hypertension. Curr Opin Cardiol. 2016;31:410–6.
29. Zoni-Berisso M, Lercari F, Carazza T, Domenicucci S. Epidemiology of atrial fibrillation: European perspective. Clin Epidemiol. 2014;6:213.
30. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, Singer DE. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnticoagulationandRiskFactorsinAtrialFibrillation (ATRIA) study. JAMA. 2001;285:2370.
31. Hakim FA, Shen W-K. Atrial fibrillation in the elderly: a review. Futur Cardiol. 2014;10:745–58.

32. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham heart study. JAMA. 1994;271:840–4.
33. Nieuwlaat R, Capucci A, Camm AJ, et al. Atrial fibrillation management: a prospective survey in ESC member countries. Eur Heart J. 2005;26:2422–34.
34. Kistler PM, Sanders P, Fynn SP, Stevenson IH, Spence SJ, Vohra JK, Sparks PB, Kalman JM. Electrophysiologic and electroanatomic changes in the human atrium associated with age. J Am Coll Cardiol. 2004;44:109–16.
35. Tadic M, Ivanovic B, Cuspidi C. What do we actually know about the relationship between arterial hypertension and atrial fibrillation? Blood Press. 2014;23:81–8.
36. Manolis AJ, Rosei EA, Coca A, et al. Hypertension and atrial fibrillation: diagnostic approach, prevention and treatment. Position paper of the working group 'hypertension arrhythmias and thrombosis' of the European Society of Hypertension. J Hypertens. 2012;30:239–52.
37. Allessie M. Electrical, contractile and structural remodeling during atrial fibrillation. Cardiovasc Res. 2002;54:230–46.
38. Bosch R. Ionic mechanisms of electrical remodeling in human atrial fibrillation. Cardiovasc Res. 1999;44:121–31.
39. Patterson E, Po SS, Scherlag BJ, Lazzara R. Triggered firing in pulmonary veins initiated by in vitro autonomic nerve stimulation. Heart Rhythm. 2005;2:624–31.
40. Ruilope LM, Schmieder RE. Left ventricular hypertrophy and clinical outcomes in hypertensive patients. Am J Hypertens. 2008;21:500–8.
41. Goette A, Staack T, Röcken C, Arndt M, Geller JC, Huth C, Ansorge S, Klein HU, Lendeckel U. Increased expression of extracellular signal-regulated kinase and angiotensin-converting enzyme in human atria during atrial fibrillation. J Am Coll Cardiol. 2000;35:1669–77.
42. Ogunsua AA, Shaikh AY, Ahmed M, McManus DD. Atrial fibrillation and hypertension: mechanistic, epidemiologic, and treatment parallels. Methodist Debakey Cardiovasc J. 2015;11:228–34.
43. Borson S. Cognition, aging, and disabilities: conceptual issues. Phys Med Rehabil Clin N Am. 2010;21:375–82.
44. Hugo J, Ganguli M. Dementia and cognitive impairment. Clin Geriatr Med. 2014;30:421–42.
45. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed; 2013. https://doi.org/10.1176/appi.books.9780890425596.
46. Cacciatore F, Abete P, Mazzella F, et al. Frailty predicts long-term mortality in elderly subjects with chronic heart failure. Eur J Clin Investig. 2005;35:723–30.
47. Alzheimer's Association. 2013 Alzheimer's disease facts and figures. Alzheimers Dement J Alzheimers Assoc. 2013;9:208–45.
48. Helzner EP, Scarmeas N, Cosentino S, Tang MX, Schupf N, Stern Y. Survival in Alzheimer disease: a multiethnic, population-based study of incident cases. Neurology. 2008;71:1489–95.
49. Sneed JR, Culang-Reinlieb ME. The vascular depression hypothesis: an update. Am J Geriatr Psychiatry. 2011;19:99–103.
50. McKeith IG, Dickson DW, Lowe J, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB consortium. Neurology. 2005;65:1863–72.
51. Rabinovici GD, Miller BL. Frontotemporal lobar degeneration. CNS Drugs. 2010;24:375.
52. Kalaria RN. Cerebrovascular disease and mechanisms of cognitive impairment: evidence from clinicopathological studies in humans. Stroke. 2012;43:2526–34.
53. Murman DL. The impact of age on cognition. Semin Hear. 2015;36:111–21.
54. Della-Morte D, Guadagni F, Palmirotta R, et al. Genetics and genomics of ischemic tolerance: focus on cardiac and cerebral ischemic preconditioning. Pharmacogenomics. 2012;13:1741–57.
55. Salthouse TA. Selective review of cognitive aging. J Int Neuropsychol Soc. 2010;16:754–60.
56. Pannese E. Morphological changes in nerve cells during normal aging. Brain Struct Funct. 2011;216:85–9.
57. Masliah E, Mallory M, Hansen L, DeTeresa R, Terry RD. Quantitative synaptic alterations in the human neocortex during normal aging. Neurology. 1993;43:192–7.
58. Rivard L, Khairy P. Mechanisms, clinical significance, and prevention of cognitive impairment in patients with atrial fibrillation. Can J Cardiol. 2017;33:1556–64.
59. Ding M, Qiu C. Atrial fibrillation, cognitive decline, and dementia: an epidemiologic review. Curr Epidemiol Rep. 2018;5:252–61.
60. Cacciatore F, Gallo C, Ferrara N, et al. Morbidity patterns in aged population in southern Italy. A survey sampling. Arch Gerontol Geriatr. 1998;26:201–13.
61. Cacciatore F, Testa G, Langellotto A, et al. Role of ventricular rate response on dementia in cognitively impaired elderly subjects with atrial fibrillation: a 10-year study. Dement Geriatr Cogn Disord. 2012;34:143–8.
62. Takeda S, Sato N, Morishita R. Systemic inflammation, blood-brain barrier vulnerability and cognitive/non-cognitive symptoms in Alzheimer disease: relevance to pathogenesis and therapy. Front Aging Neurosci. 2014;6. https://doi.org/10.3389/fnagi.2014.00171
63. Wersching H, Duning T, Lohmann H, et al. Serum C-reactive protein is linked to cerebral microstructural integrity and cognitive function. Neurology. 2010;74:1022–9.
64. Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. Lancet Neurol. 2010;9:689–701.
65. Wardlaw JM, Smith EE, Biessels GJ, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. Lancet Neurol. 2013;12:822–38.
66. Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MMB. Silent brain infarcts and the risk of dementia and cognitive decline. N Engl J Med. 2003;348:1215–22.

67. Stefansdottir H, Arnar DO, Aspelund T, Sigurdsson S, Jonsdottir MK, Hjaltason H, Launer LJ, Gudnason V. Atrial fibrillation is associated with reduced brain volume and cognitive function independent of cerebral infarcts. Stroke. 2013;44:1020–5.
68. Saito T, Kawamura Y, Tanabe Y, Asanome A, Takahashi K, Sawada J, Katayama T, Sato N, Aizawa H, Hasebe N. Cerebral microbleeds and asymptomatic cerebral infarctions in patients with atrial fibrillation. J Stroke Cerebrovasc Dis. 2014;23:1616–22.
69. Rollo J, Knight S, May HT, Anderson JL, Muhlestein JB, Bunch TJ, Carlquist J. Incidence of dementia in relation to genetic variants at PITX2, ZFHX3, and ApoE ε4 in Atrial Fibrillation patients: ATRIAL FIBRILLATION AND DEMENTIA. Pacing Clin Electrophysiol. 2015;38:171–7.
70. Deneke T, Jais P, Scaglione M, et al. Silent cerebral events/lesions related to atrial fibrillation ablation: a clinical review: silent cerebral events/lesions related to AF ablation. J Cardiovasc Electrophysiol. 2015;26:455–63.
71. Medi C, Evered L, Silbert B, Teh A, Halloran K, Morton J, Kistler P, Kalman J. Subtle post-procedural cognitive dysfunction after atrial fibrillation ablation. J Am Coll Cardiol. 2013;62:531–9.
72. Bunch TJ, Crandall BG, Weiss JP, et al. Patients treated with catheter ablation for atrial fibrillation have long-term rates of death, stroke, and dementia similar to patients without atrial fibrillation. J Cardiovasc Electrophysiol. 2011;22:839–45.

Part II

Inflammatory Processes Perturbing Brain-Heart Dialogue

Immune System and Mind-Body Medicine: An Overview

6

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Contents

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*,
https://doi.org/10.1007/978-3-030-28008-6_9

Abstract

About one century ago, the discoveries made in the field of physical and medical science led to a reconsideration of the way science focuses on nature and on human beings. Subsequent research contributed to a relevant amount of papers on mind-body medicine, which reported remarkable efficacy of this discipline as therapeutic support in several pathologies.

Nevertheless, such evidence lacked a solid hypothesis on a possible biochemical pathway connecting the mind and the body. In this chapter, it is proposed that the occurrence of a cross talk between the immune and the neuroendocrine systems might be the underlying mechanism of action of mind-body medicine. This cross talk can be considered as "bit of information" connecting the cells of the entire organism. Quantum biology, a new field of research which recently comes to the attention of investigators, might provide a solid scientific base to explore "information" inside mind-body connections and could likely offer scientists a new paradigm to decode many medical issues. Quantum biology has been also proposed to explain important functions of the brain and of the immune system.

Keywords

Immune system · Nervous system · Neuroimmune cross talk · Cardiovascular disease · Mind-body medicine · Quantum biology

Introduction

Between the nineteenth and twentieth centuries, the discoveries made in the field of physical and medical science by Einstein, Heisenberg, Freud, and Jung led to a deep reconsideration of the way we see the universe, the reality, and finally the nature of human being. Various schools of thought developed new theories and visions [1, 2] to describe the human being in his complexity, dismantling the old paradigms. Wilhelm Reich (1897–1957), one of the Freud's students, developed the idea of muscular armor, expression of inner features such as personality, and environmental physical and psychological traumatic influences. Such an "armor" is manifest through the movements and the shape of the body, these theories being the foundation of innovations such as body psychotherapy, gestalt therapy, bioenergetics analysis, and primal therapy [3–5]. Reich, and even more so his student Alexander Lowen (1910–2008) [6, 7], considered the inner world of the mind as one of the "architects" of the body, at the basis of several physical symptoms and diseases. They considered specific sections of the body (i.e., thorax, diaphragm, shoulders, and pelvis) as the physical parts where mind perturbations might imprint visible signs and, based on these theories, developed several therapies by acting on the body, with the aim of making his natural energy to flow. This natural flow would support the healing of traumas and neurosis inside the mind. Despite strong controversies about Reich's theories [8], his legacy contributed to a relevant amount of studies on body-mind medicine. Nevertheless, these theories and the related experiments lacked a solid hypothesis on a possible biochemical pathway connecting the mind and the subject's inner world with the physical nature of the body. In this chapter, a hypothesis will be proposed on the background of the findings from 25 years of research [9], i.e., the occurrence of a neuroendocrine dialogue, with the immune system being one of the pathways able to connect mind inputs to body response. In the next sections, the most recent findings about this dialogue and its influence on organs and cells will be reviewed, together with its possible role in mind-body techniques. A particular attention will be given to the heart involvement, and a section will be devoted on factors which perturb the brain-heart dialogue by activating the immune system. Moreover, a new hypothesis on the nature of mind and consciousness will be introduced.

Clinical Evidence on Mind-Body Techniques (MBTs)

According to Astin [10] "mind-body medicine includes a variety of techniques designed to facilitate the mind's capacity to affect bodily function and symptoms." Symptoms included psychological states like anxiety as well as biological parameters like cholesterol level or heart rate. Therefore, the focus would be on finding the most likely pathways able to translate a mind-state into biochemical instructions for peripheral cells. When referring to mind-state, we do not only mean neural control of metabolic functions but also psychological patterns which often lie in the subconscious mind. A detailed description of current

knowledge in psychiatry is beyond the scope of the present chapter, but it is important to consider that several biochemical pathways are influenced by all the processes taking place in the brain and such pathways finally regulate peripheral organs and cells [9, 11].

The main MBTs reviewed by Astin are:

- Relaxation techniques, to reduce muscular tension or sympathetic arousal.
- Meditation, in particular transcendental meditation and mindfulness, which are the two most extensively investigated.
- Guided imagery, involving the generation of different mental images.
- Hypnosis, defined as a state of attentive and focal concentration in combination with a relative suspension of peripheral awareness.
- Biofeedback, which involves the use of devices to amplify physiological processes usually difficult to perceive, like blood pressure or muscle activity modulation.
- Cognitive behavioral therapy, which "emphasizes the role of cognitive processes in shaping affective experience and argues that problematic emotions, such as anger, depression, and anxiety, result from irrational or faulty thinking" [10].
- Psychoeducational approaches, combining techniques like relaxation and meditation with patient education, which consist in teaching patients about their symptoms, treatments, and behaviors.

The strongest evidence supporting therapeutic properties of MBTs was found in the fields of cardiovascular diseases, oncology, surgery, pain, and insomnia, and among techniques, contemplative activities, like mindfulness and transcendental meditation, resulted of remarkable efficacy.

MBTs and Cardiovascular Diseases

In two independent meta-analyses [12, 13] conducted on 37 and 23 clinical studies, respectively, the additional impact of psychoeducational and psychosocial programs for coronary disease patients was examined. Programs included health education (HE) (systematic instructional activities to facilitate positive changes in unhealthy behaviors), stress management (SM) (psychotherapeutic interventions, relaxation training, or supportive interventions) [12], relaxation techniques, group and individual psychotherapy, or breathing relaxation therapy [13].

The main results of HE and SM applied as secondary prevention, in the first meta-analysis [12], were an important reduction in both cardiac mortality and recurrence of myocardial infarction and significant positive effects on cholesterol, body weight, smoking behavior, physical exercise, eating habits, and blood pressure (e.g., a mean systolic blood pressure reduction of −14 mmHg and a mean diastolic blood pressure reduction of −11 mmHg, as described in a more recent review [14]). However, no effects were found in regard to anxiety, depression, or coronary bypass surgery. In the second meta-analysis [13], 2024 patients receiving psychosocial treatment vs 1156 control subjects were evaluated. Treated patients showed greater reductions in psychological distress, systolic blood pressure, heart rate, and cholesterol level. Control subjects showed greater mortality and cardiac events recurrence rates during the first 2 years of follow-up with log-adjusted odds ratios of 1.70 for mortality (95% confidence interval [CI], 1.09–2.64) and 1.84 for cardiac events recurrence (CI, 1.12–2.99). The benefits were clearly evident during the first 2 years, but the mortality reduction became nonsignificant when patients were observed for longer time. As a conclusion, authors reported that MBTs improving relaxation and management of anger, hostility, and stress were beneficial and were therefore to be recommended as part of cardiac rehabilitation.

Finally, a systematic review and meta-analysis of stress reduction programs in hypertensive subjects found that transcendental meditation program was associated with significant mean blood pressure (BP) reduction (−5.0 mm Hg systolic and −2.8 mm Hg diastolic) [15]. The clinical implication is important since by using a low-cost approach, complementary to standard pharmacological treatments, it can be possible to remarkably improve the outcomes.

MBTs and Oncology

In two meta-analyses of 45 and 116 studies on oncologic patients, relaxation, hypnosis, and supportive group therapy were found to improve mood, quality of life, and coping with both the disease and the treatment-related side effects [16, 17]. Psychoeducational care was found to benefit adults with cancer in relation to anxiety, depression, mood, nausea, vomiting, pain, and knowledge, despite the fact that no effects on tumor size were reported. Statistically significant beneficial effects were found in relation to all seven of the outcomes; however it was not possible to differentiate among the effectiveness of various types of psychoeducational care.

MBTs and Surgery

A meta-analysis conducted on 191 studies of the effects of psychoeducational care on the recovery of adult surgical patients found small to moderate sized beneficial effects on recovery, postoperative pain, and psychological distress, and the message of the authors was that with a small investment of resources, it was possible to improve patient welfare and recovery. They concluded that, given the current trends toward outpatient surgery, innovative mechanisms able to ensure a comprehensive psychoeducational care for surgical patients are undoubtedly needed [18].

MBTs and Pain

In a report for the Agency for Healthcare Research and Quality (AHRQ, Rockville, MD) [19], investigators assessed which noninvasive nonpharmacological treatments for common chronic pain conditions (such as low-back/neck pain or osteoarthritis) could improve function and pain for at least 1 month after treatment. They based their work on 202 trials, many of which small, enrolling patients with moderate baseline pain intensity and comparing MBTs against usual care. They concluded that MBTs were most consistently associated with durable slight to moderate improvements in function and pain for specific chronic pain conditions. They also recommended to focus future strategies on use of nonpharmacological therapies for specific chronic pain conditions.

MBTs and Insomnia

In the beginning of the 1990s, a meta-analysis on studies involving more than 2000 patients suffering insomnia was performed [20], to examine the efficacy of psychological treatments. Morin and colleagues described that an average of 5 h treatment produced important changes in two of the four parameters analyzed (sleep latency and time awake after sleep onset). Few years later, Morin published a randomized controlled trial on 78 subjects to study clinical efficacy of cognitive behavioral therapy (CBT), with/without temazepam, compared to temazepam alone or to placebo, in treating late-life insomnia [21]. The main findings were that the combined therapy was effective for the short-term management of insomnia, but sleep improvements were better sustained over the long period with the CBT approach alone. CBT for insomnia is now commonly recommended as first-line treatment for chronic insomnia [22]. Moreover, there is a growing body of evidence suggesting that other MBTs, like yoga, tai-chi, and mindfulness, may improve insomnia symptoms [23]. Mindfulness, in particular, shows the potentiality to be considered as a possible second-line or adjunctive therapy to CBT [23], considering that it was found to improve sleep quality as measured by Pittsburgh Sleep Quality Index (PSQI) scores, and was also as effective as pharmacotherapy with eszopiclone in improving Insomnia Severity Index, PSQI, and other measures of insomnia outcome [24]. Mindfulness was developed in clinics by Jon Kabat-Zinn at the University of Massachusetts Medical Center to facilitate adaptation to medical illness, in a program involving chronic pain patients [25], and it has been used in the last decades to teach patients how to deal with distress commonly associated with several chronic illness [26–32].

Contemplative Activities and Respiratory Vagal Nerve Stimulation Hypothesis

In a very recent review, Gerritsen and colleagues describe cumulative number of scientific publications on contemplative activities (ContActs) like yoga, meditation, and mindfulness, from the 1945–2017, obtained from Web of Science in January 2018 [33]. The number of clinical trials on these disciplines increased from less than 20 in the year 2000 to about 250 in 2014, describing positive effects of ContActs on physical and mental health and on cognitive performance. In particular, ContActs had anti-inflammatory effects, in terms of CRP and TNF reduction, increased cardiopulmonary health, and had beneficial effects in managing chronic pain and in improving muscle flexibility and bone density. In several trials and meta-analysis, ContActs were found to reduce multiple physiological stress markers like heart rate, blood pressure, cortisol levels, and inflammatory bodies [34–37]. In the case of mindfulness-based cognitive therapy, also symptoms of affective psychopathology (depression, anxiety, and post-traumatic stress disorder) were reduced [38–43]. In particular, investigators of the PREVENT trial, in their work published in 2015 on The Lancet [39], concluded supporting mindfulness-based cognitive therapy, in combination with tapering or discontinuing antidepressant treatment, as an alternative therapeutic solution to pharmacological treatment alone for prevention of depressive relapse or recurrence at similar costs.

Gerritsen and colleagues proposed a neurophysiological model, called respiratory vagal nerve stimulation (rVNS), to explain the ContActs beneficial effects described in the trials and in the meta-analysis reports. They notice that various ContActs have in common regulation or attentive awareness of breathing and propose that these specific respiration styles could phasically and tonically stimulate the vagal nerve, thus improving heart rate variability, baroreceptor reflex, and cholinergic anti-inflammatory pathway [44], all mechanisms with cardiovascular and neurological protective properties. Such a hypothesis lacks specific experimental studies but offers food for thoughts and indications for future perspectives. Authors concluded hoping that neuroscience will focus on rVNS respiratory patterns as potential cognitive and mental health enhancers.

Studies Limitations

One of the main limitations in most mind-body studies reviewed was the absence of a placebo group. In fact practitioners cannot typically be blinded to the treatment, and it is often not possible to blind patients to group assignment. There is thus a need of stronger protocols to better control potential measurement confounders. Many researchers have also noted that an important number of patients refused psychosocial interventions; therefore the reported results only represent individuals willing to accept the participation in these studies. The beneficial results found should therefore be considered to apply only to those patients interested in participating in psychosocial interventions, creating a possible bias. Also the limited number of published trial is an important issue, especially when compared to the number of large clinical trial investigating the effects of a specific drug. Here the problem might be of financial nature, the subjects interested in such studies being usually the associations of patients or of practitioners, and the budget available is inevitably low. Nevertheless, research is still ongoing, and a work by Taylor and colleagues suggested possible mechanisms underlying MBTs observed effects, highlighting the role of immune system, neurological mechanisms, and psychophysiological aspects in mind-body medicine [9]. In the next section, these neuro-immune mechanisms will be explored and described.

Brain-Heart Connections: Link with the Immune System

Parasympathetic Nervous System

The first sentence of the review "The Inflammatory Reflex" [44] is a phrase of Moliere (1622–1673): "The mind has great influence

over the body, and maladies often have their origin there."

The author Kevin Tracey chose this concept to present the discovery of the cholinergic anti-inflammatory pathway, an unexpected property of parasympathetic nervous system which can inhibit inflammatory cytokine production from immune cells. Cholinergic anti-inflammatory pathway is an axis connecting the brain with several organs, including the heart, through the vagus nerve which exits from the medulla oblongata reaching the reticuloendothelial system (liver, heart, spleen, and gastrointestinal tract). Inflammatory products from periphery activate afferent signals that are transferred to the nucleus tractus solitarius, followed by activation of efferent vagus fibers. The subsequent acetylcholine secretion reaches immune cells decreasing inflammatory response, by acting on the key receptor α7 nAChR, the α7 subunit of the nicotinic acetylcholine receptor, expressed on their membrane. The evidence that immune cells express receptors for neurotransmitters and that autonomic nervous system (ANS) modulates immune cells functions had remarkable consequences in the field of neurology and of immunology. Very soon also cardiovascular research was influenced by this new finding, opening a scenario where cardiologist could experiment novel therapeutic approaches [45–47].

In fact, in the last 15 years, evidence showed that activation of nicotinic pathway, with vagal stimulation (VS), reduced the extent of myocardial infarction in experimental models of cardiac ischemic injury and that part of this cardioprotection was due to its anti-inflammatory effect [46–48].

Together with its anti-inflammatory effect, cholinergic anti-inflammatory pathway was found to enhance the capillary density in myocardial ischemic tissues [49], to improve survival after experimental heart failure [46] and to protect against mitochondrial transition pore opening during ischemia and reperfusion injury in rat heart [50]. At clinical level, several studies explored the possible therapeutic role of vagal stimulation (VS) in patients suffering heart failure, and investigations are still ongoing [45, 51, 52].

Interestingly, Tracey himself considers cholinergic anti-inflammatory pathway as a "bridge" to explain the therapeutic effects seen in mind-body medicine classical techniques, like acupuncture, biofeedback, meditation, cognitive and relaxation therapies, or hypnosis [44, 53]. He gives an intriguing interpretation: these techniques could act trough an indirect stimulation of vagus nerve, thus decreasing inflammation and improving health status. The cholinergic anti-inflammatory pathway could be considered one of the pathways able to translate mind information into biochemical instructions for peripheral targets, and the "tool kit" for this process seems to be the immune system.

Sympathetic Nervous System

Cardiac lesions produced by nervous system dysfunction have been clearly described [54], and in general the concept of nervous system dysfunction affecting visceral organs was first proposed by Pavlov and Selye [55, 56] several decades ago. Recently, the influence of the sympathetic system (SNS) on immunity was summarized in an interesting review by Pongratz and Straub [57] who describe SNS having a dual function on immune system. On the one hand, SNS exerts an anti-inflammatory action at the site of inflammation, but on the other hand, at systemic level, it supports leukocytes recruitment and antigen processing. SNS innervates the spleen, lymph nodes, and thymus, regulating immune mediators synthesis and release [11], and sympathetic neurotransmitters like norepinephrine (NE) or neuropeptide Y (NPY) have direct interaction with macrophage, dendritic cells, and T and B cells, modulating phagocytosis, proliferation, and cytokines production [57]. Cytokines, in turn, were found to signal the brain via nerve routes, influencing behavior and recovery from stress or traumatic injury [58].

Contrary to cholinergic anti-inflammatory pathway, SNS-immune cross talk often leads to harmful effects to the cardiovascular system. Ziegler and colleagues [59] found that local cardiac sympathetic denervation in mice, performed

simultaneously with myocardial infarction, improved cardiac functions and decreased myocardial inflammation and hypertrophy with respect to controls after 2 weeks. Also in a setting of experimental hypertension [60], sympathectomy normalized myocardial levels of IFN-gamma, IL-6, and IL-10 in spontaneously hypertensive rats (SHR) and reduced blood pressure and cardiac fibrosis. These results suggest that SNS interaction with inflammatory cells in the heart has a key, and sometimes deleterious, role in modulating myocardial remodeling secondary to infarction or hypertension.

The involvement of immune activation in many cardiac pathologies and the existence of the brain-heart axis are currently accepted by scientific community [56, 61–69]. The finding that immune system reciprocally interacts with nervous system in modulating organ response to injury, including the heart, probably fills a gap and provides a useful description of a sequence of metabolic events from the center to the periphery.

The studies about the role of immune system in the brain-heart axis perturbation are unveiling a complex cross talk in which immune mediators seem to act both as messengers between the two main organs [70] and the actors putting the messages into effect. An interesting experimental evidence in this sense comes from a study by Kashyap and colleagues [71]. They treated mice with renal artery stenosis to develop hypertension and gave a CCL2 receptor blockade. In this group of animals, there was an attenuated renal atrophy, despite mice experienced a sustained hypertension. Finally, in other studies, investigators found that in case of autonomic storm, responsible for cardiac infarction without artery occlusion, a massive radical release occurred, and interestingly, the same contraction band necrosis seen in the heart after autonomic storm was reported in case of inflammatory cardiac reperfusion injury [54, 56, 72]. Samuels summarized the cascade of events that from sympathetic nervous system, dysfunction leads to heart tissue damage, and as key point at the end of the cascade, he indicated free radical release as the final actor injuring the cells [56]. Free radicals are one of the main hallmarks of inflammation, a chemical "weapon" released by leukocytes to kill pathogen organisms.

It is becoming increasingly evident that there is a cardiovascular-immune-neural axis that at peripheral sites shows plasticity and integration: innate immune system stimulates autonomic nervous system through immune mediators released from immune cells, and this activation is integrated at the hypothalamic level [58, 73–75]. Mutually, autonomic nervous system [44, 76] can modulate the functions of immune system cells through receptors expressed on their surface. This mutual "dialogue" was found to be relevant to cardiovascular disease, and a deeper understanding of its functioning could reveal new therapeutic opportunities.

Factors Activating the Immune System which Perturb the Brain-Heart Dialogue

There are factors activating the immune system which perturb the dialogue between ANS and cardiovascular system. Ischemia and stress are examples of topical issues of common interest.

Ischemia and Hypertension

Several inputs, both from external and internal environment, can affect the cardiovascular-immune-neural axis. Stressors like ischemia or hypertension can perturb brain-heart dialogue also by modulating inflammatory processes [77–79].

It is known that patients with coronary artery disease (CAD) can develop accelerated cognitive decline; in particular those affected by major depression and that depressive symptoms can lead to an increased risk of cardiovascular events [80, 81]. These phenomena are linked, and the immune system is considered an important connecting pathway which can modulate the outcome [80, 82]. A small study involving patients with CAD [81] showed that some platelet-activating factors (PAFs), which are proteins modulating many leukocyte functions, were associated with a reduced global cognitive performance and that this association was even higher in a subgroup

suffering depression. Some investigators focused their attention on TNF-alpha role in cognitive disruption after infarction. Meissner and colleagues [83] described TNF-alpha-dependent loss of cortical dendritic spine density in a mouse model of heart failure (HF) following coronary artery ligation. In HF mice, cerebral TNF-alpha levels were increased and microglia activated, indicating brain inflammation, and reduction of cortical dendritic spines and morphological changes occurred. The use of TNF-alpha scavenger or genetic deletion attenuated cortical dendritic spines reduction.

Liu and colleagues [80] reported data, from both experimental and clinical studies, highlighting the role of inflammation in the relationship between depression and acute myocardial infarction (AMI), in particular in relation to the post-AMI depression. They reviewed the role of TNF-alpha in depression after myocardial infarction (AMI) and suggested a possible mechanism of this cytokine in favoring depression by inducing alterations in blood-brain barrier (BBB) permeability, thus altering biochemically psychiatric patterns at central level. This hypothesis was proposed by considering the following observations:

- Depressed and AMI patients were found to have an increased inflammatory activation [84, 85].
- Both conditions are present in a relevant number of patients and are clearly correlated, but the underlying mechanisms are unknown [86].
- TNF-alpha was found to increase BBB permeability in in vitro models [87, 88].
- TNF-alpha caused increase BBB permeability in both swine and rats [89, 90].
- Several investigators associated inflammation after AMI with possible BBB alteration [91]. This alteration could allow immune mediators infiltration, and, interestingly, cytokine-dependent reduction in serotonin availability was described as a factor contributing to depression [92].
- Increased cytokine activation in specific brain regions can activate brain renin-angiotensin-aldosterone system in rats [93–95].
- TNF-alpha inhibition in patients and in animal models can decrease depressive symptoms [96–98].
- Finally, optimal treatment of cardiovascular disease in AMI patients usually has no major effects on depression. Moreover, treatment of depression in these patients, despite being associated with some improvement in depressive symptoms, does not improve cardiac outcomes [99]. This observation suggests that the link connecting the two clinical situations probably is not confined in each pharmacological metabolic pathway, but it likely lies in the cross talk between the central nervous and the immune systems, in particular in the TNF-alpha-dependent BBB disruption. This event probably causes biochemical alterations in those brain areas related with regulation of serotonin and of neuroendocrine molecules involved in depressive symptoms.

Several mechanisms were proposed to explain BBB disruption caused by TNF-alpha, such as the cyclooxygenase (COX) pathway, nitric oxide release, or upregulation of intracellular adhesion molecules [56]; nevertheless a clear evidence in patients is still lacking. Authors concluded suggesting the central role of inflammation, especially of possible TNF-alpha-dependent BBB alterations, as a common denominator of AMI, stress, neuroendocrine dysfunction, and depression. The problem of BBB permeability has been an emerging issue in the last years and has been associated with cardiovascular and metabolic dysfunctions in laboratory animals [100–102].

In addition to ischemia and hypertension, other factors not immediately attributable to biochemical alterations can have a profound effect in perturbing brain-heart axis, too, through their action on immune system. Stress is considered one of the most important factors, and it is the target of many mind-body medicine therapeutic techniques.

Stress

Stress is recognized as an important risk factor which can exacerbate a disease or even trigger a

pathologic response [11]. Stress is often split into two main categories, "exteroceptive," when the individual need to respond to external inputs facing challenges, and "interoceptive," occurring during or after physiological perturbations like injuries, inflammation, or chronic diseases [103]. Stress stimulates allostasis (which means maintaining stability through change) both in the physical body and in the psychological patterns and triggers the activation of specific neuro-immune pathways, with the aim of providing an adequate response [104, 105]. When the body-mind system is overwhelmed by stressors, the condition called "allostatic load" can start autonomic dysfunction and stress-related pathologic conditions, including hypertension and particular types of heart disease [56, 106, 107].

It was proposed that the immunological alterations associated with stress represent an adaptation of the common response to infection and several investigators have described the impact of stress on immune system, both in humans and in animal models [102, 108, 109]. In a model of chronic psychological stress in mice, bone marrow-derived microglia infiltrated the paraventricular nucleus likely through a mechanism involving the two immune axis MCP-1/CCR2 and CXCL12/CXCR4 [102]. Santisteban and colleagues reported evidence that infiltration of bone marrow-derived microglia into the brain and resident microglia activation in autonomic brain regions represent a hallmark of neuroinflammation in neurogenic hypertension [79, 110]. CXCL12 and its receptor CXCR4 are expressed in the bone marrow and in many other tissues and play a central role in the mobilization of stem cells from the bone marrow. Some of these progenitors differentiate into inflammatory cells which can infiltrate peripheral tissues. At molecular level, the CXCL12 gene contains 1 of the 27 single-nucleotide polymorphisms which were associated with increased risk of coronary artery disease [111–113]. In a mouse model of post-traumatic stress disorder, social stress led to myocarditis and vasculitis through a mechanism involving complement and cytokines activation, cell cycle processes, and tissue remodeling [114]. Also in human subjects, stress was related with inflammation increase followed by various pathologic conditions: the immune mediators interleukin-6 and C-reactive protein, for instance, were found to be stress-related molecules responsible for atherosclerosis development [115], and a positive correlation between C-reactive protein (CRP) and mental stress induced-myocardial ischemia was described by Soufer and colleagues [116]. The link between stress, inflammation, and various diseases was extensively reviewed by Liu and colleagues, who described also the role of stress-related inflammation in cardiovascular diseases [115], and by Munakata [117] and Black [118] who indicated in the neuroinflammation the pathway likely involved in the stress-related increase of blood pressure. To support these observations, methods reducing stress were found able to reduce inflammatory response and to improve health conditions. In expert meditators and in subjects performing several mind-body techniques (MBTs), there was a decreased expression of pro-inflammatory genes, a better autonomic response, and a reduced intrinsic epigenetic age acceleration [106, 109, 119–123].

In summary, MBTs might act by modulating ANS, which in turn would orchestrate immune reactions in a beneficial way, that is, less inflammation and decreased oxidative stress. Most of the above-described pathologies have a strong inflammatory component. Therefore modulating inflammation in most cases would mean modulate the disease itself. Moreover, by reducing stress impact in daily life, MBTs would probably inhibit those inflammatory processes triggered by stress itself. Once again, inflammation seems to be the last step of a multifactorial cascade from the environment (both inside and outside the body) to the cell metabolism. Nevertheless, further studies are needed to verify if MBTs have the property of modulating ANS toward anti-inflammatory processes and to clarify the precise biochemical steps of this possible mechanism. Authors suggested that an array of mind-body therapies can be used as effective adjuncts to conventional medical treatment for a number of common clinical

conditions, creating thus opportunities for further clinical research.

"Information": A Key Element?

In the interdisciplinary approach of many MBTs, "information" is often cited as a key property of the human organism to integrate internal and external inputs, including therapies, to reach a favorable medical outcome [5–7, 9, 11]. This characteristic feature is considered "innate" and is often used to explain to the patient the healing process driven by the specific technique used. Nevertheless, a clear understanding of how "information" spreads throughout the entire organism, reaching every single cell process, is still lacking, especially if we take into account physical parameters such as velocity or thermodynamics. Quantum biology [124], a new field of research recently come to the attention of investigators, might provide a solid scientific base to explore in depths information inside mind-body connections and could likely offer scientists a new paradigm to decode many medical issues, especially those currently lacking a biochemical explanation or a pharmacological remedy. Seth Lloyd defines quantum mechanics a collection of "digital gift to nature," and information would be one of these gifts [125]. The information is constituted by fundamental units called bits, each representing the distinction between two possible states. The other gifts are the information processing, which in nature reaches higher levels of efficiency (e.g., in the DNA), and the randomness, which allows for variations, essential for the evolutionary process [125]. Superimposition, entanglement, and other quantum properties, described in the next section, are the way quantum uses to process and spread information.

Quantum biology takes advantage of recent progress in atomic-scaled biological chemistry and studies behavior of subatomic particles involved in biochemical processes, like electrons and protons responsible for biochemical bonds in peptides [126] or the single potassium ion in an ion channel on a cell membrane [127]. In the next paragraphs, quantum biology will be introduced, and its possible key role in decoding some human biology processes will be explored.

Quantum Biology: A Possible Mechanism Underlying Mind-Body Medicine?

Between late 1920s and mid-1960s, Niels Bohr (1885–1962) and Erwin Schrödinger (1887–1961), two of the main physicists who studied atomic structure and developed quantum mechanics, dealt with the issue of physic aspects of life [128, 129]. Bohr exposed his hypotheses in a series of lectures about the quantum and the description of the nature (in 1929), about the connection between biology and atomic physics (in 1937), and between quantum physics and the problem of life (in 1962) [128]. Schrödinger tried to explore phenomena like the property of gene structure, which involves a relative small number of atoms, to display "a most regular and lawful activity — with a durability or permanence that borders upon the miraculous" [129]. In the late 1960s, Frohlich suggested that in biological systems, thanks to their dielectric properties, a random supply of energy might not be completely thermalized but in part used to maintain a coherent wave in the substance [130]. He considered the existence of a long-range coherence in the living systems which, even if relatively stable, are in some respects far from thermal equilibrium. From a physical point of view, cells membrane, with a remarkable thickness and a complicate shape, can maintain a strong dipolar layer thanks to local vibrations, in which the positive and the negative part of a particular membrane section vibrate against each other leading to an oscillating electric dipole. The author concluded that biological systems might have the ability of storing supplied energy in a highly ordered form [130]. Nevertheless, until the beginning of the twenty-first century, most of the scientists considered the living cell an environment too warm and wet and too noisy to allow delicate quantum processes. An important turning point was the discovery that three of the main biological phenomena, photosynthesis, enzyme reaction, and avian compass,

actually function through the quantum properties of superimposition (photosynthesis), proton tunneling (enzyme reaction), and entanglement (avian compass) [124, 131–139].

These properties can be described with mathematical functions; nevertheless, such a specific description would require a technical knowledge not common in the medical and biological community. However, many educational books are available (the reader is referred to work by Jim Al-Khalili [140, 141]), and several collaborations between biologists and physicists are producing interesting research papers [127, 142, 143]. In the next paragraph, a non-mathematical description of quantum biology basic principles will be provided.

Photosynthesis. Superimposition is described as a property of the waves and of the quantum particles, which can exist in two different states at the same time. There is an image commonly used to explain superimposition to nonspecialized public (Fig. 1), in which the reader can see one vase OR two faces, but they exist at the same time. It is "the choice" of the reader's mind to make visible one or the other. This "choice" might represent what is described as wave function collapse, when the wave is reduced to a single state. This is exemplified by the assessment of position instead of velocity (wave function collapse occurs when the position of an electron has been determined; in this case the electron's state becomes an "eigenstate of position," meaning that its position has a known value, but velocity is unknown) [144, 145]. The electrons in the photosynthetic processes are in a superimposed state until they collapse, according to the variable environmental conditions, and trigger the biochemical cascade transforming photons in chemical energy, in the best solar panel known.

Enzyme reaction. Proton tunneling refers to quantum tunneling property, which is the phenomenon where a particle tunnels through a barrier that it classically cannot surmount [146] (Fig. 2). In some enzyme-catalyzed reactions, protons move from one molecule to another by tunneling, with particles passing through an

Fig. 1 One vase or two faces image, to intuitively describe quantum superimposition

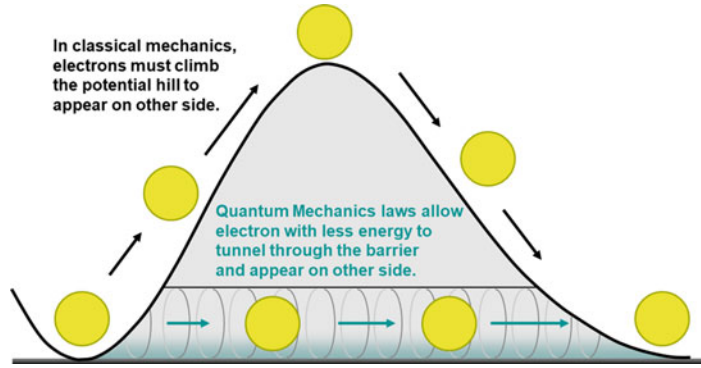

Fig. 2 Quantum tunneling

energy barrier rather than having to increase the energy to overpass it [134–136, 140]. In particular, investigators described the reaction pathway for tryptamine oxidation by aromatic amine dehydrogenase and showed that proton transfer occurs to the oxygen molecule of aspartic acid 128 beta in a reaction dominated by tunneling over about 0.6 angstroms [134].

Avian compass. Some migratory birds have the ability to sense variations in earth's magnetic field and to discriminate between the pole and the equator. The bird's eye contains molecular structures each absorbing an optical photon, and the absorption of a single photon creates two unpaired electrons which exist in a state of quantum entanglement, a form of coherence in which the orientation of one spin remains correlated with that of the other, no matter how far apart the radicals move [124]. Each of these unpaired electrons has an intrinsic angular momentum, or spin, that can be reoriented by a magnetic field, and when the radicals separate, one unpaired electron is influenced by the magnetism of a near atomic nucleus in the bird's eye; the other feels only earth's magnetic field and is away from the atomic nucleus influencing the former electron. The two unpaired electrons, despite the distance separating them, remain "in contact" in an entanglement state, giving the bird the ability to hook earth's magnetic field until reaching the geographical destination. Investigators found that in this living system, this entanglement is sustained for at least tens of microseconds, more than what occurs in the best comparable artificial molecular systems [138]. Recently, type IV cryptochrome was found to be the most likely candidate magneto-receptor of this light-dependent magnetic compass [139].

If some of the basic life functions are explained with quantum mechanics, it is plausible to imagine a similar approach for human biology. Several investigators tried to uncover possible quantum properties in the central nervous system, studying mind and consciousness, and in the immune system, which are both characterized by a network structure and by an incredible efficiency in terms of information transfer and subsequent biochemical response.

The Definition of "Mind"

In 2013 Sahu and colleagues published a manuscript where they described a particular physical property of the brain microtubule [147], that is, that a microtubule is a memory-switching element which shows quantum vibrations. Microtubules are major components of the cell structural skeleton, and authors suggest that EEG might derive from a deeper level of such vibrations and conclude that treating brain microtubule vibrations could be beneficial for patients suffering mental, neurological, and cognitive diseases. This discovery corroborates a theory of consciousness named orchestrated objective reduction (Orch-OR) conceived by Sir Roger Penrose and Stuart Hameroff in the mid-1990s [148]. This theory hypothesized that mind is a quantum computer able to manage multilevel layers of information and the according reactions. The unit of such a computer would be the microtubule structure thank to the quantum

property of tubulin to be in two superimposition states. These quantum states might extend through the nervous system by entanglement between adjacent neurons through gap junctions. They suggested that quantum vibrational computations in microtubules are "orchestrated" ("Orch") by synaptic inputs and memory stored in microtubules and terminate according to the Diòsi-Penrose scheme of "objective reduction" ("OR"), hence "Orch OR."

Clinical trials using transcranial ultrasound to trigger brief brain stimulation aimed at microtubule resonances with megahertz mechanical vibrations reported improvements in mood [149] and are considered potentially useful against Alzheimer's disease and brain injury in the future.

Other investigators consider tubulin "too big" to allow quantum processes and identify in the cellular ion channels in the nerves a biological structure governed by quantum processes [127, 140], accepting anyway the idea of a quantum behavior of the brain.

Immune System and "Quantum Immunology"

A single autoimmune T-cell receptor (TCR) is able to recognize more than a million different peptides, and this property is at the basis of the self-non-self-discrimination, one of the most important biological functions. The conceptual basis to explain the self-non-self-discrimination phenomena was first proposed by Burnet with the clonal selection theory [150], which implies that each TCR interacts with a specific antigenic peptide-major histocompatibility complex (pMHC) ligand. Nevertheless, evidence from both experimental and theoretical approach showed that each TCR is, on the contrary, capable of interacting with several ligands, a property known as TCR degeneracy [151]. On the basis of their experimental results, Antipas and colleagues proposed that the TCR degeneracy might be caused by interactions at atomic level between the two proteins, whereby different pMHC ligands, with almost identical stereochemistries, can induce different quantum chemical behavior in the single TCR, followed by activation of different downstream signaling, according to the specific insult. This phenomenon would depend directly on the peptide's electron spin density and would be expressed by the protonation state of the peptide's N-terminus [126, 152, 153]. In other words, the interaction would take place at the atomic level of the primary protein structure of the two proteins involved and would follow quantum mechanics roles. This implies that the fundamental properties of the immune system behavior would lie in the quantum level of reality, justifying the term quantum immunology proposed by Antipas and colleagues [126].

Conclusion: Mind-Body Medicine and Quantum Biology – A New Paradigm?

Considering all the above-reported evidence, it is possible to speculate about a new paradigm arising from recent progress in either medicine, biology, or physics.

1. Nervous system and peripheral cells have a mutual information exchange through the action of immune system which is in cross talk with both structures.
2. Sympathetic and parasympathetic nervous systems' opposite effects go beyond the well-known action on heart rate, being involved in continuous allostatic response to face internal and external inputs perturbing the entire psychophysical system.
3. Several factors, from the external environment, from the inner world of the consciousness and subconsciousness, and from physical body dysfunctions, can perturb the allostatic balance maintained by the incessant dialogue between nervous system, immune system, and peripheral cells.
4. The ability of these systems to spreads information throughout the entire organism, triggering biochemical responses, might be explained by quantum properties of the subatomic particles that constitute biological molecules, in particular peptides.

5. The evidence that photosynthesis, enzyme functions, avian compass, ion channels, tubulin, and T cells recognition of antigens are based on quantum properties like entanglement, superimposition, tunneling, and quantum chemical behavior allows researchers to postulate a new way of approaching biological and medical problems. This way might involve the use of low-frequency electromagnetic fields or other forms of waves controls, already under investigations [154–157], to trigger biochemical reactions with therapeutic purposes.
6. In case the ORCH-OR theory will be definitively demonstrated, the consequences in the fields of neurology, psychiatry, and, in general, in medicine will be huge and will probably explain many phenomena reported by mind-body therapists. Indeed, if the entire mind and the autonomic nervous system prove to be a sort of quantum computer in continuous entanglement with itself and with the entire internal and external environment, it would be clear that those MBTs able to manipulate the organism at several level might trigger an integrated and coherent response.
7. Finally, if the quantum behavior of immune cells will be further demonstrated, the role of a cross talk between brain, immune system, and peripheral cells would be of greater importance.

In conclusion, if the quantum biology research will continue to develop so rapidly, we can expect the emergence of a new type of medicine, which will probably be called quantum medicine.

References

1. Easton SC. Rudolf Steiner: herald of a new epoch. SteinerBooks, Later printing editor. 1980. p 376.
2. Wellbeloved S. Gurdjieff: the key concepts. Routledge Key Guides. Press P, Routledge, editor. 2003.
3. Reich W, Mary Boyd Higgins DJ. Beyond psychology: letters and journals 1934–1939. Farrar S and G, editor.
4. Reich W. Character analysis. 3rd ed: Farrar, Straus and Giroux, New York, USA; 1980.
5. Janov A. The new primal scream: primal therapy twenty years on. Abacus, editor.
6. Lowen A. The language of the body: physical dynamics of character structure. Inc LS, editor.
7. Lowen A. Bioenergetics. Penguin, editor.
8. Brady ME. The strange case of Wilhelm Reich. Bull Menninger Clin. 1948;12(2):61–67.
9. Taylor AG, Goehler LE, Galper DI, Innes KE. Top-down and bottom-up mechanisms in mind-body medicine: development of an integrative framework for psychophysiological research. Explor (NY). 2010;6 (1):29–41.
10. Astin JA, Shapiro SL, Eisenberg DM, Forys KL. Mind-body medicine: state of the science, implications for practice. J Am Board Fam Med [Internet]. 2003;16(2):131–47. Available from: http://www.jabfm.org/cgi/doi/10.3122/jabfm.16.2.131
11. Vitetta L, Anton B, Cortizo F, Sali A. Mind-body medicine: stress and its impact on overall health and longevity. Ann N Y Acad Sci. 2005;1057:492–505.
12. Dusseldorp E, van Elderen T, Maes S, Meulman J, Kraaij V. A meta-analysis of psychoeducation programs for coronary heart disease patients. Health Psychol. 1999;18(5):506.
13. Linden W, Stossel CMJ. Psychosocial interventions for patients with coronary artery disease: a meta-analysis. Arch Intern Med. 1996;156(8):745–52.
14. Linden W, Moseley JV. The efficacy of behavioral treatments for hypertension. Appl Psychophysiol Biofeedback. 2006;31(1):51–63.
15. Rainforth MV, Schneider RH, Nidich SI, Gaylord-King C, Salerno JW, Anderson JW. Stress reduction programs in patients with elevated blood pressure: a systematic review and meta-analysis. Curr Hypertens Rep. 2007;9(6):520–8.
16. Meyer TJ, Mark MM. Effects of psychosocial interventions with adult cancer patients: a meta-analysis of randomized experiments. Health Psychol. 1995;14 (2):101–8.
17. Devine EC, Westlake SK. The effects of psychoeducational care provided to adults with cancer: meta-analysis of 116 studies. Oncol Nurs Forum. 1995;22 (9):1369–81.
18. Devine EC. Effects of psycho- educational care for adult surgical patients: a meta-analysis of 191 studies. Patient Educ Couns. 1992;19:129–42.
19. Skelly AC, Chou R, Dettori JR, Turner JA, Friedly JL, Rundell SD, et al. Noninvasive nonpharmacological treatment for chronic pain: a systematic review 2018; (209). Available from: https://www.ncbi.nlm.nih.gov/pubmed/30179389
20. Morin M, Culbert P. Nonpharmacological interventions for insomnia: a meta-analysis of treatment efficacy. Am J Psychiatry. 1994;151:1172–80.
21. Morin CM, Colecchi C, Stone J, Sood R, Brink D. Behavioral and Pharmacological Therapies for Late-Life Insomnia. JAMA [Internet]. 1999;281(11):991. Available from: http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.281.11.991

22. Trauer JM, Qian MY, Doyle JS, Rajaratnam SMW, Cunnington D. Cognitive behavioral therapy for chronic insomnia – a systematic review and meta-analysis. Ann Intern Med. 2015;163(3):191–205.
23. Zhou ES, Gardiner P, Bertisch SM. Integrative medicine for insomnia. Med Clin North Am [Internet]. Elsevier Inc. 2017;101(5):865–79. Available from: https://doi.org/10.1016/j.mcna.2017.04.005
24. Kay-Stacey M, Attarian H. Advances in the management of chronic insomnia. BMJ. 2016;354:i2123.
25. Kabat-Zinn J. An outpatient program in behavioral medicine for chronic pain patients based on the practice of mindfulness meditation: theoretical considerations and preliminary results. Gen Hosp Psychiatry. 1982;4(1):33–47.
26. Bishop SR. What do we really know about mindfulness-based stress reduction? Psychosomatic Medicine. 2002;64:71–84.
27. Santorelli SF. Mindfulness – based stress reduction (Mbsr): standards of practice. The Center for Mindfulness in Medicine, Health Care, and Society University of Massachusetts Medical School. 2014;(February):1–24. http://www.umassmed.edu/PageFiles/63144/mbsr_standards_of_practice_2014.pdf
28. Kabat-zinn J, Ph D, Massion A, Kristeller J, Peterson LG, Fletcher E, et al. Effectiveness of a meditation-based stress reduction program in the treatment of anxiety disorders. Am J Psychiatry. 1992;149 (July):936–43.
29. Ludwig DS, Kabat-zinn J. Mindfulness in medicine. JAMA. 2008;300(11):1350–2.
30. Paulson S, Davidson R, Jha A, Kabat-Zinn J. Becoming conscious: the science of mindfulness. Ann N Y Acad Sci. 2013;1303(1):87–104.
31. Crane RS, Brewer J, Feldman C, Kabat-Zinn J, Santorelli S, Williams JMG, et al. What defines mindfulness-based programs? The warp and the weft. Psychol Med. 2017;47(6):990–9.
32. Kabat-Zinn J. Too early to tell: the potential impact and challenges – ethical and otherwise – inherent in the mainstreaming of dharma in an increasingly dystopian world. Mindfulness (N Y) [Internet]. Mindfulness. 2017:1125–35. Available from: http://link.springer.com/10.1007/s12671-017-0758-2
33. Gerritsen RJS, Band GPH. Breath of life: the respiratory vagal stimulation model of contemplative activity. Front Hum Neurosci [Internet]. 2018;12 (February):397. Available from: https://www.frontiersin.org/article/10.3389/fnhum.2018.00397/full
34. Ospina MB, Bond K, Karkhaneh M, Tjosvold L, Vandermeer B, Liang Y, et al. Meditation practices for health: state of the research. Evid Rep Technol Assess. 2007;155:1–263.
35. Morgan N, Irwin MR, Chung M, Wang C. The effects of mind-body therapies on the immune system: meta-analysis. PLoS One. 2014;9:e100903.
36. Jahnke R, Larkey L, Rogers C, Etnier J, Lin F. A comprehensive review of health benefits of Qigong and Tai Chi. Am J Health Promot. 2010;24:e1–e25.
37. Büssing A, Michalsen A, Khalsa SBS, Telles S, Sherman KJ. Effects of yoga on mental and physical health: a short summary of reviews. Evid Based Complement Altern Med. 2012;2012:165410.
38. Chiesa A, Serretti A. Mindfulness based cognitive therapy for psychiatric disorders: a systematic review and meta-analysis. Psychiatry Res. 2011;187:441–53.
39. Kuyken W, Hayes R, Barrett B, Byng R, Dalgleish T, Kessler D, et al. Effectiveness and cost-effectiveness of mindfulness-based cognitive therapy compared with maintenance antidepressant treatment in the prevention of depressive relapse or recurrence (PREVENT): a randomised controlled trial. Lancet. 2015;386:63–73.
40. Grossman P, Niemann L, Schmidt S, Walach H. Mindfulness based stress reduction and health benefits: a meta-analysis. J Psychosom Res. 2004;57:35–43.
41. Pascoe MC, Thompson DR, Jenkins ZM, Ski CF. Mindfulness mediates the physiological markers of stress: systematic review and meta-analysis. J Psychiatr Res. 2017;95:156–78.
42. Balasubramaniam M, Telles S, Doraiswamy PM. Yoga on our minds: a systematic review of yoga for neuropsychiatric disorders. Front Psych. 2013;3:117.
43. Gard T, Hölzel BK, Lazar SW. The potential effects of meditation on age-related cognitive decline: a systematic review. Ann N Y Acad Sci. 2013;1307:89–103.
44. Tracey KJ. The inflammatory reflex. Nature. 2002;420(6917):853–9.
45. Schwartz PJ, De Ferrari GM, Sanzo A, Landolina M, Rordorf R, Raineri C, et al. Long term vagal stimulation in patients with advanced heart failure. First experience in man. Eur J Heart Fail. 2008;10 (9):884–91.
46. Li M, Zheng C, Sato T, Kawada T, Sugimachi M, Sunagawa K. Vagal nerve stimulation markedly improves long-term survival after chronic heart failure in rats. Circulation. 2004;109(1):120–4.
47. Calvillo L, Vanoli E, Andreoli E, Besana A, Omodeo E, Gnecchi M, et al. Vagal stimulation, through its nicotinic action, limits infarct size and the inflammatory response to myocardial ischemia and reperfusion. J Cardiovasc Pharmacol. 2011;58(5):500–7.
48. Uitterdijk A, Yetgin T, te Lintel HM, Sneep S, Krabbendam-Peters I, van Beusekom HMM, et al. Vagal nerve stimulation started just prior to reperfusion limits infarct size and no-reflow. Basic Res Cardiol. 2015;110(5):1–14.
49. Li XW, Wang H. Non-neuronal nicotinic alpha 7 receptor, a new endothelial target for revascularization. Life Sci. 2006;78(16):1863–70.
50. Katare RG, Ando M, Kakinuma Y, Arikawa M, Handa T, Yamasaki F, et al. Vagal nerve stimulation prevents reperfusion injury through inhibition of opening of mitochondrial permeability transition pore independent of the bradycardiac effect, J Thorac Cardiovasc Surg [Internet]. The American Association for Thoracic Surgery. 2009;137(1):223–31.

Available from: https://doi.org/10.1016/j.jtcvs.2008.08.020
51. Hauptman PJ, Schwartz PJ, Gold MR, Borggrefe M, Van Veldhuisen DJ, Starling RC, et al. Rationale and study design of the INcrease of Vagal TonE in Heart Failure study: INOVATE-HF. Am Heart J [Internet]. Mosby, Inc. 2012;163(6):954–962.e1. Available from: https://doi.org/10.1016/j.ahj.2012.03.021
52. De Ferrari GM, Tuinenburg AE, Ruble S, Brugada J, Klein H, Butter C, et al. Rationale and study design of the neurocardiac therapy for heart failure study: NECTAR-HF. Eur J Heart Fail. 2014;16(6):692–9.
53. Tracey KJ. Physiology and immunology of the cholinergic anti-inflammatory pathway. J Clin Invest. 2007;117:289–96.
54. Melville KI, Blum B, Shister HESM. Cardiac ischemic changes and arrhythmias induced by hypothalamic stimulation. Am J Cardiol. 1963;12:781–91.
55. Selye H. The chemical prevention of cardiac necrosis. Press. NR, editor. New York; 1958.
56. Samuels MA. The brain-heart connection. Circulation. 2007;116(1):77–84.
57. Georg Pongratz RHS. The sympathetic nervous response in inflammation. Arthritis Res Ther. 2014;16:504.
58. Chrousos GP. The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. N Engl J Med. 1995;332(20):1351–62.
59. Ziegler KA, Ahles A, Wille T, Kerler J, Ramanujam D, Engelhardt S. Local sympathetic denervation attenuates myocardial inflammation and improves cardiac function after myocardial infarction in mice. Cardiovasc Res. 2018;114(2):291–9.
60. Levick SP, Murray DB, Janicki JS, Brower GL. Sympathetic nervous system modulation of inflammation and remodeling in the hypertensive heart. Hypertension. 2010;55(2):270–6.
61. Frangogiannis NG, Smith CW, Entman ML. The inflammatory response in myocardial infarction. Cardiovasc Res. 2002;53(1):31–47.
62. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, et al. Anti-inflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med [Internet]. 2017;377:1119–31. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1707914
63. Chandrasekar B, Smith JB, Freeman GL. Ischemia-reperfusion of rat myocardium activates nuclear. Circulation. 2001 (May 8);103(18):2296–302.
64. Harrison DG, Marvar PJ, Titze JM. Vascular inflammatory cells in hypertension. Front Physiol. 2012;3:1–8.
65. Finsen AV, Ueland T, Sjaastad I, Ranheim T, Ahmed MS, Dahl CP, et al. The homeostatic chemokine CCL21 predicts mortality in aortic stenosis patients and modulates left ventricular remodeling. PLoS One. 2014;9(11):e112172.
66. Nogueira LG, Santos RHB, Ianni BM, Fiorelli AI, Mairena EC, Benvenuti LA, et al. Myocardial Chemokine Expression and Intensity of Myocarditis in Chagas Cardiomyopathy Are Controlled by Polymorphisms in CXCL9 and CXCL10. PLoS Negl Trop Dis. 2012;6(10):e1867.
67. de Jager SCA, Bongaerts BWC, Weber M, Kraaijeveld AO, Rousch M, Dimmeler S, et al. Chemokines CCL3/MIP1 alpha, CCL5/RANTES and CCL18/PARC are independent risk predictors of short-term mortality in patients with acute coronary syndromes. PLoS One. 2012;7(9):e45804.
68. Daemen MJAP. The heart and the brain: an intimate and underestimated relation. Netherlands Hear J. 2013;21(2):53–4.
69. Fioranelli M, Bottaccioli AG, Bottaccioli F, Bianchi M, Rovesti M, Roccia MG. Stress and inflammation in coronary artery disease: a review psychoneuroendocrineimmunology-based. Front Immunol. 2018;9:2031.
70. Dutta P, Courties G, Wei Y, Leuschner F, Gorbatov R, Robbins C, et al. Myocardial infarction accelerates atherosclerosis. Nature [Internet]. 2012;19(487):325–9. Available from: http://www.nature.com/authors/editorial_policies/license.html#terms
71. Kashyap S, Warner GM, Hartono SP, Boyilla R, Knudsen BE, Zubair AS, et al. Blockade of CCR2 reduces macrophage influx and development of chronic renal damage in murine renovascular hypertension. Am J Physiol Renal Physiol [Internet]. 2015;310(5):F372–84. Available from: http://ajprenal.physiology.org/content/310/5/F372.abstract?etoc
72. Reimer KA, Jennings RB. Myocardial ischemia, hypoxia, and infarction. In: Fozzard HA, et al., editors. The heart and cardiovascular system. New York: Press, Raven; 1986. p. 1133–201.
73. Haskó G, Szabó C. Regulation of cytokine and chemokine production by transmitters and co-transmitters of the autonomic nervous system. Biochem Pharmacol. 1998;56(9):1079–87.
74. Davatelis G, Wolpe SD, Sherry B, Dayer JM, Chicheportiche R, Cerami A. Macrophage inflammatory protein-1. a prostaglandin-independent endogenous pyrogen. Science (80-). 1989;243(4894):1066–8.
75. Shanks J, Herring N. Peripheral cardiac sympathetic hyperactivity in cardiovascular disease: role of neuropeptides. Am J Physiol Regul Integr Comp Physiol [Internet]. 2013;305(12):R1411–20. Available from: https://www.ncbi.nlm.nih.gov/pubmed/24005254
76. Bellinger DL, Millar BA, Perez S, Carter J, Wood C, ThyagaRajan S, et al. Sympathetic modulation of immunity: relevance to disease. Cell Immunol. 2008;252(1–2):27–56.
77. Frangogiannis NG, Youker KA, Rossen RD, Gwechenberger M, Lindsey MH, Mendoza LH, et al. The microcirculation as a foundation of cardiovascular disease cytokines and the microcirculation in ischemia and reperfusion. J Mol Cell Cardiol. 1998;30:2567–76.
78. Harrison DG. The immune system in hypertension. Trans Am Clin Clim Assoc. 2014;125:130–40.

79. Santisteban MM, Ahmari N, Carvajal JM, Zingler MB, Qi Y, Kim S, et al. Involvement of bone marrow cells and neuroinflammation in hypertension. Circ Res. 2015;117:178–91.
80. Liu H, Luiten PGM, Eisel ULM, Dejongste MJL, Schoemaker RG. Depression after myocardial infarction: TNF-α-induced alterations of the blood-brain barrier and its putative therapeutic implications, Neurosci Biobehav Rev [Internet]. Elsevier Ltd. 2013;37(4):561–72. Available from: https://doi.org/10.1016/j.neubiorev.2013.02.004
81. Mazereeuw G, Herrmann N, Xu H, Figeys D, Oh PI, AL Bennett S, et al. Platelet-activating factors are associated with cognitive deficits in depressed coronary artery disease patients: a hypothesis-generating study. J Neuroinflammation. 2014;11:1–8.
82. Van Exel E, De Craen AJM, Remarque EJ, Gussekloo J, Houx P, Bootsma-Van Der Wiel A, et al. Interaction of atherosclerosis and inflammation in elderly subjects with poor cognitive function. Neurology. 2003;61(12):1695–701.
83. Meissner A, Visanji NP, Momen MA, Feng R, Francis BM, Bolz SS, et al. Tumor necrosis factor-α underlies loss of cortical dendritic spine density in a mouse model of congestive heart failure. J Am Heart Assoc. 2015;4(5):1–17.
84. Muller N, Myint AM, Schwarz MJ. Inflammatory biomarkers and depression. Neurotox Res. 2011;19:308–18.
85. Bodi V, Sanchis J, Nunez J, Mainar L, Minana G, Benet I, Solano C, Chorro FJ, Llacer A. Uncontrolled immune response in acute myocardial infarction: unraveling the thread. Am Heart J. 2008;156:1065–73.
86. Goldston K, Baillie AJ. Depression and coronary heart disease: a review of the epidemiological evidence, explanatory mechanisms and management approaches. Clin Psychol Rev. 2008;28:288–306.
87. de Vries HE, Blom-Roosemalen MC, van Oosten M, de Boer AG, van Berkel TJ, Breimer DD, Kuiper J. The influence of cytokines on the integrity of the blood–brain barrier in vitro. J Neuroimmunol. 1996;64:37–43.
88. Descamps L, Cecchelli R, Torpier G. Effects of tumor necrosis factor on receptor-mediated endocytosis and barrier functions of bovine brain capillary endothelial cell monolayers. J Neuroimmunol. 1997;74:173–84.
89. Megyeri P, Abraham CS, Temesvari P, Kovacs J, Vas T, Speer CP. Recombinant human tumor necrosis factor alpha constricts pial arterioles and increases blood–brain barrier permeability in newborn piglets. Neurosci Lett. 1992;148:137–40.
90. Mayhan WG. Cellular mechanisms by which tumor necrosis factor-alpha produces disruption of the blood–brain barrier. Brain Res. 2002;927:144–52.
91. Abbott NJ. Inflammatory mediators and modulation of blood–brain barrier permeability. Cell Mol Neurobiol. 2000;20:131–47.
92. Muller N, Schwarz MJ. The immune-mediated alteration of serotonin and glutamate: towards an integrated view of depression. Mol Psychiatry. 2007;12:988–1000.
93. Felder RB, Francis J, Zhang Z, Wei S-G, Weiss RM, Johnson AK. Heart failure and the brain: new perspectives. Am J Physiol Regul Integr Comp Physiol [Internet]. 2003;284(2):R259–76. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12529279
94. Leenen FH. Brain mechanisms contributing to sympathetic hyperactivity and heart failure. Circ Res. 2007;101:221–3.
95. Li YF, Patel KP. Paraventricular nucleus of the hypothalamus and elevated sympathetic activity in heart failure: the altered inhibitory mechanisms. Acta Physiol Scand. 2003;177:17–26.
96. Ertenli I, Ozer S, Kiraz S, Apras SB, Akdogan A, Karadag O, Calguneri M, Kalyoncu U. Infliximab, a TNF-alpha antagonist treatment in patients with ankylosing spondylitis: the impact on depression, anxiety and quality of life level. Rheumatol Int. 2012;32:323–30.
97. Tyring S, Gottlieb A, Papp K, Gordon K, Leonardi C, Wang A, Lalla D, Woolley M, Jahreis A, Zitnik R, Cella D, Krishnan R. Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial. Lancet (London, UK). 2006;367:29–35.
98. Grippo AJ, Francis J, Weiss RM, Felder RB, Johnson AK. Cytokine mediation of experimental heart failure-induced anhedonia. Am J Physiol Regul Integr Comp Physiol. 2003;284:R666–73.
99. Thombs BD, de Jonge P, Coyne JC, Whooley MA, Frasure-Smith N, Mitchell AJ, Zuidersma M, Eze-Nliam C, Lima BB, Smith CG, Soderlund K, Ziegelstein RC, Thombs BD, de Jonge P, Coyne JC, Whooley MA, Frasure-Smith N, Mi RC. Depression screening and patient outcomes in cardiovascular care: a systematic review. JAMA. 2008;300:2161–71.
100. Soulet D, Rivest S. Bone-marrow-derived microglia: myth or reality? Curr Opin Pharmacol. 2008;8:508–18.
101. Davoust N, Vuaillat C, Androdias G, Nataf S. From bone marrow to microglia: barriers and avenues. Trends Immunol. 2008;29:227–34.
102. Ataka K, Asakawa A, Nagaishi K, Kaimoto K, Sawada A, Hayakawa Y, et al. Bone marrow-derived microglia infiltrate into the paraventricular nucleus of chronic psychological stress-loaded mice. PLoS One. 2013;8(11):e81744.
103. Sawchenko PE, Li HY, Ericsson A. Circuits and mechanisms governing hypothalamic responses to stress: a tale of two paradigms. Prog Brain Res. 2000;122:61–78.
104. Sterling P, Eyer J. Allostasis: a new paradigm to explain arousal pathology. Handb Life Stress Cogn Heal, New York. 1988;(November):629–47.
105. McEwen BS. Protection and damage from acute and chronic stress: allostasis and allostatic overload and

relevance to the pathophysiology of psychiatric disorders. Ann N Y Acad Sci. 2004;1032:1–7.
106. Lucini D, Riva S, Pizzinelli P, Pagani M. Stress management at the worksite: reversal of symptoms profile and cardiovascular dysregulation. Hypertension. 2007;49(2):291–7.
107. Cuffee Y, Ogedegbe C, Facep MPH, Williams NJ. Psychosocial risk factors for hypertension: an update of the literature. Curr Hypertens Rep 2014. 2014;16 (10):1–18.
108. Maier SF, Watkins LR. Cytokines for psychologists: implications of bidirectional immune-to-brain communication for understanding behavior, mood, and cognition. Psychol Rev. 1998;105:83–107.
109. Webster Marketon JI, Glaser R. Stress hormones and immune function. Cell Immunol. 2008;252(1–2):16–26.
110. Jun JY, Zubcevic J, Qi Y, Afzal A, Carvajal JM, Thinschmidt JS, et al. Brain-mediated dysregulation of the bone marrow activity in angiotensin II-induced hypertension. Hypertension. 2012;60:1316.
111. Schrader AJ, Lechner O, Templin M, Dittmar KE, Machtens S, Mengel M, Probst-Kepper M, Franzke A, Wollensak T, Gatzlaff P, Atzpodien J, Buer J, Lauber J. CXCR4/CXCL12 expression and signalling in kidney cancer. Br J Cancer. 2002;86:1250–6.
112. Moll NM, Ransohoff RM. CXCL12 and CXCR4 in bone marrow physiology. Expert Rev Hematol. 2010;3(3):315–22.
113. Mega JL, Stitziel NO, Smith JG, Chasman DI, Caulfield MJ, Devlin JJ, Nordio F, Hyde CL, Cannon CP, Sacks FM, Poulter NR, Sever PS, Ridker PM, Braunwald E, Melander O, Kathiresan SSM. Genetic risk, coronary heart disease events, and the clinical benefit of statin therapy: an analysis of primary and secondary prevention trials. Lancet. 2015;385: 2264–71.
114. Cho J-H, Lee I, Hammamieh R, Wang K, Baxter D, Scherler K, et al. Molecular evidence of stress-induced acute heart injury in a mouse model simulating posttraumatic stress disorder. Proc Natl Acad Sci [Internet]. 2014;111(8):3188–93. Available from: http://www.pnas.org/cgi/doi/10.1073/pnas.1400113111
115. Liu Y-Z, Wang Y-X, Jiang C-L. Inflammation: the common pathway of stress-related diseases. Front Hum Neurosci [Internet]. 2017;11(June):1–11. Available from: http://journal.frontiersin.org/article/10.3389/fnhum.2017.00316/full
116. Soufer R, Jain HYA. Heart-brain interactions in mental stress-induced myocardial ischemia. Curr Cardiol Rep. 2009;11(2):133–40.
117. Munakata M. Clinical significance of stress-related increase in blood pressure: current evidence in office and out-of-office settings. Hypertens Res. 2018;41(8): 553–69.
118. Black PH, Garbutt LD. Stress, inflammation and cardiovascular disease. J Psychosom Res. 2002;52 (1):1–23.
119. Segerstrom SC, Miller GE. Psychological stress and the human immune system: a meta- analytic study of 30 years of inquiry. Psychol Bull. 2004;130 (4):601–30.
120. Bhasin MK, Dusek JA, Chang BH, Joseph MG, Denninger JW, Fricchione GL, et al. Relaxation response induces temporal transcriptome changes in energy metabolism, insulin secretion and inflammatory pathways. PLoS One. 2013;8:5:e62817.
121. Kaliman P, Álvarez-López MJ, Cosín-Tomás M, Rosenkranz MA, Lutz A, Davidson RJ. Rapid changes in histone deacetylases and inflammatory gene expression in expert meditators. Psychoneuroendocrinology. 2014;40(1):96–107.
122. Buric I, Farias M, Jong J, Mee C, Brazil IA. What is the molecular signature of mind-body interventions? A systematic review of gene expression changes induced by meditation and related practices. Front Immunol. 2017;8(June):1–17.
123. Chaix R, Alvarez-López MJ, Fagny M, Lemee L, Regnault B, Davidson RJ, et al. Epigenetic clock analysis in long-term meditators. Psychoneuroendocrinology [Internet]. Elsevier Ltd. 2017;85:210–4. Available from: https://doi.org/10.1016/j.psyneuen.2017.08.016
124. Ball P. Physics of life: the dawn of quantum biology. Nature. 2011;474(7351):272–4.
125. Lloyd S. A quantum of natural selection. Nat Phys. 2009;5(3):164–6.
126. Germenis AE, Manoussakis MN, Georgios SE. The Dawn of Quantum Immunology – 2016;1(December 2015):3–6.
127. Summhammer J, Salari V, Bernroider G. A Quantum-mechanical description of ion motion within the confining potentials of voltage gated ion channels. 2012;11(2):123–135. Available from: https://arxiv.org/abs/1206.0637
128. Bohr N. I quanti e la vita unita' della natura. Unita' della conoscenza. Boringhieri B, editor. Hoepli, Milan, Italy; 2012.
129. Schrödinger E, Penrose R. What is life?: with mind and matter and autobiographical sketches (canto). Cambridge: Cambridge University Press; 1992.
130. Frohlich H. Long-range coherence and energy storage in biological systems. International Journal of Quantum Chemistry. 1968;11:641–9.
131. Collini E, Wong CY, Wilk KE, Curmi PMG, Brumer P, Scholes GD. Coherently wired light-harvesting in photosynthetic marine algae at ambient temperature. Nature [Internet]. Nature Publishing Group. 2010;463 (7281):644–7. Available from: https://doi.org/10.1038/nature08811
132. Engel GS, Calhoun TR, Read EL, Ahn TK, Mančal T, Cheng YC, et al. Evidence for wavelike energy transfer through quantum coherence in photosynthetic systems. Nature. 2007;446(7137): 782–6.
133. Hildner R, Brinks D, Nieder JB, Cogdell RJ, Van Hulst NF. Quantum coherent energy transfer over varying pathways in single light-harvesting complexes. Science (80-). 2013;340(6139):1448–51.

134. Masgrau L, Roujeinikova A, Johannissen LO, Hothi P, Basran J, Ranaghan KE, et al. Atomic description of an enzyme reaction dominated by proton tunneling. Science (80-). 2006;312(5771):237–41.
135. Garcia-Viloca M, Gao J, Karplus M, Truhlar DG. How enzymes work: analysis by modern rate theory and computer simulations. Science (80-). 2004;303 (5655):186–95.
136. Ball P. By chance, or by design? Nature. 2004;431 (7007):396–7.
137. Ritz T, Adem S, Schulten K. A model for photoreceptor-based magnetoreception in birds. Biophys J. 2000;78(2):707–18.
138. Gauger EM, Rieper E, Morton JJL, Benjamin SC, Vedral V. Sustained quantum coherence and entanglement in the avian compass. Phys Rev Lett [Internet]. 2011;040503(January):1–4. Available from: about:blank
139. Pinzon-Rodriguez A, Bensch S, Muheim R. Expression patterns of cryptochrome genes in avian retina suggest involvement of Cry4 in light-dependent magnetoreception. J R Soc Interface [Internet]. 2018;15(140):20180058. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5908540/
140. Al-Khalili J. Life on the edge: the coming of age of quantum biology: Bantam Press, London, UK; 2014.
141. Al-Khalili J. Quantum: a guide for the perplexed. UK ed. W&N; 2012.
142. Abbott D, Rea-Banacloche J, Davies P, Hameroff SR, Zeilinger A, Eisert J, et al. Plenary debate: quantum effects in biology: trivial or not? Fluct Noise Lett [Internet]. 2008;8(1):C5–26. Available from: http://www.worldscientific.com/doi/abs/10.1142/S0219477508004301
143. Franco MI, Turin L, Mershin A, Skoulakis EMC. Molecular vibration-sensing component in Drosophila melanogaster olfaction. Proc Natl Acad Sci [Internet]. 2011;108(9):3797–802. Available from: http://www.pnas.org/cgi/doi/10.1073/pnas.1012293108
144. Fitzpatrick R. Quantum Mechanics [Internet]. Available from: http://farside.ph.utexas.edu/teaching/qm/lectures/
145. Elion WJ, Matters M, UG& JEM. Direct demonstration of Heisenberg's uncertainty principle in a superconductor. Nature. 1994;371(6498):594–5.
146. Razavy M. Quantum theory of tunneling. Hackensack: World Scientific; 2003. p. 4, 462.
147. Sahu S, Ghosh S, Hirata K, Fujita D, Bandyopadhyay A. Multi-level memory-switching properties of a single brain microtubule. Appl Phys Lett. 2013;102 (12):1–6.
148. Hameroff S, Penrose R. Consciousness in the universe a review of the 'Orch OR' theory. Phys Life Rev. Elsevier B.V. 2014;11:39–78.
149. Hameroff S, Trakas M, Duffield C, Annabi E, Gerace MB, Boyle P, et al. Transcranial ultrasound (TUS) effects on mental states: a pilot study. Brain Stimul. 2013;6(3):409–15.
150. Burnet FM. The clonal selection theory of acquired immunity. Burnet FM: University Press; 1959.
151. Cohn M. An in depth analysis of the concept of "polyspecificity" assumed to characterize TCR/BCR recognition. ImmunolRes. 2008;40:128–47.
152. Antipas GSE, Germenis AE. Quantum chemical calculations predict biological function: the case of T cell receptor interaction with a peptide/MHC class I. Front Chem [Internet]. 2015;3(February):1–7. Available from: http://journal.frontiersin.org/Article/10.3389/fchem.2015.00009/abstract
153. Antipas GSE, Germenis AE. Atomic coordination reflects peptide immunogenicity. Front Mol Biosci [Internet]. 2016;2(January). Available from: http://journal.frontiersin.org/Article/10.3389/fmolb.2015.00077/abstract
154. Ventura C, Bianchi F, Cavallini C, Olivi E, Tassinari R. The use of physical energy for tissue healing. Eur Hear J Suppl [Internet]. 2015, 17(suppl A):A69–73. Available from: http://eurheartjsupp.oxfordjournals.org/cgi/doi/10.1093/eurheartj/suv010
155. Gaetani R, Ledda M, Barile L, Chimenti I, De Carlo F, Forte E, et al. Differentiation of human adult cardiac stem cells exposed to extremely low-frequency electromagnetic fields. Cardiovasc Res. 2009;82(3):411–20.
156. Rizzo NR, Hank NC, Zhang J. Detecting presence of cardiovascular disease through mitochondria respiration as depicted through biophotonic emission. Redox Biol [Internet]. Elsevier. 2016;8:11–7. Available from: https://doi.org/10.1016/j.redox.2015.11.014
157. Yang M, Ding W, Liu Y, Fan H, Bajpai RP, Fu J, Pang J, Zhao XHJ. Ultra-weak photon emission in healthy subjects and patients with type 2 diabetes: evidence for a non-invasive diagnostic tool. Photochem Photobiol Sci. 2017;(Mar 17);16(5):736–743. https://doi.org/10.1039/c6pp00431h

Nociception, Sympathetic Nervous System, and Inflammation

7

When the Heart and the Skin Speak the Same Language

Veronica Dusi

Contents

Abstract

Sympathetically maintained pain syndromes (SMPs) are a heterogeneous group of painful disorders typically worsened by sympathetic activation and improved by sympathetic blockade. From a clinical standpoint, SMPs have long been known, and the first attempt to percutaneously block a sympathetic ganglion to

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*,
https://doi.org/10.1007/978-3-030-28008-6_63

control pain was reported in 1934. Nevertheless, the pathophysiology of these disorders is yet to be fully elucidated. A pathological nociceptive activation/pain processing, autonomic dysregulation, and immune-inflammatory dysfunctions are thought to be the main mechanisms. Of note, similar mechanisms may also be involved in pathological pain perception at the cardiac level, as it likely happens in the cardiac syndrome X. In this chapter, an overview of the molecular mechanisms linking inflammation, sympathetic nervous system (SNS) overactivity, and nociceptive activation at the cutaneous as well as the cardiac level will be provided first. The surgical procedures of sympathetic block/removal used to treat sympathetically mediated cutaneous and cardiac conditions will be then discussed. Finally, a working hypothesis for the emerging clinical issue of post-thoracoscopic sympathectomy neuropathic pain will be provided. Indeed, thousands of people all over the world underwent thoracoscopic sympathectomy (consisting in the surgical removal of the first sympathetic thoracic ganglia) for essential hyperhidrosis, with few or no reported cases of postoperative neuropathic pain. On the contrary, neuropathic pain is being reported with increasing frequency in patients with channelopathies/cardiomyopathies undergoing thoracoscopic sympathectomy for antiarrhythmic purposes. These patients, particularly those with cardiomyopathies, have exaggerated sympathetic tone and reflexes, combined with neuronal remodeling processes affecting the sympathetic ganglia. Neuropathic pain in this setting might be related to postdenervation supersensitivity, consistently favored by the abovementioned mechanisms.

Keywords

Sympathetically maintained pain syndromes · Cardiac syndrome X · Cardiac sympathetic denervation · Thoracoscopic sympathectomy · Postoperative neuropathic pain

Introduction

The two branches of the autonomic nervous system (ANS), namely, the sympathetic (SNS, thoracolumbar) and the parasympathetic (PNS, craniosacral) nervous system, share a common embryonal origin from the neuronal crest [1]. From a functional point of view, they mediate peripheral effects in the supplied tissues in response to the demands of the sensory system and the central nervous system (CNS). Sympathetic control originates from preganglionic neurons in segments T1–L3 of the spinal cord, while parasympathetic outflow stems from preganglionic neurons in nuclei of CNS and in segments S2–S4 of the spinal cord [2, 3]. Most autonomic effectors are modulated by dual, continuous sympathetic and parasympathetic influences. Of note, the sympathetic-parasympathetic interaction, which occurs at several levels from the periphery to the CNS, is complex and goes far beyond pure antagonism. It has long been known that SNS and PNS are functionally complementary and are both essential to guarantee physiological homeostasis in health and adequate response to pathological stimuli. Despite that, only in the present century the strong influences of the ANS on inflammation and immune response started to be unraveled. Even more recent is the discovery that the ANS, besides strongly influencing pain perception at the central level, is also involved in modulating nociceptive activation at the peripheral level. Finally, the strong contribution of inflammatory processes affecting the ANS in several pathological conditions is an area of intense research. In this chapter, we will debate the similarities between the skin and the heart concerning the mutual interplay between nociception, SNS, and inflammation. A pathophysiological description and some clinical examples of sympathetically mediated/favored nociception at the cutaneous and cardiac level will be presented first. The surgical procedures of sympathetic block/removal used to treat sympathetically mediated cutaneous and cardiac conditions will be then discussed. Finally, a working hypothesis of the mechanisms leading to post operatory neuropathic pain after thoracoscopic

sympathectomy in patients with cardiac disorders will be presented.

Cutaneous and Cardiac Innervation

Summary: Cutaneous and cardiac innervations have similarities and peculiarities. At both levels, the afferent (sensitive) innervation conveys information about physical stimuli, chemical stimuli, and painful stimuli. The skin has specialized sensitive structures as well as naked nerve endings, while the heart only has the seconds. In both districts, TRPV1 (transient receptor potential cation channel subfamily V member 1) channels expressed on afferent fibers play an important role in sensitive activation. Painful information from both districts conveys on the dorsal horn of the spinal cord.

Efferent innervation both at the cutaneous and at the cardiac level is provided by autonomic fibers only. The skin receives sympathetic efferent fibers that control blood vessel, hair bulbs, arrector pili muscles, and sweat glands, with primarily thermoregulatory purposes in physiological conditions. Except for the trigeminal district, the skin lacks a direct parasympathetic innervation. On the other hand, the heart has both a sympathetic and a parasympathetic efferent innervation, which physiologically modulates all the electrical and mechanical properties of the heart. Figures 1 and 2 show the main components of cutaneous and cardiac innervation, respectively.

Cutaneous Innervation

The skin is our main source of interaction with the surrounding world. It is constituted by two mutually dependent layers, the epidermis and the dermis, that cover a deeper fatty subcutaneous layer, the panniculus adiposus. The epidermis primarily derives from surface ectoderm, but it is subsequently colonized by pigment-containing melanocytes of neural crest origin, antigen-processing Langerhans cells of bone marrow origin, and pressure-sensing Merkel cells of neural crest origin. The dermis has a mesoderm origin and contains collagen, elastic fibers, blood vessels, sensory structures, and fibroblasts [4].

As a sensitive organ, the skin is provided with highly specialized sensitive structures able to detect various physical stimuli such as light touch, pressure, cold, and heat. On the contrary, painful stimuli are transmitted through naked nerve endings, mostly located in the basal layer of the epidermis and in the dermis. These specialized peripheral sensory neurons are also known as nociceptors. The overall morphology of these cell types is highly conserved among animal species, from rodents to humans [5]. Still, cutaneous nociceptors are an extremely heterogeneous group of neurons, and the phenotypical differences reflect their capability of being activated by different types of noxious stimuli.

Adequate stimuli encompass temperature extremes ($> \sim 40\ ^\circ C$–$45\ ^\circ C$ or $< \sim 15\ ^\circ C$), intense pressure, and chemicals signaling potential or actual tissue damage. Cutaneous nociceptors are usually electrically silent [6]. Indeed, action potential generation and transmission only occur after noxious stimulation and do not automatically translate in pain perception, which is a very complex summation process with multiple sites of modulation along the neuraxis [7]. Like other primary somatosensory neurons, nociceptors are pseudounipolar neurons having their cell body in the dorsal root ganglion (DRG) or trigeminal ganglion (TG). Their peripheral sensory endings are in tight proximity to keratinocytes, mast cells, and Langerhans cells, providing them the capability to constantly monitor the status of the skin. Nociceptive afferent information travels with different conduction velocities depending on the characteristics of the axons. Most nociceptors have small diameter unmyelinated axons (C-fibers) supporting conduction velocities in the range between 0.4 and 1.4 m/s [8]. They are responsible for the low onset perception of pain. On the other hand, a minority but very important subgroup of nociceptor is served by larger diameter myelinated axons (A-fibers, mostly in the Aδ range), able to guarantee conduction velocity as high as

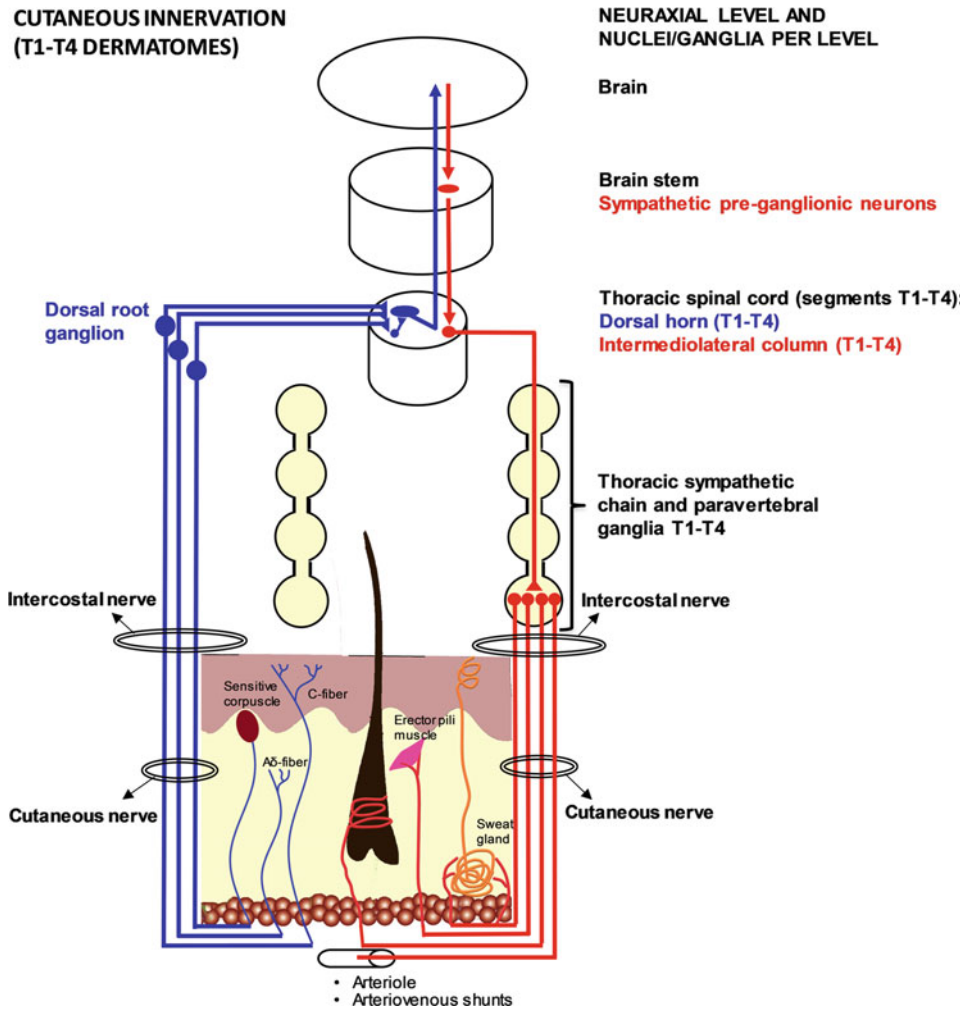


Fig. 1 Cutaneous innervation in humans (T1–T4 dermatomes). Blue: afferent nervous system with its ganglia: nodose ganglia and T1–T4 dorsal root ganglia (DRG). Red: sympathetic efferent nervous system. The three strata of the skin, represent, from the top to the bottom, epidermis, dermis, and subcutis. All the afferent and efferent structures except for the nuclei in the central nervous system (CNS) are bilateral, although mostly represented as unilateral for simplicity. There are several types of sensitive corpuscles in the skin, but only one is reported for simplicity. Brain stem nuclei involved in pain processing are not reported either

5–30 m/s. Those neurons are essential for the initial fast-onset pain perception which is a crucial alerting signal in all animal species [6]. The conduction velocity together with the sensitivity and threshold to different noxious stimuli is used to classify nociceptive neurons [9]. The most represented units are those provided with C-type fibers and sensing thermal, mechanical, and chemical stimuli (polymodal units) [10, 11]. A-fiber nociceptors are predominately heat- and/or mechanosensitive. The specificity for the type of excitatory stimulus is based on a differential molecular expression profile, particularly regarding the chemical sensors. C-type nociceptor normally insensitive to mechanical and heat stimulation might become sensitive during inflammation [12, 13]. Therefore, inflammatory mediators are not only able to lower the activation threshold of a specific noxious stimulus but also to promote the sensing of other type of stimuli. Despite the molecular profile associated with stimulus specificity is yet to be fully elucidated,

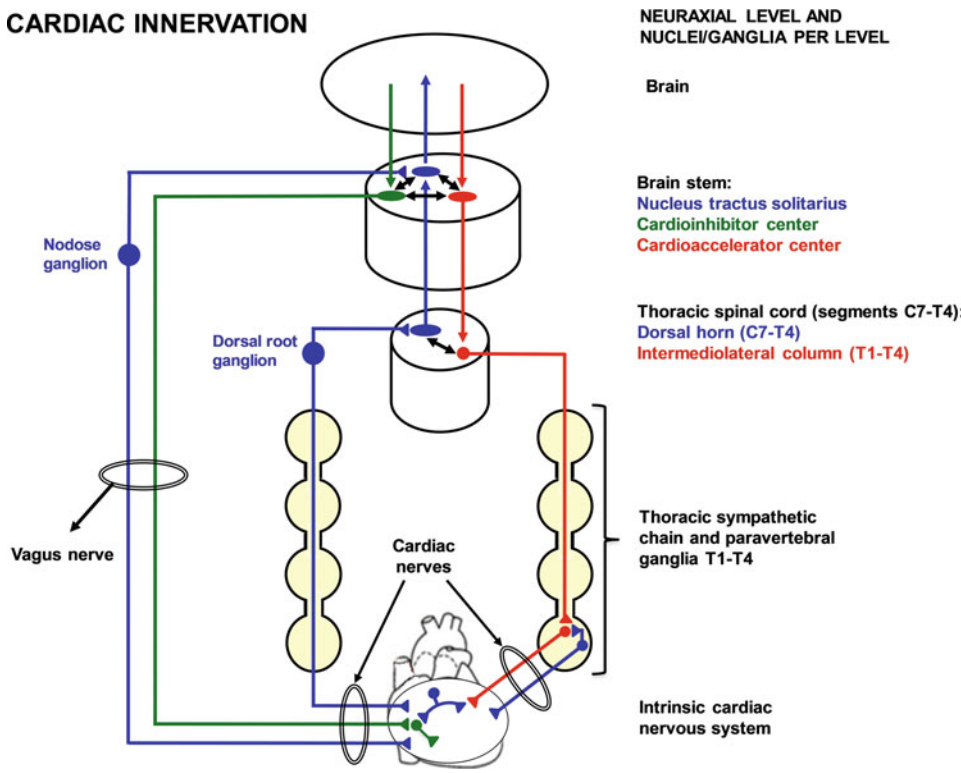


Fig. 2 Cardiac nervous system organization in humans. Blue: afferent nervous system with its ganglia: nodose ganglia and C7–T4 dorsal root ganglia (DRG). Green: parasympathetic efferent nervous system. Red: sympathetic efferent nervous system. All the afferent and efferent structures except for the autonomic nuclei in the central nervous system are bilateral, although mostly represented as unilateral for simplicity. Cardiac afferent fibers traveling across the paravertebral sympathetic ganglia (usually referred to as cardiac sympathetic afferent fibers) directly reach the DRG without having synapsis before. These fibers mediate cardio-cardiac sympathoexcitatory spinal reflexes that significantly increase the sympathetic output to the heart. The direct nociceptive pathway from the dorsal horn to the cortex is not shown for simplicity. Cardiac sympathetic denervation (CSD) consists in the surgical removal of the thoracic sympathetic chain and paravertebral ganglia from T1 to T4. Since ipsilateral DRG are spared by CSD, an afferent reinnervation from the DRG to the heart is theoretically possible with time. On the other hand, the efferent sympathetic system from T1 to T4 is interrupted at a preganglionic level; therefore, no ipsilateral efferent sympathetic reinnervation is possible after CSD. Modified from V. Dusi et al [214] with permission

some pathways were indeed defined. Concerning chemical signaling, the ion channel TRPA1 (transient receptor potential ankyrin 1) has been identified as a general sensor for noxious irritating electrophilic compounds including allyl isothiocyanate ([mustard oil, AITC) and cinnamaldehyde, the active pungent ingredients in hot mustard and cinnamon, respectively [14, 15]. Not only TRPA1 is sensitized by inflammatory mediators [16], but endogenous reactive chemicals may also act as effective agonists of the channel [17]. Interestingly, the burning sensation of hot mustard (AITC) that can be evoked in a subgroup of TRPA1-expressing neurons might be also mediated by another channel, namely, the TRPV1 (transient receptor potential cation channel subfamily V member 1) channel. Indeed, AITC is a strong chemical activator of a subset of TRPV1-expressing neurons. TRPV1, also known as capsaicin receptor or vanilloid receptor 1 (VR1), is a cationic ion channel that besides mediating nociception (for both chemical and heat noxious stimuli) [18] is also involved in body temperature monitoring and regulation [19].

Of note, TRPV1 is also highly expressed at the cardiac level, as will be explained later.

Sympathetic innervation to the skin has a primarily thermoregulatory function. Sympathetic efferent fibers control blood vessels (sudomotors), hair bulbs (pilomotors), and sweat glands (sudomotors) [3, 20, 21]. Of note, sympathetic inputs to the sweat glands are the only one mediated by acetylcholine (acting via M3 muscarinic receptor) rather than noradrenaline. In physiological conditions, the intensity of skin sympathetic nerve activity is mainly determined by the environmental temperature and the emotional state of the subject. Both nutritive skin body flow and arteriovenous skin body flow are under sympathetic control (alfa and beta-adrenergic). The second one is mediated by low-resistant arteriovenous shunts that play a central role in thermoregulation [3, 20]. Of note, three local axon reflexes contribute to skin blood flow regulation, two of which under sympathetic control: the axon flare response, the sudomotor axon reflex, and the venoarteriolar reflex. Particularly relevant here is the axon flare response, a form of neurogenic inflammation mediated by nociceptor C-fiber terminals [22]. Nociceptive activation by chemical or mechanical stimuli produces antidromic release of neuropeptides (mainly substance P and calcitonin gene-related peptide) that, in turn, cause local blood vessel dilatation and increase in permeability both directly and indirectly through mast cell degranulation and subsequent histamine secretion. Folgueras et al. [23] even suggested that mast cell degranulation generally requires direct interaction between mast cells and peripheral nerve terminals, which they found to be mediated by the calcium-dependent cell adhesion molecule N-cadherin.

Finally, from an anatomical point of view, cutaneous nerves (that contains both sensitive afferent and sympathetic efferent fibers) follow the route of blood vessels to the skin. Each cutaneous nerve may contain fibers from several individual spinal nerves. The skin area supplied by a single spinal nerve, or a single segment of the spinal cord, is termed as dermatome, and adjacent dermatomes may overlap considerably. It follows that cutaneous nerve areas are generally broader and wider than dermatomes.

Cardiac Innervation

The cardiac neuraxis is structurally and functionally extremely complex and can be divided into two systems: the extrinsic and the intrinsic cardiac nervous system (ICNS). The former follows typical patterns in most people, although variants are seen [24–26]. It is constituted by the mediastinal cardiac plexus, the paravertebral sympathetic ganglia, the nodose ganglia, the dorsal root ganglia (DRG), the spinal cord, and the brain stem. The main extracardiac afferent stations, containing pseudounipolar neural cells, are the nodose ganglia (inferior ganglia of the vagus nerve) and the DRG (from C7 to T4–T5 spinal cord level) [27–29]. These neurons have long peripheral branches that travel along cardiac nerves. Afferent fibers traveling along vagal nerve branches (commonly defined as cardiac parasympathetic afferent fibers) go straight from the heart to the nodose ganglia, which are located at the level of the transverse process of the first cervical vertebra. Afferent fibers projecting to the DRG (commonly referred to as cardiac sympathetic afferent fibers) travel across the paravertebral sympathetic ganglia, without having synapsis. Of note, a small percentage of neuronal bodies of sensory neurons have been recently identified also in other intrathoracic extracardiac ganglia [30].

Cardiac sympathetic preganglionic neurons have their soma in the intermediolateral column of spinal cord (T1–T4 levels) and synapses on postganglionic neuron located in the lower cervical and upper thoracic paravertebral ganglia. The lowest cervical ganglion (C8) and the highest thoracic ganglion (T1) are usually fused to constitute the left and the right stellate ganglia (also referred to as cervicothoracic ganglia). These structures convey a consistent amount of cardiac sympathetic postganglionic fibers. The remaining is mainly provided by the left and right T2–T4 paravertebral ganglia. Most of parasympathetic preganglionic neurons are in the ventral lateral region of the nucleus ambiguus. Efferent fibers enter the cervical trunks of the vagus nerves and then synapse on the postganglionic parasympathetic neuron located within various atrial and

ventricular ganglia of the cardiac plexus [31]. Finally, the ICNS is constituted of multiple ganglionated plexi located in the epicardial fat. It contains a plethora of neuronal bodies, including afferent and efferent neurons as well as interneurons and local circuit neurons.

From a functional point of view, cardiac afferent fibers can be classified as mechanosensory, chemosensory, or multimodal (transducing both modalities) [32, 33]. All of them can be activated during myocardial ischemia and can mediate cardiac nociception. Of note, cardiac sympathetic afferent fibers are considered the main anatomical pathway for cardiac nociception [33, 34].

Like in the skin, also at the cardiac level, TRPV1 channels play an important role in facilitating noxious activation and are expressed in both unmyelinated C-fibers and thinly myelinated Aδ-fibers [35]. As already mentioned, TRPV1 channels can be activated by several chemical and physical stimuli including bradykinin [36], noxious heat (>43 °C) [37], endovanilloids [38], protons (extracellular Ph < 6) [39], and free radicals [40]. A direct capability of TRPV1 channels to respond to mechanical stimuli has never been demonstrated so far, although hypothesized [41, 42]. Indeed, TRPV1 channels are members of the superfamily of transient receptor potential (TRP) protein channels, known for being multitasking. Mechanical force has been proposed as a unifying, common strategy for TRP channel gating. Of note, TRP channels are capable of functioning as stretch-activated channels even when stimuli that initiate the cascade signaling are not mechanical [41].

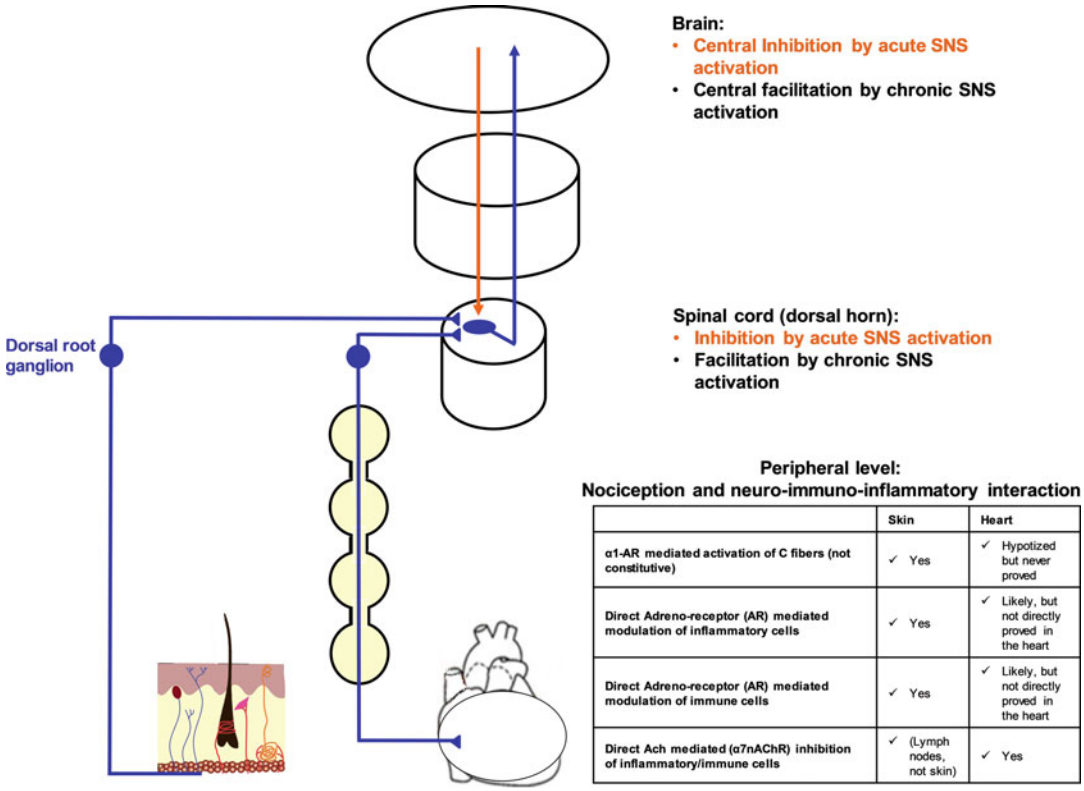
Cardiac afferent fibers providing the specialized mechanosensitive and chemosensitive receptors include both sympathetic and parasympathetic fibers. Sympathetic afferent fibers are quantitatively predominant at the ventricular level, with the potential exception of the inferodorsal wall [43]. Indeed, inferior myocardial ischemia in humans is often associated with robust transient vagal reflexes producing bradycardia and hypotension [43, 44]. This phenomenon, also referred to as Bezold-Jarisch reflex [45], has been explained by the preferential distribution of cardiac receptors along with afferent vagal pathways in the inferior wall of the left ventricle.

ANS, Inflammation, and Nociceptor Activation

Summary: The interaction between ANS and pain is complex and takes place at several levels of the neuraxis. In this section, the focus will be on the peripheral mechanisms leading to a chronic increase in nociceptor activation. Both at the cutaneous level and at the cardiac level, the main actors are immune/inflammatory dysfunction, autonomic dysregulation, and microvessel dysfunction. All these mechanisms can exponentially potentiate one each and contribute to establish a vicious circle. At the cutaneous level and in the setting of a previous injury, sympathetic activation can directly evoke nociceptive activation through α 1-AR-mediated pathways. Despite molecular data are still lacking, clinical evidence suggests that similar mechanisms may also take place at the cardiac level. Both at the cutaneous and at the cardiac level, the ANS has a major, direct, role in modulating the immune/inflammatory response through the sympathetic/parasympathetic interaction. Most cell types involved in immune/inflammatory responses were proved to express adrenergic and/or cholinergic receptors. Figure 3 summarizes the main mechanisms involved.

In healthy subjects, short-term activation of the SNS suppresses pain mainly by descending inhibition of nociceptive transmission in the spinal cord. In reverse, chronic activation of the SNS may consistently increase pain perception through several mechanisms. In the periphery, inflammation and nociceptive activation are both enhanced. At the spinal level, descending inhibition is reversed to facilitation [46]. Finally, at the cortical level, the awareness of all these changes leads to anxiety, which furthermore amplifies pain perception, affects pain behavior, and depresses mood [47].

The mutual interplay between nociception and SNS as key components of the alert system is further confirmed by embryological data. Indeed, somatic nociceptive sensory nerves are sub-classified into nerve growth factor (NGF) and glial cell line-derived neurotrophic factor (GDNF)-dependent nerves [48]. NGF is a



	Skin	Heart
α1-AR mediated activation of C fibers (not constitutive)	✓ Yes	✓ Hypotized but never proved
Direct Adreno-receptor (AR) mediated modulation of inflammatory cells	✓ Yes	✓ Likely, but not directly proved in the heart
Direct Adreno-receptor (AR) mediated modulation of immune cells	✓ Yes	✓ Likely, but not directly proved in the heart
Direct Ach mediated (α7nAChR) inhibition of inflammatory/immune cells	✓ (Lymph nodes, not skin)	✓ Yes

Fig. 3 Autonomic nervous system, inflammation, and pain perception, with focus on the peripheral mechanisms leading to a chronic increase in nociceptor activation at the cutaneous and at the cardiac level. Brain stem nuclei involved in pain processing are not reported for simplicity

prototypic member of the neurotrophin family that is pivotal in the differentiation, survival, and synaptic activity of the cardiac sympathetic nervous system [49, 50]. NGF knockout mice showed a poor degree of differentiation of neurons in the DRG and absence of the pain reflex to tail pinch [51]. In diabetic rats, a reduced NGF expression was found to correlate with deterioration in cutaneous sensory function and decrease in CGRP- and substance P-immunopositive nerves (both markers of NGF-dependent nociceptive sensory nerves) [52, 53]. Similar findings were confirmed at the cardiac level. The development and regulation of the cardiac sensory nervous system were proved to be dependent on NGF synthesized in the heart, and diabetes-induced NGF reduced expression was associated with cardiac sensory neuropathy [54].

ANS and Nociceptor Activation at Cutaneous Level

The physiological activation of postganglionic sympathetic efferent fibers of the skin during cooling or stress tasks is not associated with pain in healthy subjects. Even the injection of clinically active doses of catecholamines is not painful. The potential of catecholamine injection to produce an activation of C-fibers under the threshold for nociception but enough to induce an axon reflex flare [19] was specifically assessed, with negative findings [55]. However, an axon reflex flare can be induced in case of catecholamine delivery by constant current iontophoresis (transdermal drug delivery by the application of a voltage gradient on the skin) [56], suggesting that, during coactivation of C-fibers by the electrical current, catecholamines might increase excitability or

sensitize nociceptors in intact skin. Accordingly, cutaneous injection of catecholamines [57] was proved to sensitize heat-sensitive C-fibers. Indirect effects (e.g., local vasoconstriction) combined with the direct activation of constitutionally present but physiologically less important α1-adrenoreceptor (AR) on C-fibers have been advocated as concurrent mechanisms [58]. The α1-AR agonist phenylephrine evokes thermal hyperalgesia in the mildly burnt skin of human volunteers, and the α 1-AR antagonist terazosin blocks this response [59]. In contrast, in the same model, two agonists and antagonists had no effect on thermal hyperalgesia in the healthy skin.

The effects on C-fibers of acetylcholine (ACh), the second transmitter of the SNS at the cutaneous level (sudomotor fibers), are different. Injection of ACh induces a dose-dependent burning sensation [60]. Iontophoresis of Ach, besides inducing an axon reflex sweating, is associated with a simultaneous neurogenic flare response [61]. Nevertheless, physiological concentrations of Ach in human tissue are expected to be rapidly degraded by choline esterases [28]. Overall, the impact of ACh release in human skin on C-fiber-mediated nociceptive activation is controversial. Bernardini et al. [62] suggested that depending on the type of ACh receptors, nicotinic or muscarinic (M2), expressed on C-fibers, ACh might also reduce nociceptor responses.

ANS, Inflammation, and Immune Response at Cutaneous Level

Catecholamine was proved to modulate the activity of dendritic cells, a class of antigen-presenting cells crucial for immune surveillance and coordination of the host response [63]. Compared to macrophages and B cells, dendritic cells are the most effective antigen-presenting cells [64]. Mature dermal resident dendritic cells, also known as Langerhans cells, may arise from circulating common dendritic cell precursors or from circulating monocytes [65]. The accumulation, activation, and maturation of resident dendritic cells and their circulating precursors are promoted by antigen capture and/or nociceptive activation, such as during trauma or local inflammation [66–68]. After activation, mature dendritic cells migrate to the draining lymph node to promote either adaptive or innate immune responses. In both cases, the consequent inflammatory cascade leads to a regional response associated with activation and colony expansion of monocytes, dendritic cells, and osteoclasts within the blood stream and bone marrow [69, 70]. The tight anatomical association between dendritic cells and epithelial nerve fibers [71, 72] was the first evidence suggesting the existence of a "neuro-immuno-cutaneous system," potentially very relevant in the pathophysiology of inflammatory disorders. Subsequently, dendritic cells were found to express multiple neuronal markers as well as neurotransmitter and neuropeptide receptors [73–77]. Moreover, IL-6 (and other neurotrophins) produced by Langerhans cells can stimulate nerve differentiation [78]. Dendritic cells express both α1 and β2 adrenergic receptors (ARs), with opposite biological effects. α1-ARs stimulate while β2-ARs inhibit dendritic cell migration. Accordingly, β2AR activation in skin and bone marrow-derived dendritic cells in response to norepinephrine (NE) decreases interleukin-12 (IL-12) and increases anti-inflammatory IL-10 production which in turn downregulates the inflammatory cascade [79]. During inflammation, immune cells undergo downregulation of β2 and upregulation of α1-ARs [80], resulting in amplification of the inflammatory cascade. Similarly, whenever α1-ARs become overexpressed by the resident or recruited immune cells, SNS activation is predicted to cause pain and other inflammatory signs via cytokine release. This is also the case of some allergic responses, where contact sensitizers may inhibit local NE turnover in the skin, resulting in immune reaction amplification [80]. Finally, SNS may also indirectly modulate inflammation through its effect on lymph nodes and lymphatic vessels, both provided of catecholaminergic sympathetic innervation. Lymphatic vessel constriction associated with SNS over activation can amplify the inflammation-related edema [81].

Moreover, there are also consistent data suggesting the presence of adrenergic receptor-

mediated pathways on human monocytes/macrophages. β2-ARs are mainly considered anti-inflammatory, although Grisanti et al. [82] recently suggested the existence of β-AR (possibly β1-AR) mediated pro-inflammatory responses. α-AR may potentially mediate both pro- and anti-inflammatory responses, and careful investigations are still needed to define their rule.

Another cellular type strongly involved in the immune-inflammatory cutaneous response and modulated by catecholamine are the mast cells, albeit direct data on the cutaneous subtype are scarce. Both ligand-binding studies and functional data suggest that β-AR might inhibit IgE-mediated histamine release from mast cells [83]. Accordingly, β-AR antagonists were able to prevent desensitization of β-AR on human lung mast cells induced by isoprenaline [84]. The inhibitory adrenergic effect on human lung mast cells as well as mast cells cultured from peripheral blood and isolated form the intestinal mucosa seems to be mediated by β2-AR [85, 86]. The effects on intestinal mast cells are not limited to inhibition of IgE-dependent release of histamine. Adrenaline, noradrenaline, and salbutamol were also proved to inhibit lipid mediators and TNF-α release, as well as proliferation, migration, and adhesion to fibronectin and human endothelial cells [87, 88]. Data about the presence and the role of an α1-AR mediated pathway in mast cells are scarce [89]. Recently, Prey and coworkers [90] demonstrated that human mast cells stain positive for both β1-AR and β2-AR but are negative for β3-AR. As already mentioned, the skin lacks a direct parasympathetic innervation, with the only exclusion of the trigeminal district. Nevertheless, PNS modulates cutaneous immunity and inflammation through its effects on local lymph nodes and systemic cytokine release. These effects are part of the so-called cholinergic anti-inflammatory pathway, a strong anti-inflammatory pathway mediated by the vagus nerve through the release of acetylcholine [91–95]. First proposed by Tracey and colleagues, the anti-inflammatory reflex mainly consists in the direct inhibition of pro-inflammatory cytokine release (i.e., TNFα, IL-1, IL-18) from local macrophages and monocyte-derived dendritic cells induced by neuronal released ACh. The molecular mechanism is the binding of ACh to the α7 subunit of nicotinic receptors (α7nAChR) [91, 92, 96]. Only in the spleen the effect is not directly mediated by neuronal released Ach. Indeed, postganglionic splenic neurons originating in the celiac ganglion are adrenergic, not cholinergic [97], and NE release subsequently stimulates ACh-producing T cells [98, 99]. The autonomic modulation of lymph node function was first suggested by Wülfing and Günther [100], who showed that these structures are surrounded and penetrated by a rich neuronal meshwork that encapsulates dendritic cells and macrophages.

Finally, ACh has also been implicated in the balance of self-tissue recognition versus antigen detection response of dendritic and other immune cells [64, 100]. Both ACh receptors and ACh-synthesizing enzymes are highly expressed in human dendritic cells. The final effect of Ach depends on the maturation state of dendritic cells and is mediated by different subtypes of cholinergic receptors. In immature dendritic cells, ACh stimulates both antigen processing and pro-inflammatory cytokine release, whereas the opposite occurs in mature dendritic cells [64, 100].

ANS, Nociceptor Activation, and Inflammation at Cardiac Level

In humans, the mutual interplay between ANS, nociceptor activation, and inflammation at the cardiac level is fundamental to be understood because it largely drives the clinical presentation and the outcome of patients with acute myocardial ischemia.

First, it is to be underscored that the cardiac muscle, as opposed to the skin, is provided by a double autonomic innervation (sympathetic and parasympathetic). Therefore, as any other organ provided with a vagal efferent innervation, the heart is directly exposed to the vagal anti-inflammatory reflex. This concept might seem almost obvious now but took long to be directly demonstrated in the heart. In 2011, Calvillo et al. [101] clearly showed that ACh exerts direct anti-inflammatory and anti-apoptotic effects at the cardiac

level through nicotinic pathways. Indeed, right vagal stimulation (VS) applied from 5 minutes before myocardial ischemia to 5 minutes after reperfusion in anesthetized rats, was associated with a decrease in infarct size and in inflammatory markers independently of the heart rate. The beneficial effects of VS were associated with a two fold decrease in the signal intensity of two key cytokines involved in the recruitment of neutrophils (LIX, the IL-8 analogue in the rat) and macrophages (MCP-1) and already known to be essential for the entire innate immune process associated with myocardial reperfusion injury [102].

The strong and direct anti-inflammatory effect of vagal activity at cardiac level is a key component of sympathetic-parasympathetic antagonism. It follows that the impact of autonomic balance at cardiac level goes even beyond the control of all electrical and mechanical properties of the heart (inotropy, chronotropy, dromotropy, and lusitropy). Of note, sympathetic-parasympathetic antagonism involves several mechanisms along the entire neuraxis, from the periphery to the CNS. At the peripheral (cardiac) level, it includes both presynaptic and postsynaptic mechanisms. Presynaptic antagonism refers to the capability to both types of autonomic neurons, when activated, to inhibit the synaptic release of neurotransmitters in the other cellular type [103–105]. This effect may by consistently magnified by other neuropeptides, particularly in the case of sympathetic efferent fibers. Indeed, NE itself is not thought to significantly regulate cardiac vagal Ach release within humans or guinea pigs' hearts [106, 107], although there is evidence of a short-lived inhibition on Ach release due to NE in rat atria via α-AR [108]. On the other side, neuropeptide Y (NPY), a sympathetic co-transmitter mainly secreted during high- frequency neuronal activation [109], strongly concurs to inhibit Ach release from cardiac vagal postganglionic nerves [110–113] through Y2 receptor activation [114]. A similar effect was also demonstrated for the sympathetic co-transmitter galanin [115]. The opposite effects of NE and Ach on cardiomyocytes at postsynaptic level are mainly mediated by the activation of antagonist intracellular pathway following β1-AR and M2 receptor binding, respectively.

Concerning the direct effects of sympathetic activation on inflammation, as already mentioned AR are expressed on all the main cell types involved in the immune-inflammatory response, including macrophage, dendritic cells, and T and B cells. Of note also NPY receptors have been identified on these cell types, modulating phagocytosis, proliferation, and cytokine production [116]. Nociceptor activation transmitted by sympathetic afferent fibers is associated with a strong cardio-cardiac sympathetic afferent reflex (CSAR) leading to a powerful increase in sympathetic efferent drive to the heart [117]. Spinal sympathetic efferent neurons as well as sympathetic efferent neurons in the intrinsic cardiac nervous system are involved in this multiple loop reflex [118]. In turn cardiac sympathetic efferent activation, among the other effects, will further favor inflammation and indirectly sensitize nociceptor, acting as a vicious circle. CSAR, acutely aimed to sustain cardiac output, has the drawback of a consistent increase in metabolic demand, inflammation, and arrhythmic susceptibility.

Clinical Examples of the Mutual Interplay Between Nociception, Sympathetic Nervous System, and Inflammation

Complex Regional Pain Syndrome (CRPS)

Summary: Complex regional pain syndrome (CRPS), classified among the sympathetically maintained pain syndromes, is a challenging clinical disorder leading to debilitating chronic pain. It may occur after a trauma (either directly damaging a peripheral nerve or not) or, in a minority of cases, even in the absence of it. The pathophysiology of CRPS hasn't been fully elucidated yet. Several abnormalities have been consistently reported, and a unifying theory including all of them has been recently proposed. Cutaneous dendritic cells, involved in both inflammatory and immune responses at the cutaneous level, seem

to play a central rule. Their pathological activation in the setting of a sympathetic neuronal damage may lead to autoantigen presentation and consequent production of autoantibodies. The presence of autoantibodies against adrenergic receptors acting as agonists, combined with supersensitivity to circulating catecholamines, might help to explain the favorable response of CRPS, at least in the early stages, to pharmacological/surgical intervention blocking the SNS.

The SNS has been clinically implicated in numerous pain syndromes, generally referred to as sympathetically maintained pain syndromes (SMP). One of the most frequent among them is the complex regional pain syndrome (CRPS), a form of chronic pain usually affecting an arm or a leg. CRPS is classified in two subtypes, with similar signs and symptoms, but different causes. CRPS Type 1 (once known as reflex sympathetic dystrophy syndrome) occurs after an injury/trauma not directly damaging nerves in the affected limb. The pain is typically not limited to the distribution of a single peripheral nerve and is disproportionate to the triggering event. CRPS Type 2 (once referred to as causalgia) follows a distinct nerve injury but is not necessarily limited to the distribution of the injured nerve [119]. Of note, only 0.5–2% of injury/trauma patients develop CRPS [120], and some patients with CRPS have no history of trauma at all [121]. Clinical presentation is extremely heterogeneous between different subjects and even in the same subject according to the stage of the disease, including warm or cold limb, edema, allodynia, hyperalgesia, abnormal sweating, and skin and nail tissue changes [122]. In the chronic phase of the disease, most of the peripheral signs may disappear leaving chronic severe pain as the main symptom [123]. CRPS is a clinical challenge because the diagnostic criteria continue to be refined, reflecting the uncertainness on the pathophysiological mechanisms, and effective therapeutic strategies, particularly in the advanced stages of the disease, are scarce. Of note, the positive response to the use of sympathetic nerve blocks as a treatment for CRPS generally lasts less than 12 months from the onset of symptoms [124–126]. The pathogenic involvement of SNS, inflammation, and immunity (with a central role for dendritic cells) is known, particularly in the first stages of the disease, but a definitive explanation for this condition and its temporal evolution are still lacking. Recently, Russo et al. [127] proposed a four-component model of CRPS including tissue trauma, pathological pain processing, autonomic dysregulation, and immune dysfunction. According to their hypothesis, these four components can vary in degree among different subjects in terms of homeostatic disturbance and relative time course of activation. Particularly relevant to our topic is the relationship between autonomic dysregulation (excess of sympathetic activity relative to parasympathetic activity) and immune dysfunction. Pathogenic autoantibodies against β2-AR, α1-AR, and M2 muscarinic receptors have been consistently identified in a subset of CPRS patients [128, 129]. In a mouse IgG-transfer-trauma model for CRPS, serum IgG from chronic CRPS patients induced key clinical indicators of the human disease, namely, swelling and mechanical hyperalgesia, which supports the autoimmunity concept [130]. It is tempting to speculate that the relative sympathetic overactivity in the first stages of CRPS might be related either to autoantibodies acting as adrenergic agonists on sympathetic neurons or to adrenergic supersensitivity in the setting of a progressive neuronal sympathetic damage (or to a combination of both). Indeed, whereas efferent denervation in the striated muscle produces paralysis and atrophy, autonomic postganglionic efferent denervation produces an exaggerated response of the target when it is exposed to the neurotransmitter [131]. This phenomenon, called denervation supersensitivity, is mediated by several molecular mechanisms and might sensitize cutaneous nociceptors due to an increased expression of α-ARs [132]. Of note, sympathetic relative overactivity associated with parasympathetic dysfunction may also further potentiate the autoimmune response through mature dendritic cells persistent activation and inhibition of the anti-inflammatory reflex. In established chronic cases of CRPS, the unfavorable interplay of tissue damage, abnormal pain processing and spinal cord/central sensitization, and immune dysfunction

might explain the lack of response to sympathetic nerve block [133].

Cardiac Syndrome X (CSX)

Summary: Among patients undergoing coronary angiography because of angina symptoms typical enough to suggest coronary artery disease, 10–30% are found to have "normal" or "near-normal" epicardial coronary arteries at angiography. A subgroup of these patients, more typically postmenopausal females, presents features of "cardiac syndrome X" (CSX). Two main pathogenetic hypotheses, not mutually exclusive, have been proposed for this syndrome: the ischemic one, postulating a primary role for coronary microvascular dysfunction, and the nonischemic one, postulating a crucial role for impaired pain perception/myocardial hypersensitivity to pain. Accordingly, autonomic dysregulation and systemic inflammation, two abnormalities consistently detected in CSX patients, may be involved/associated with both microvascular dysfunction and impaired pain perception, further supporting the contribution of both mechanisms. Figure 4 summarizes the actual view about the main mechanisms involved in the pathophysiology of CSX and the possible spectrum of combinations.

The cardiac painful condition better known as cardiac syndrome X (CSX) is traditionally defined by the triad: angina-like pain exclusively or predominantly induced by effort, ST segment depression during spontaneous or provoked angina, and normal epicardial coronary arteries at angiography [134]. Any other cardiac condition (such as cardiomyopathy, left ventricular hypertrophy, valvular heart disease) or systemic diseases (such as hypertension or diabetes) known to influence vascular function must be ruled out. Patients with coronary artery spasm and those with objectively documented extracardiac causes for the pain (such as chest wall syndrome, psychological

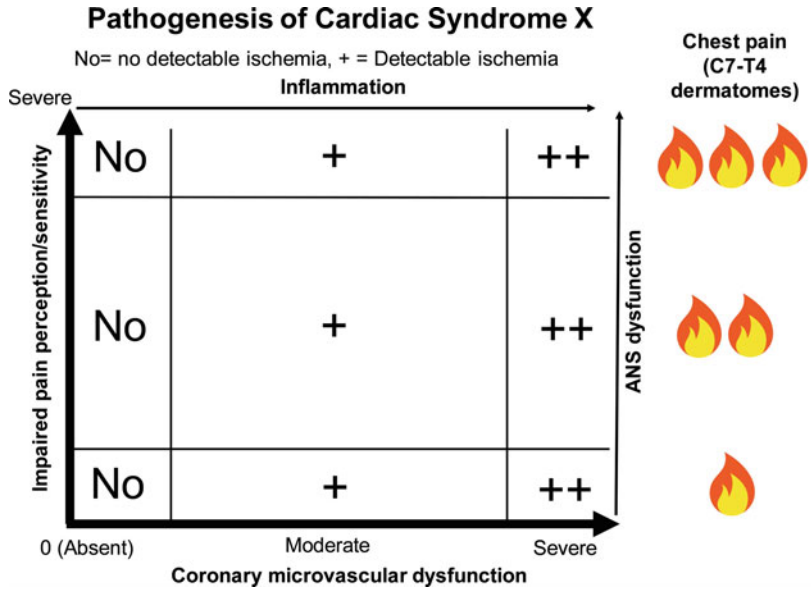


Fig. 4 Pathogenesis of cardiac syndrome X (CSX). The two main mechanisms implicated in CSX, namely, impaired pain perception/sensitivity and coronary microvascular dysfunction may coexist, with different degrees of severity, in the same patient, leading to different possible combinations of detectable ischemia and intensity of chest pain. Of note, chest pain compatible with CSX may also be related to a purely impaired pain perception/sensitivity in the absence of coronary microvascular dysfunction and detectable signs of cardiac ischemia (nonischemic hypothesis of CSX). Autonomic dysregulation and systemic inflammation may be involved/associated with both microvascular dysfunction and impaired pain sensitivity, further supporting the contribution of both mechanisms in CSX pathogenesis. Adapted from Kaski JC [216]

disturbances, and esophageal spasm) are also excluded. CSX is particularly common in postmenopausal women and is often hard to diagnose and even more to treat. Like for CRPS, the difficulties in the management reflect the lack of a unique pathophysiological explanation for this syndrome, despite the sometimes very debilitating symptoms. Several studies suggested a primary microvascular dysfunction as the main cause of CSX, and indeed the term CSX is often used as a synonym for microvascular angina [135]. Still, despite the latest technologies, as compared to traditional angiography, which allow to detect even subtle impairment in the coronary flow reserve, the so-called ischemic hypothesis of CSX has never been conclusively demonstrated in all patients. In reverse, an alternative "non-ischemic hypothesis" has been proposed. The "nonischemic hypothesis" proposes that primary alterations in pain perception and/or myocardial hypersensitivity rather than microvascular dysfunction/myocardial ischemia alone might be the causes leading to chest discomfort in a subgroup of CSX patients [136]. The advent of accurate neural and metabolic imaging techniques has provided a major contribution to the development of this hypothesis.

Cannon et al. [137] were among the first to suggest an impaired pain perception/hypersensitivity in CSX. Patients suffering angina despite normal/near-normal coronary arteries, as compared to patients with established coronary artery disease, hypertrophic cardiomyopathy, and valvular heart disease, had an increased cardiac sensitivity to several stimuli including catheter manipulation, intracoronary injection of contrast medium, and cardiac pacing at various heart rates: CSX patients experienced significantly greater chest pain than the other groups in response to all three stimuli. Intriguingly, altered pain sensitivity in CSX patients was proved to be a generalized phenomenon, including increased susceptibility to peripheral stimuli such as electrical and thermal skin stimulation and application of a forearm tourniquet [137–139]. These results well match with previous data on patients with silent myocardial ischemia. Falcone et al. [140] found a significant difference in dental pain threshold and reaction in patients with and those without anginal symptoms during exercise testing, suggesting that the lack of cardiac symptoms despite an ongoing myocardial ischemia might be at least partially related to a generalized, non-segmental hyposensitivity to pain.

Various aspects of the nociceptive pathway have been investigated in CSX patients. Lagerqvist et al. [141] showed an exaggerated response to exogenous adenosine. This algogenic effect is thought to be mediated via activation of A1 receptors expressed on the perivascular sympathetic nerve endings. Furthermore, administration of theophylline (a nonspecific A1/A2 antagonist) increased anginal threshold in these patients. Still, the lack of response to bamiphylline (A1 receptor-specific inhibitors) in the same group of patients questions this intriguing mechanism as the main responsible for increased nociception in CSX. More recently, abnormalities in central pain processing in CSX were also proposed, including ineffective thalamic gate allowing unregulated transmission of nociceptive stimuli to the cortex [142] and lack of habituation to repeated painful nociceptive stimuli [143].

Overall, like for the ischemic hypothesis, the exact mechanisms and anatomical locations of the neural abnormalities leading to abnormal pain perception/modulation remain incompletely understood. Yet, it must be acknowledged that the two hypotheses are not mutually exclusive, particularly if we bear in mind the tight relationship between nociception, inflammation, and SNS activation at cardiac level. Accordingly, Crea and Lanza [135] proposed a possible functional link between coronary microvascular abnormalities and enhanced pain perception in CSX. The alterations in cardiac afferent fibers might be the functional response to repeated episodes of microvascular dysfunction. Alternatively, the increased reactivity of cardiac afferent fibers to usually innocuous stimuli may be brought about by systemic inflammation and/or metabolic abnormalities. Another possibility is that a primary abnormality in cardiac afferent and autonomic neural activity may be responsible for the abnormal microvascular responses, possibly also through mechanisms of neurogenic inflammation. Several data support a combined hypothesis as well as the involvement of SNS abnormalities

and inflammation. First, both endothelium-dependent and endothelium-independent mechanisms of microcirculatory dysfunction have been detected in each CSX patient. Some patients simultaneously exhibit a profoundly abnormal coronary microvascular vasoconstrictive response (as investigated by coronary responses to ergonovine, hand grip, and/or cold pressor test), potentially due to an increased sympathetic tone/exaggerated response to α1-AR activation (having a vasoconstrictor effect on coronary vessels) [144]. Plus, Madaric et al. [145] showed that CSX patients may have an exaggerated myocardial β-adrenergic stimulation and/or response leading to significantly higher intraventricular flow velocities (IFV) in response to dobutamine, in the absence of dobutamine-induced wall motion abnormalities. Accordingly, treatment with the selective – β1-AR blocker bisoprolol resulted in both a reduction in angina score and normalization of IFV. Finally, neuropeptide Y was recently proved to cause transient myocardial ischemia in patients with CSX (probably through constriction of the small intramyocardial vessels), but not in control subjects or coronary artery disease patients [146].

The involvement of inflammation among the pathophysiological mechanisms of CSX patients is well defined. Accordingly, traditional cardiovascular risk factors, insulin resistance [147], and estrogen deficiency [148] have been reported to be highly prevalent in CSX patients. Long et al. [149] al showed that in CSX patients, the severity of angina during exercise stress test was associated to both increased serum high-sensitive C-reactive protein levels and decreased brachial artery flow-mediated dilatation in response to hyperemia (a marker of systemic endothelial dysfunction).

Potential Rule of TRPV-1 Pathways in CSX

Summary: The molecular/neuronal pathways involved in the increased sensitivity to pain in CSX patients are still under investigation. A peripheral mechanism of increased nociceptive activation appears particularly appealing and might also concur to explain the autonomic dysfunction observed in some patients. Indeed, the repetitive activation of sympathetic afferent fibers by nociceptor stimuli may lead to a chronic increase of the sympathetic output to the heart, as well as a decrease of the parasympathetic tone. TRPV-1 channels are constitutively expressed on cardiac afferent fibers and can respond to multiple stimuli including physical and chemical stimuli. Therefore, an abnormal afferent signaling through TRPV-1 channels might be implicated in the abnormal pain sensitivity in CSX. Additionally, TRPV-1 channels are also expressed on inflammatory cells (not constitutively) and on endothelial cells, and a direct connection between TRPV1 dysregulation and coronary microvascular dysfunction has been described in animal models.

A very appealing molecular pathway linking nociception, SNS activity, and inflammation, potentially implicated in the pathophysiology of CSX (besides many other cardiovascular conditions) [150], is represented by TRPV-1 channels. TRPV-1 channels are expressed by several cellular types at the cardiac level including not only cardiac-sensitive fibers but also cardiac monocytes/macrophages, vascular smooth muscle cells, and endothelial cells [151]. Shipp et al. [152] suggested that in mice with metabolic syndrome (a condition that shares several risk factors with CSX), lowered glucose tolerance and increased obesity may lead to a reduced expression of TRPV1 on cardiac monocytes. In turn, TRPV1 downregulation was associated with compromised myocardial energy supply and metabolism. Bratz et al. [153] further extended these observations showing that in mice with metabolic syndrome, a reduced TRPV1 functional expression and/or dysfunction may underline the coronary microvascular dysfunction via a nitric oxide-dependent and large conductance calcium-sensitive potassium channel-dependent pathway [154]. Worth to mention here, the expression of TRPV1 channels on cardiac afferent fibers is thought to be constitutive, while TRPV1 expression on bone marrow-derived macrophages was showed to be a protective pathway mainly activated by stressors. Pretreatment of bone marrow-derived macrophages with evodiamine or capsaicin (TRPV1 agonists) was proved to alleviate lipid accumulation and impaired the production of MCP-1, MIP-2, and IL-6 [155]. Consistently,

TRPV1 knockout mice undergo excessive inflammation, disproportional left ventricular remodeling, and deteriorated cardiac function after myocardial infarction (MI), with increased mortality [156]. On the contrary, chemical selective ablation of TRPV1-expressing cardiac afferent fibers by epicardial application of resiniferatoxin (RTX), a toxic activator of the VR1 channel, provided powerful protective effects against adverse cardiac remodeling and autonomic dysfunction induced by MI in rats [157]. The advocated mechanism is the acute and chronic inhibition of CSAR. Indeed, TRPV1-mediated CSAR activation was shown to be upregulated in congestive heart failure (CHF) animal models [158]. The biological complexity of TRPV1 mediated pathways in the heart is further substantiated by a very recent work of Yoshie and colleagues [159]. They showed that cardiac TRPV1 afferent fiber depletion by epicardial RTX application enhances, rather than reduces, reflex efferent sympathetic control of normal porcine hearts, producing an increase in basal activity of the stellate ganglia as well as an increased responsiveness to cardiac stressors. These results might seem contradictory as compared with RTX effects in infarcted animals. Yet, it must be remembered that TRPV1 expression on cardiac-sensitive fibers is constitutive and that no specialized "high-threshold" fibers (or nociceptive fibers) have been described in the myocardium. Therefore, the same TRPV1 channels leading to an excessive CSAR in the setting of pathological processes such as myocardial infarction and/or cardiomyopathies may have an important regulatory function in the beat-to-beat physiological control of the heart.

Sympathetic Ganglia Block/Removal as a Common Treatment for SMPs, Essential Hyperhidrosis, Angina Pectoris, and Ventricular Arrhythmias

Not surprisingly in view of the frequently observed clinical relationship between chronic SNS activation and pain, several attempts to control pain through sympathetic nerve block/removal have been performed over the years.

Due to the relatively accessible anatomical location, the stellate ganglia (SG) have been a preferential site of intervention. Percutaneous pharmacological blockade of SG (SGB) via anatomical landmarks has been safely reported since 1934 [160] for the treatment of sympathetic-related pain syndromes. More recently, an ultrasound-guided approach [161] has been reported. In responder patients, the beneficial effects on pain control of SGB generally exceed the half-life of drug used to perform the block (such as lidocaine or bupivacaine) but rarely last longer than few weeks. As already mentioned, the efficacy of SGB in CRPS type I is dependent on the time interval between symptom onset and treatment initiation, with significantly less efficacy after the first 6–12 months [162].

To achieve long-lasting effects and because the second and third thoracic ganglia are considered pivotal in the upper limb sympathetic innervation, several techniques of surgical removal of the first thoracic sympathetic ganglia were implemented over the years. The first thoracic sympathectomy was performed by Alexander in 1889 to treat an epileptic patient, but the procedure gained larger popularity only in the 1920s for the treatment of essential palmar and axillary hyperhidrosis [163]. Accessing the sympathetic chain in the chest cavity by conventional surgical methods ("open sympathectomy") was technically complex. The posterior thoracotomic approach, requiring resection of the ribs, was developed in 1908. A less invasive but more surgically challenging approach, namely, the supraclavicular approach, was proposed in 1935. Finally, in 1942, Hughes was the first to report about thoracoscopic sympathectomy [164]. The procedure was systematically developed as a minimally invasive surgical technique only several years later (1980s) and started to spread all over the world since the early 2000s. Nowadays, the so-called video-assisted thoracoscopic surgery (VATS) is largely used for the treatment of several conditions related to disruption of the sympathetic activity to the

skin such as essential (or primary) palmar/axillar hyperhidrosis, Raynaud's syndrome, and SMP/CRPS. Case series of thousands of patients affected by palmar/axillar hyperhidrosis treated with VATS sympathectomy/sympatholysis have been reported, showing an overall very good safety profile of the procedure [165, 166]. The only significant side effect described was the excessive compensatory increase in sweating in other parts of the body, being the abdomen, thorax, back, thighs, and/or groin regions the more likely to be affected. According to the distribution of pain/hyperhidrosis, sympathectomy/sympatholysis typically targets T2–T3 for the treatment of palmar affections and T2–T3–T4 for the treatment of palmar/axillary combined conditions [167]. The lower half of the stellate ganglia (T1) is usually spared to avoid Horner's syndrome. Despite the significant number of patients undergoing upper thoracic sympathectomy for these indications, few data on the immunohistochemistry and the anatomopathology of the removed sympathetic ganglia have been reported so far. Dai et al. [168] found an increased expression of choline acetyltransferase (ChAT) and vasoactive intestinal peptide (VIP) in sympathetic ganglia obtained from patients with palmar hyperhidrosis as compared to controls. More recently, Chen et al. [169] studied the ganglionic expression levels of ChAT, VIP, and synaptophysin in 66 patients with palmar hyperhidrosis undergoing thoracoscopic T4 sympathectomy. They found no differences in patients reporting compensatory hyperhidrosis after sympathectomy as compared to those who did not developed the complication. Of note, ChAT and VIP can be considered as nonspecific markers of cholinergic preganglionic sympathetic nerve activity. Therefore, they only provide limited information about resting sympathetic preganglionic trafficking. Indeed, the driving hypothesis of the first study, namely, that patient with hyperhidrosis have a functional overactivity of the sympathetic postganglionic fibers that travel through the upper thoracic sympathetic ganglia, is supported by several clinical data [170, 171].

Cardiac Sympathetic Denervation: History and Current Indications

In 1916, Jonnesco [172] was the first to surgically remove the left SG in a patient suffering incapacitating angina pectoris and ventricular arrhythmias. Both conditions were effectively suppressed. Still, the fear of potential detrimental effects of left stellectomy on the coronary flow initially limited the diffusion of the technique. In 1929, Leriche and Fontaine [173] clearly showed that cardiac sympathetic nerves exert a vasoconstrictive effect on the coronary arteries rather than a vasodilator one as previously thought. Subsequently, several clinical studies in Europe and in the USA explored the antianginal effects of left SG surgical removal [174–176], overall confirming Jonnesco's findings. The optimal antianginal efficacy was provided by cervicothoracic sympathectomy, consisting in the surgical removal of the stellate ganglion together with T2–T4 thoracic ganglia. The procedure, also known as cardiac sympathetic denervation (CSD), generally spared the upper half of the stellate ganglia (where most of the ocular fibers transit) to avoid Horner' syndrome. Finally, in the 1960s, despite its efficacy, left CSD (LCSD) was progressively abandoned for the treatment of angina due to the widespread diffusion of surgical coronary artery bypass graft and of β-AR blockers [177]. LCSD usage was subsequently resumed for the treatment of ventricular arrhythmias (VAs) in patients affected by long QT syndrome (LQTS), an inherited arrhythmogenic disorder characterized by increased susceptibility of structurally normal hearts to catecholamines. First proposed by Moss and McDonald in 1971 [178], LCSD usage in LQTS was then largely promoted by the Italian group of PJ Schwartz [179–181] who also provided a strong and comprehensive experimental rationale for the procedure (direct acute antiadrenergic effects combined with increase in the ventricular fibrillation threshold) [182–185]. Nowadays, LCSD is a mainstay in the management of both LQTS and catecholaminergic polymorphic ventricular tachycardia (CPVT) [186] another inherited arrhythmogenic disorder characterized by increased susceptibility of the

heart to catecholamines [214]. LCSD with antiarrhythmic purposes was initially performed through the supraclavicular approach [187], subsequently abandoned in favor of VATS. In 2012, the American group of Ackerman (Mayo Clinic, Rochester) [188] provided the first clinical evidence of LCSD effectiveness in patients with structural heart diseases (SHD) and refractory VAs. A vast program of CSD in patients with SHD was subsequently undertaken by the group of Shivkumar (UCLA, Los Angeles). In this setting, bilateral CSD (BCSD) was suggested to be more effective than LCSD in reducing VA recurrences [189] and improving outcome [190, 215]. The UCLA group also reported the first human analysis of the removed sympathetic ganglia. First, they showed a significant neuronal enlargement and an increased synaptic density in the stellate ganglia of patients with SHD who received CSD as compared to controls [191]. Few years later, they further enriched the description of the sympathetic ganglia in the same type of patients [192] showing the presence, besides neuronal hypertrophy, of inflammation, neurochemical remodeling, oxidative stress, and satellite glial cell activation. These data fully confirmed preclinical findings showing a significant and bilateral extracardiac neuronal remodeling in the setting of SHD [193, 194]. Of note, Rizzo et al. [195] recently found mild but distinct inflammatory infiltrates composed of CD3 + and CD8+ T cells and macrophages in the sympathetic ganglia of LQTS/CPVT patients undergoing LCSD because of refractory VAs. Accordingly, they proposed T-cell-mediated cytotoxicity toward ganglion cells as a potential pro-arrhythmic mechanism in these patients with structurally normal heart, leading to an increase in cardiac sympathetic efferent activity.

Neuropathic Pain After Cardiac Sympathetic Denervation: Is It Post-denervation Supersensitivity?

As already mentioned, VATS is now the most common surgical technique used to perform high thoracic sympathectomy, both for cardiac and for non-cardiac conditions. The intervention is performed under general anesthesia through three small thoracic incisions per side in each of three different intercostal spaces. LCSD in patients with channelopathies and sympathectomy for cutaneous conditions usually require less than 1 h to be performed [196], while CSD in SHD generally takes longer mainly because of the hemodynamic and respiratory liability of the patients. The UCLA group reported a median surgical time of 164 min for BCSD in SHD patients [197].

In recent years, VATS usage has been consistently implemented in major thoracic surgery [198]. In this setting, VATS implementation was associated with a significant reduction in mortality and morbidity, including a reduced incidence in postoperative neuropathic pain (also known as post-thoracotomy pain) [199]. This type of pain, not uncommon after major thoracic surgery, can become chronic and disabling. It is typically associated with burning, shooting, shocking, and pressure-like sensations [200]. A recent study reported a median interval from surgical treatment to the onset of neuropathic pain of 7 days [200]. Despite its causes are yet to be fully elucidated, postoperative neuropathic pain incidence after major thoracic surgery has been associated with patient-related characteristics (such as preoperative use of hypnotic medication), as well as procedure-related characteristics (such as the duration of the surgery, the type of surgery, and the early postoperative pain intensity) [200, 201]. Accordingly, despite the consistent overall amount of patients who received VATS sympathectomy all over the word for the treatment of essential hyperhidrosis, a significant incidence of post-procedural neuropathic pain was never reported. On the contrary, frequent cases of post-sympathectomy neuropathic pain had been reported in the 1960s with the classical thoracotomic approach [202].

In 2014, Vaseghi et al. [189] observed, among the 41 patients with SHD who received VATS-CSD (14 LCSD and 27 BCSD), a 10% incidence of compensatory sweating and a 12% incidence (3 BCSDs and 1 LCSD patient) of symptoms compatible with postoperative neuropathic pain. In 2016, Antiel et al. (Mayo Clinic) [203] published

a detailed analysis focused on the quality of life (QOL) after VATS-LCSD in 62 patients with potentially life-threatening cardiac channelopathies/cardiomyopathies. They all filled in dedicated surveys assessing general, physical, and psychosocial QOL. Overall, these patients showed a high degree of satisfaction with the procedure. Nevertheless, a not negligible incidence of shoulder blade pain and chest pain was noticed. The presence of specific characteristics of the pain (such as a burning sensation) suggesting a neuropathic origin was not assessed. The results were presented according to the age at the time of LCSD: pediatric patients had a mean age of 9, while adult patients had a mean age of 29 years. Only a minority had SHD, being the majority LQTS/CPVT patients. The incidence of persistent shoulder blade pain after LCSD was 17% in child and 53% in adults, while persistent chest pain was reported by 33% of the child and 29% of the adults. To prevent this side effect, the main centers all over the world performing VATS-CSD are now administering gabapentin prophylactically [204]. In our preliminary experience in Pavia, we recently reported [205] an incidence of transient neuropathic pain of 26% among 27 patients (22% BCSD in SHD) who received VATS-CSD, despite the perioperative administration of gabapentin. In all cases, the symptoms resolved, generally in the first 1–2 months after the procedure. The most common sites of pain were the shoulder blade region and the mammalian region, and patients developing transient neuropathic pain often also complained about significant compensatory hyperhidrosis. The onset of symptoms was typically delayed and occurred after hospital discharge, with the peak 1–2 weeks after surgery (personal observations).

Although it is likely that the pathophysiology of neuropathic pain after CSD (such as the one of post-thoracotomy pain) is complex and that procedural as well as patient-related factors are involved, the fact that no or very few similar cases were reported in patients undergoing VATS sympathectomy for non-cardiac reasons is extremely intriguing. From an anatomical point of view, the cutaneous regions more frequently affected (the shoulder blade region and the mammalian region) seem to overlap with the thoracic lower boundaries of the dermatomes T1–T4, at least according to the classical anatomical map of Keenan e Garret [206]. These dermatomes are largely deprived of their sympathetic innervation as consequence of CSD but still have intact sensitive innervation through the DRG (Fig. 1). Therefore, the compensatory increase in cutaneous sympathetic output under T4 (to preserve thermoregulation) combined with the exposure to circulating catecholamines may evoke post-denervation supersensitivity phenomena in these areas leading to nociceptor C-fiber exaggerated activation. The crucial junction to sustain this hypothesis deals with the mechanisms leading to α-AR overexpression on nociceptive C-fibers, which, as previously mentioned, is not constitutive. VATS-related cutaneous incisions are minute and quickly recovering. Still, they may activate the inflammatory cascade and favor nociceptor sensitization. Moreover, a tiny amount of air (subcutaneous emphysema) in the thoracic wall, often subclinical, is not rarely observed in patients treated with VATS and may contribute to increase α-AR expression on nociceptive C-fibers. Both these mechanisms, in variable degrees according to the amount of acute post operatory pain and the amount of emphysema, could potentiate the plausible main driver of nociceptor sensitization: the sympathetic efferent fiber axonal degeneration. As already proposed by ER Perl [132], post-ganglionectomy peripheral degeneration of sympathetic efferent fibers may strongly promote α-AR expression in the surrounding C-fibers. Nociceptor sensitization to sympathetic stimulation and adrenergic substances via α-AR were proved after partial injury of mixed peripheral nerves [207–209] and had even been reported after regional thoracotomic sympathectomy. Of note, features of adrenergically induced responses after sympathectomy appeared to be different from those seen after mixed peripheral nerve damage [210]. Accordingly, from a clinical standpoint, post-CSD neuropathic pain symptoms seem to lack a clear sympathetic trigger (on the contrary, symptoms are often more accentuated during night and/or at rest, personal observation).

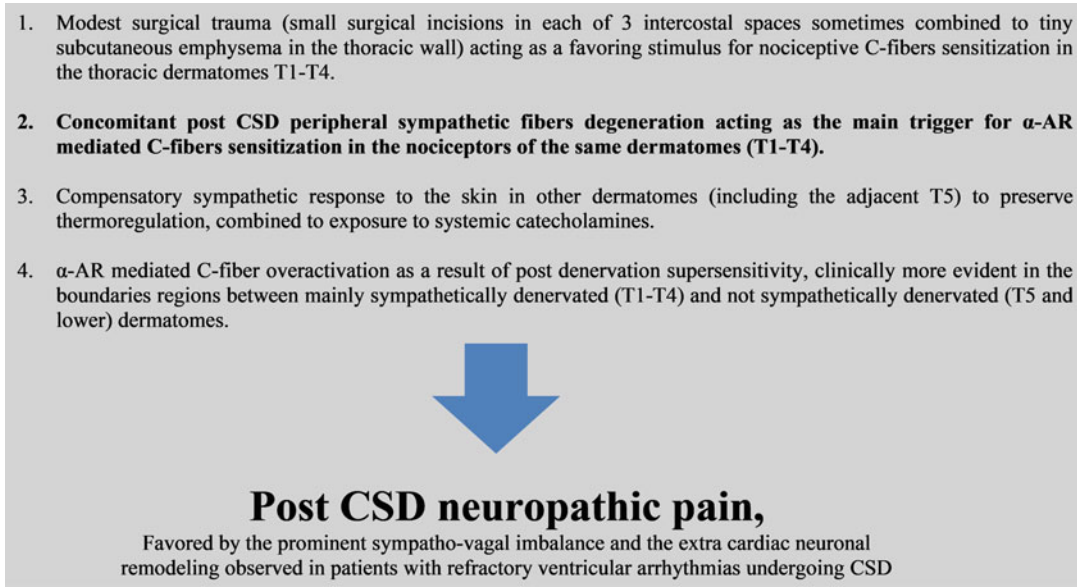


Fig. 5 Working hypothesis for the genesis of post-cardiac sympathetic denervation (CSD) neuropathic pain

Yet, up to this point, the clinical dilemma is still not solved: why subjects with cardiac arrhythmias appear to be at so higher risk of post-VATS sympathectomy neuropathic pain as compared to patients with essential hyperhidrosis? The answer will not surprise the careful reader. Patients with SHD undergoing CSD have a prominent sympathovagal imbalance due to underlying cardiomyopathy [211], characterized by exaggerated sympathetic tone and reflexes combined to increased levels of circulating catecholamines [212]. Moreover, the prominent neuronal remodeling of cardiac sympathetic ganglia is likely associated with an accentuated inflammatory response after ganglionectomy. In turn, the exaggerated peripheral release of cytokine/grow factors may consistently increase the nociceptive-sensitizing effects as well as the neurogenic pro-inflammatory effects in the denervated dermatomes. Of note, the neuronal remodeling demonstrated by Rizzo et al. in patients with channelopathies might provide the basis for a similar explanation in patients with refractory ventricular arrhythmias and structurally normal heart. Figure 5 briefly summarizes the overall hypothesis.

Worth to mention here, neuropathic pain was almost never reported in the past in both LQTS/CPVT patients [181, 186] and post-myocardial infarction patients [213] treated with supraclavicular LCSD, despite a more extended and deeper surgical incision and a less delicate manipulation of the sympathetic chain. The low incidence of neuropathic pain might be explained with the non-thoracic site of the surgical access, less likely to contribute to sensitization of nociceptive C-fibers in the denervated dermatomes.

Conclusion

The two branches of the autonomic nervous system, namely the sympathetic and the parasympathetic nervous system, are involved in the regulation of almost all functions and processes of the human body, including inflammatory responses, peripheral nociception, and central pain perception. Chronic sympathetic nervous system overactivity, combined with pathological nociceptive sensitivity/pain processing and immuno-inflammatory dysfunctions, has been

implicated in the pathogenesis of disabling pain syndromes both at the cutaneous and at the cardiac level, such as the complex regional pain syndrome and the cardiac syndrome X, respectively. Intriguingly, in both these conditions, local pain perception can be independent from the actual presence of a noxious stimulus, can be worsened by sympathetic activation, and can be improved by sympathetic blockade. Molecular pathways involved in the crosstalk between inflammation, sympathetic nervous system overactivity, and nociceptive activation at the cutaneous as well as at the cardiac level are far from being completely understood; TRPV1 (transient receptor potential cation channel subfamily V member 1) channels might play an important role. Finally, in this chapter, a working hypothesis for the emerging clinical issue of neuropathic pain following thoracoscopic sympathectomy in patients with refractory ventricular arrhythmias is provided. These patients, particularly those with cardiomyopathies, have exaggerated sympathetic tone and reflexes, combined with an inflammatory neuronal remodeling affecting cardiac sympathetic ganglia. In this setting, the onset of neuropathic pain at the cutaneous level might be related to post-denervation supersensitivity of nociceptive fibers to catecholamines mediated by non-constitutive α-adrenergic receptors.

Cross-References

- ▶ Neuromodulation for Chronic Refractory Angina
- ▶ When the Heart Hurts

References

1. Vincentz JW, Rubart M, Firulli AB. Ontogeny of cardiac sympathetic innervation and its implications for cardiac disease. Pediatr Cardiol. 2012;33:923–8. https://doi.org/10.1007/s00246-012-0248-1.
2. Janig W, Habler HJ. Organization of the autonomic nervous system: structure and function. In: Vinken PJ, Bruyn GW, editors. Handbook of clinical neurology, Vol 74; series 30: the autonomic nervous system. Part I. Normal functions. Amsterdam: Elsevier Science Publisher; 1999. p. 1–52.
3. Gibbins I. Peripheral autonomic nervous system. In: Paxinos G, editor. The human nervous system. San Diego: Academic; 1990. p. 93–123.
4. Carlson BM. Integumentary, skeletal, and muscular systems. Human embryology and developmental biology. St. Louis: Mosby; 1994. p. 153–81.
5. Foulkes T, Wood JN. Pain genes. PLoS Genet. 2008; 4(7):e1000086. https://doi.org/10.1371/journal.pgen.1000086.
6. Woolf CJ, Ma Q. Nociceptors—noxious stimulus detectors. Neuron. 2007;55(3):353–64. https://doi.org/10.1016/j.neuron.2007.07.016.
7. Willis WD, Coggeshall RE. Sensory mechanisms of the spinal cord. 3rd ed. New York: Kluwer Academic/Plenum; 2004.
8. Djouhri L, Lawson SNA. [beta]-fiber nociceptive primary afferent neurons: a review of incidence and properties in relation to other afferent A-fiber neurons in mammals. Brain Res Brain Res Rev. 2004;46(2): 131–45. https://doi.org/10.1016/j.brainresrev.2004.07.015.
9. Kumazawa T, Mizumura K, Kruger L, editors. The Polymodal receptor – a gateway to pathological Pain. Progress in brain research, vol. 113. New York: Elsevier; 1996.
10. Lewin GR, Moshourab R. Mechanosensation and pain. J Neurobiol. 2004;61(1):30–44. https://doi.org/10.1002/neu.20078.
11. Cain DM, Khasabov SG, Simone DA. Response properties of mechanoreceptors and nociceptors in mouse glabrous skin: an in vivo study. J Neurophysiol. 2001;85(4):1561–74. https://doi.org/10.1152/jn.2001.85.4.1561.
12. Schmidt R, Schmelz M, Forster C, Ringkamp M, Torebjörk E, Handwerker H. Novel classes of responsive and unresponsive C nociceptors in human skin. J Neurosci. 1995;15:333–41.
13. Meyer RA, Davis KD, Cohen RH, Treede RD, Campbell JN. Mechanically insensitive afferents (MIAs) in cutaneous nerves of monkey. Brain Res. 1991; 561(2):252–61.
14. Jordt SE, Bautista DM, Chuang HH, McKemy DD, Zygmunt PM, Högestätt ED, et al. Mustard oils and cannabinoids excite sensory nerve fibres through the TRP channel ANKTM1. Nature. 2004;427(6971): 260–5. https://doi.org/10.1038/nature02282.
15. Bandell M, Story GM, Hwang SW, Viswanath V, Eid SR, Petrus MJ, et al. Noxious cold ion channel TRPA1 is activated by pungent compounds and bradykinin. Neuron. 2004;41(6):849–57.
16. Dai Y, Wang S, Tominaga M, Yamamoto S, Fukuoka T, Higashi T, et al. Sensitization of TRPA1 by PAR2 contributes to the sensation of inflammatory pain. J Clin Invest. 2007;117(7):1979–87. https://doi.org/10.1172/JCI30951.
17. Bang S, Hwang SW. Polymodal ligand sensitivity of TRPA1 and its modes of interactions. J Gen Physiol. 2009;133(3):257–62. https://doi.org/10.1085/jgp.200810138.

18. Caterina MJ, Leffler A, Malmberg AB, Martin WJ, Trafton J, Petersen-Zeitz KR, et al. Impaired nociception and pain sensation in mice lacking the capsaicin receptor. Science. 2000;288:306–13.
19. Schepersm RJ, Ringkamp M. Thermoreceptors and thermosensitive afferents. Neurosci Biobehav Rev. 2010;34(2):177–84. https://doi.org/10.1016/j.neubiorev.2009.10.003.
20. Johnson JM. Non-thermoregulatory control of human skin blood flow. J Appl Physiol. 1986;61:1613–22.
21. Cheshire WP, Low PA. Disorders of sweating and thermoregulation. Continuum: lifelong learning in. Neurology. 2007;13(6):143–64.
22. Low PA, Sletten DM. Laboratory evaluation of autonomic failure. In: Low PA, Banarroch EE, editors. Clinical autonomic disorders: evaluation and management. 3rd ed. Philadelphia: Wolters Kluwer-Lippincott Williams & Wilkins Publishers; 2007. p. 130–63.
23. Folgueras AR, Valdés-Sánchez T, Llano E, Menéndez L, Baamonde A, Denlinger BL, et al. Metalloproteinase MT5-MMP is an essential modulator of neuro-immune interactions in thermal pain stimulation. Proc Natl Acad Sci U S A. 2009;106:16451–6. https://doi.org/10.1073/pnas.0908507106.
24. Kawashima T. The autonomic nervous system of the human heart with special reference to its origin, course, and peripheral distribution. Anat Embryol. 2005;209:425–38. https://doi.org/10.1007/s00429-005-0462-1.
25. Armour JA, Murphy DA, Yuan B-X, MacDonald S, Hopkins DA. Gross and microscopic anatomy of the human intrinsic cardiac nervous system. Anat Rec. 1997;247:289–98.
26. Janes RD, Brandys JC, Hopkins DA, Johnstone DE, Murphy DA, Armour JA. Anatomy of human extrinsic cardiac nerves and ganglia. Am J Cardiol. 1986;57(4):299–309.
27. Hougland MW, Durkee KH, Hougland AE. Innervation of Guinea pig heart by neurons sensitive to capsaicin. J Auton Nerv Syst. 1986;15:217–25.
28. Khabarova AY. The afferent innervation of the heart. New York: Consultants Bureau; 1963. p. 1–475.
29. Kuo DC, Gravitz JJ, DeGroat WC. Tracing of afferent and efferent pathways in the left cardiac nerve of the cat using retrograde and transganglionic transport of horseradish peroxidase. Brain Res. 1984;321:111–8.
30. Ardell JL. Intrathoracic neuronal regulation of cardiac function. In: Armour JA, Ardell JL, editors. Basic and clinical neurocardiology. New York: Oxford University Press; 2004. p. 118–52.
31. Armor JA. Potential clinical relevance of the 'little brain' on the mammalian heart. Exp Physiol. 2008;93:165–76.
32. Malliani A. Cardiovascular sympathetic afferent fibers. In: Adrian RH, et al., editors. Reviews of physiology, biochemistry, and pharmacology, vol. 94. Berlin: Springer; 1982. p. 11–74.
33. Schwartz PJ, Foreman RD. Cardiac pain, sympathetic afferents, and life-threatening arrhythmias. J Cardiovasc Electrophysiol. 1991;2:s100–13.
34. White JC, Bland EF. Cardiac pain, anatomic pathways and physiologic mechanisms. Circulation. 1957;16:644–55.
35. Pan HL, Chen SR. Sensing tissue ischemia: another new function for capsaicin receptors? Circulation. 2004;110:1826–31. https://doi.org/10.1161/01.CIR.0000142618.20278.7A.
36. Uchida Y, Murao S. Bradykinin-induced excitation of afferent cardiac sympathetic nerve fibers. Jpn Heart J. 1974;15:84–91. https://doi.org/10.1536/ihj.15.84.
37. Caterina MJ, Schumacher MA, Tominaga M, Rosen TA, Levine JD, Julius D. The capsaicin receptor: a heat-activated ion channel in the pain pathway. Nature. 1997;389:816–24. https://doi.org/10.1038/39807.
38. Caterina MJ, Leffler A, Malmberg AB, Martin WJ, Trafton J, Petersen-Zeitz KR, Koltzenburg M, Basbaum AI, Julius D. Impaired nociception and pain sensation in mice lacking the capsaicin receptor. Science. 2000;288:306–13.
39. Tominaga M, Caterina MJ, Malmberg AB, Rosen TA, Gilbert H, Skinner K, et al. The cloned capsaicin receptor integrates multiple pain-producing stimuli. Neuron. 1998;21(3):531–43.
40. Schultz HD, Ustinova EE. Capsaicin receptors mediate free radical-induced activation of cardiac afferent endings. Cardiovasc Res. 1998;38:348–55. https://doi.org/10.1016/S0008-6363(98)00031-5.
41. Christensen AP, Corey DP. TRP channels in mechanosensation: direct or indirect activation? Nat Rev Neurosci. 2007;8:510–21. https://doi.org/10.1038/nrn2149.
42. Thames MD, Klopfenstein HS, Abboud FM, Mark AL, Walker JL. Preferential distribution of inhibitory cardiac receptors with vagal afferents to the inferoposterior wall of the left ventricle activated during coronary occlusion in the dog. Circ Res. 1978;43:512–9.
43. Webb SW, Adgey AA, Pantridge JF. Autonomic disturbance at onset of acute myocardial infarction. Br Med J. 1972;3:89–92.
44. Koren G, Weiss AT, Ben-David Y, Hasin Y, Luria MH, Gotsman MS. Bradycardia and hypotension following reperfusion with streptokinase (Bezold-Jarisch reflex): a sign of coronary thrombolysis and myocardial salvage. Am Heart J. 1986;112:468–71.
45. Von Bezold A, Hirt L. Uber die physiologischen Wirkungen des essigsauren veratrins. Untersuch Physiol Lab Wurzburg. 1867;1:75–156.
46. Southerland EM, Milhorn DM, Foreman RD, Linderoth B, DeJongste MJ, Armour JA, et al. Preemptive, but not reactive, spinal cord stimulation mitigates transient ischemia-induced myocardial infarction via cardiac adrenergic neurons. Am J Physiol Heart Circ Physiol. 2007;292(1):H311–7. https://doi.org/10.1152/ajpheart.00087.2006.

47. Schlereth T, Birklein F. The sympathetic nervous system and pain. NeuroMolecular Med. 2008;10(3): 141–7. https://doi.org/10.1007/s12017-007-8018-6.
48. Christianson JA, Riekhof JT, Wright DE. Restorative effects of neurotrophin treatment on diabetes-induced cutaneous axon loss in mice. Exp Neurol. 2003;179:188–99.
49. Ieda M, Fukuda K, Hisaka Y, Kimura K, Kawaguchi H, Fujita J, et al. Endothelin-1 regulates cardiac sympathetic innervation in the rodent heart by controlling nerve growth factor expression. J Clin Invest. 2004;113:876–84. https://doi.org/10.1172/JCI19480.
50. Snider WD. Functions of the neurotrophins during nervous system development: what the knockouts are teaching us. Cell. 1994;77:627–38.
51. Crowley C, Spencer SD, Nishimura MC, Chen KS, Pitts-Meek S, Armanini MP, et al. Mice lacking nerve growth factor display perinatal loss of sensory and sympathetic neurons yet develop basal forebrain cholinergic neurons. Cell. 1994;76:1001–11.
52. Fernyhough P, Diemel LT, Hardy J, Brewster WJ, Mohiuddin L, Tomlinson DR. Human recombinant nerve growth factor replaces deficient neurotrophic support in the diabetic rat. Eur J Neurosci. 1995;7:1107–10.
53. Unger JW, Klitzsch T, Pera S, Reiter R. Nerve growth factor (NGF) and diabetic neuropathy in the rat: morphological investigations of the sural nerve, dorsal root ganglion, and spinal cord. Exp Neurol. 1998; 153:23–34. https://doi.org/10.1006/exnr.1998.6856.
54. Ieda M, Kanazawa H, Ieda Y, Kimura K, Matsumura K, Tomita Y, et al. Nerve growth factor is critical for cardiac sensory innervation and rescues neuropathy in diabetic hearts. Circulation. 2006;114(22):2351–63. https://doi.org/10.1161/CIRCULATIONAHA.106.627588.
55. Zahn S, Leis S, Schick C, Schmelz M, Birklein F. No alpha-adrenoreceptor induced C-fiber activation in healthy human skin. J Appl Physiol. 2004; 96:1380–4. https://doi.org/10.1152/japplphysiol.00990.2003.
56. Drummond PD, Lipnicki DM. Noradrenaline provokes axon reflex hyperaemia in the skin of the human forearm. J Auton Nerv Syst. 1999;77:39–44.
57. Fuchs PN, Meyer RA, Raja SN. Heat, but not mechanical hyperalgesia, following adrenergic injections in normal human skin. Pain. 2001;90:15–23.
58. Drummond PD. Alpha-1 adrenoceptor stimulation triggers axon-reflex vasodilatation in human skin. Auton Neurosci. 2009a;151:159–63. https://doi.org/10.1016/j.autneu.2009.07.013.
59. Drummond PD. Alpha(1)-Adrenoceptors augment thermal hyperalgesia in mildly burnt skin. Eur J Pain. 2009b;13:273–9. https://doi.org/10.1016/j.ejpain.2008.04.008.
60. Vogelsang M, Heyer G, Hornstein OP. Acetylcholine induces different cutaneous sensations in atopic and non-atopic subjects. Acta Derm Venereol. 1995; 75:434–6.
61. Schlereth T, Brosda N, Birklein F. Spreading of sudomotor axon reflexes in human skin. Neurology. 2005;26:1417–21. https://doi.org/10.1212/01.WNL.0000158473.60148.FE.
62. Bernardini N, Sauer SK, Haberberger R, Fischer MJ, Reeh PW. Excitatory nicotinic and desensitizing muscarinic (M2) effects on C-nociceptors in isolated rat skin. J Neurosci. 2001;21:3295–302.
63. Miyan JA, Broome CS, Afan AM. Coordinated host defense through an integration of the neural, immune and haemopoietic systems. Domest Anim Endocrinol. 1998;15:297–304.
64. Fujii T, Mashimo M, Moriwaki Y, Misawa H, Ono S, Horiguchi K, et al. Physiological functions of the cholinergic system in immune cells. J Pharmacol Sci. 2017;134:1–21. https://doi.org/10.1016/j.jphs.2017.05.002.
65. Qu C, Brinck-Jensen NS, Zang M, Chen K. Monocyte-derived dendritic cells: targets as potent antigen-presenting cells for the design of vaccines against infectious diseases. Int J Infect Dis. 2014;19:1–5. https://doi.org/10.1016/j.ijid.2013.09.023.
66. Nestle FO, Di Meglio P, Qin JZ, Nickoloff BJ. Skin immune sentinels in health and disease. Nat Rev Immunol. 2009;9:679–91. https://doi.org/10.1038/nri2622.
67. Haniffa M, Gunawan M, Jardine L. Human skin dendritic cells in health and disease. J Dermatol Sci. 2015;77:85–92. https://doi.org/10.1038/nri2622.
68. Li X, Han Y, Sun E. Sniping the scout: targeting the key molecules in dendritic cell functions for treatment of autoimmune diseases. Pharmacol Res. 2016;107:27–41. https://doi.org/10.1016/j.phrs.2016.02.023.
69. Alnaeeli M, Park J, Mahamed D, Penninger JM, Teng YT. Dendritic cells at the osteo-immune interface: implications for inflammation-induced bone loss. J Bone Miner Res. 2007;22:775–80. https://doi.org/10.1359/jbmr.070314.
70. Alnaeeli M, Teng YT. Dendritic cells: a new player in osteoimmunology. Curr Mol Med. 2009;9:893–910.
71. Misery L. Langerhans cells in the neuro-immunocutaneous system. J Neuroimmunol. 1998;89:83–7.
72. Hosoi J, Murphy GF, Egan CL, Lerner EA, Grabbe S, Asahina A, et al. Regulation of Langerhans cell function by nerves containing calcitonin gene-related peptide. Nature. 1993;363:159–63.
73. Scholzen T, Armstrong CA, Bunnett NW, Luger TA, Olerud JE, Ansel JC. Neuropeptides in the skin: interactions between the neuroendocrine and the skin immune systems. Exp Dermatol. 1998;7:81–96.
74. Egan CL, Viglione-Schneck MJ, Walsh LJ, Green B, Trojanowski JQ, Whitaker-Menezes D, et al. Characterization of unmyelinated axons uniting epidermal and dermal immune cells in primate and murine skin. J Cutan Pathol. 1998;25:20–9.
75. Asahina A, Hosoi J, Grabbe S, Granstein RD. Modulation of Langerhans cell function by epidermal nerves. J Allergy Clin Immunol. 1995;96:1178–82.

76. Staniek V, Misery L, Dezutter-Dambuyant C, Claudy A, Schmitt D. Expression of neuropeptides on human epidermal Langerhans cells. Adv Exp Med Biol. 1995;378:147–50.
77. Lambert RW, Granstein RD. Neuropeptides and Langerhans cells. Exp Dermatol. 1998;7:73–80.
78. Torii H, Yan Z, Hosoi J, Granstein RD. Expression of neurotrophic factors and neuropeptide receptors by Langerhans cells and the Langerhans cell-like cell line XS52: further support for a functional relationship between Langerhans cells and epidermal nerves. J Invest Dermatol. 1997;109:586–91.
79. Maestroni GJ. Sympathetic nervous system influence on the innate immune response. Ann N Y Acad Sci. 2006;1069:195–207. https://doi.org/10.1196/annals.1351.017.
80. Heijnen CJ, Rouppe van der Voort C, Wulffraat N, van der Net J, Kuis W, Kavelaars A. Functional alpha 1-adrenergic receptors on leukocytes of patients with polyarticular juvenile rheumatoid arthritis. J Neuroimmunol. 1996;71:223–6.
81. Howarth D, Burstal R, Hayes C, Lan L, Lantry G. Autonomic regulation of lymphatic flow in the lower extremity demonstrated on lymphoscintigraphy in patients with reflex sympathetic dystrophy. Clin Nucl Med. 1999;24:383–7.
82. Grisanti LA, Woster AP, Dahlman J, Sauter ER, Combs CK, Porter JE. Alpha1- adrenergic receptors positively regulate toll-like receptor cytokine production from human monocytes and macrophages. J Pharmacol Exp Ther. 2011;338:648–57. https://doi.org/10.1124/jpet.110.178012.
83. Masini E, Blandina P, Mannaioni PF. Mast cell receptors controlling histamine release: influences on the mode of action of drugs used in the treatment of adverse drug reactions. Klin Wochenschr. 1982;60:1031–8. https://doi.org/10.1007/BF01716967.
84. Chong LK, Morice AH, Yeo WW, Schleimer RP, Peachell PT. Functional desensitization of beta agonist responses in human lung mast cells. Am J Respir Cell Mol Biol. 1995;13:540–6. https://doi.org/10.1165/ajrcmb.13.5.7576689.
85. Chong LK, Chess-Williams R, Peachell PT. Pharmacological characterisation of the beta-adrenoceptor expressed by human lung mast cells. Eur J Pharmacol. 2002;437:1–7. https://doi.org/10.1016/S0014-2999(02)01263-3.
86. Wang XS, Lau HY. Beta-adrenoceptor-mediated inhibition of mediator release from human peripheral blood-derived mast cells. Clin Exp Pharmacol Physiol. 2006;33:746–50. https://doi.org/10.1111/j.1440-1681.2006.04435.x.
87. Gebhardt T, Gerhard R, Bedoui S, Erpenbeck VJ, Hoffmann MW, Manns MP, et al. Beta2-Adrenoceptor-mediated suppression of human intestinal mast cell functions is caused by disruption of filamentous actin dynamics. Eur J Immunol. 2005;35:1124–32. https://doi.org/10.1002/eji.200425869.
88. Schulze W, Fu ML. Localization of alpha 1-adrenoceptors in rat and human hearts by immunocytochemistry. Mol Cell Biochem. 1996;163:159–65. https://doi.org/10.1007/BF00408653.
89. Prey S, Leaute-Labreze C, Pain C, Moisan F, Vergnesm P, Loot M, et al. Mast cells as possible targets of propranolol therapy: an immunohistological study of beta-adrenergic receptors in infantile haemangiomas. Histopathology. 2014;65:436–9. https://doi.org/10.1111/his.12421.
90. Tracey KJ. The inflammatory reflex. Nature. 2002;420:853–9. https://doi.org/10.1038/nature01321.
91. Pavlov VA, Tracey KJ. The cholinergic anti-inflammatory pathway. Brain Behav Immun. 2005;19:493–9. https://doi.org/10.1016/j.bbi.2005.03.015.
92. Tracey KJ. Physiology and immunology of the cholinergic anti-inflammatory pathway. J Clin Invest. 2007;117:289–96. https://doi.org/10.1172/JCI30555.
93. Pereira MR, Leite PE. The involvement of parasympathetic and sympathetic nerve in the inflammatory reflex. J Cell Physiol. 2016;231:1862–9. https://doi.org/10.1002/jcp.25307.
94. Hoover DB. Cholinergic modulation of the immune system presents new approaches for treating inflammation. Pharmacol Ther. 2017; https://doi.org/10.1016/j.pharmthera.2017.05.002.
95. Borovikova LV, Ivanova S, Zhang M, Yang H, Botchkina GI, Watkins LR, et al. Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. Nature. 2000;405:458–62. https://doi.org/10.1038/35013070.
96. Bellinger DL, Lorton D, Hamill RW, Felten SY, Felten DL. Acetylcholinesterase staining and choline acetyltransferase activity in the young adult rat spleen: lack of evidence for cholinergic innervation. Brain Behav Immun. 1993;7:191–204. https://doi.org/10.1006/brbi.1993.1021.
97. Rosas-Ballina M, Olofsson PS, Ochani M, Valdés-Ferrer SI, Levine YA, Reardon C, et al. Acetylcholine-synthesizing T cells relay neural signals in a vagus nerve circuit. Science. 2011;334:98–101. https://doi.org/10.1126/science.1209985.
98. Andersson U, Tracey KJ. Neural reflexes in inflammation and immunity. J Exp Med. 2012;209:1057–68. https://doi.org/10.1084/jem.20120571.
99. Wulfing C, Gunther HS. Dendritic cells and macrophages neurally hard-wired in the lymph node. Sci Rep. 2015;5:16866. https://doi.org/10.1038/srep16866.
100. Salamone G, Lombardi G, Gori S, Nahmod K, Jancic C, Amaral MM, et al. Cholinergic modulation of dendritic cell function. J Neuroimmunol. 2011;236:47–56. https://doi.org/10.1016/j.jneuroim.2011.05.007.
101. Calvillo L, Vanoli E, Andreoli E, Besana A, Omodeo E, Gnecchi M, et al. Vagal stimulation, through its nicotinic action, limits infarct size and the inflammatory response to myocardial ischemia and reperfusion.

J Cardiovasc Pharmacol. 2011;58(5):500–7. https://doi.org/10.1097/FJC.0b013e31822b7204.
102. Frangogiannis NG, Youker KA, Rossen RD, Gwechenberger M, Lindsey MH, Mendoza LH, et al. Cytokines and the microcirculation in ischemia and reperfusion. J Mol Cell Cardiol. 1998; 30:2567–76. https://doi.org/10.1006/jmcc.1998.0829.
103. Levy MN. Sympathetic-parasympathetic interactions in the heart. Circ Res. 1971;29:437–45.
104. Vanhoutee PM, Verbeuren TJ. Inhibition by acetylcholine of the norepinephrine release evoked by potassium in canine saphenous veins. Circ Res. 1976;39:263–9.
105. Levy MN, Blattberg B. Effect of vagal stimulation on the overflow of norepinephrine into the coronary sinus during cardiac sympathetic nerve stimulation in the dog. Circ Res. 1976;38:81–4.
106. Manabe N, Foldes FF, Torocsik A, Nagashima H, Goldiner PL, Vizi ES. Presynaptic interaction between vagal and sympathetic innervation in the heart: modulation of acetylcholine and noradrenaline release. J Auton Nerv Syst. 1991;32:233–42.
107. Schwertfeger E, Klein T, Vonend O, Oberhauser V, Stegbauer J, Rump LC. Neuropeptide Y inhibits acetylcholine release in human heart atrium by activation of Y2-receptors. Naunyn Schmiedeberg's Arch Pharmacol. 2004;369:455–61. https://doi.org/10.1007/s00210-004-0930-9.
108. Wetzel GT, Goldstein D, Brown JH. Acetylcholine release from rat atria can be regulated through an alpha 1-adrenergic receptor. Circ Res. 1985; 56:763–6.
109. Burnstock G. Do some nerve cells release more than one transmitter? Neuroscience. 1976;1:239–48.
110. Potter EK, McCloskey DI. Peripheral inhibition of cardiac vagal action by sympathetic adrenergic stimulation. Proc Aust Soc Clin Exp Pharmacol. 1982;13:99P.
111. Potter E. Presynaptic inhibition of cardiac vagal postganglionic nerves by neuropeptide Y. Neurosci Lett. 1987;83:101–6.
112. Smith-White MA, Hardy TA, Brock JA, Potter EK. Effects of a selective neuropeptide Y Y2 receptor antagonist, BIIE0246, on Y2 receptors at peripheral neuroeffector junctions. Br J Pharmacol. 2001; 132:861–8. https://doi.org/10.1038/sj.bjp.0703879.
113. Smith-White MA, Herzog H, Potter EK. Role of neuropeptide Y Y2 receptors in modulation of cardiac parasympathetic neurotransmission. Regul Pept. 2002;103:105–11.
114. Herring N, Lokale MN, Danson EJ, Heaton DA, Paterson DJ. Neuropeptide Y reduces acetylcholine release and vagal bradycardia via a Y2 receptor-mediated, protein kinase C-dependent pathway. J Mol Cell Cardiol. 2008;44:477–85. https://doi.org/10.1016/j.yjmcc.2007.10.001.
115. Herring N, Cranley J, Lokale MN, Li D, Shanks J, Alston EN, et al. The cardiac sympathetic co-transmitter galanin reduces acetylcholine release and vagal bradycardia: implications for neural control of cardiac excitability. J Mol Cell Cardiol. 2012;52: 667–76. https://doi.org/10.1016/j.yjmcc.2011.11.016.
116. Pongratz G, Straub RH. The sympathetic nervous response in inflammation. Arthritis Res Ther. 2014;16(6):504.
117. Malliani A, Schwartz PJ, Zanchetti A. A sympathetic reflex elicited by experimental coronary occlusion. Am J Phys. 1969;217:703–9.
118. Foreman RD, Linderoth B, Ardell JL, Barron KW, Chandler MJ, Hull SS, et al. Modulation of intrinsic cardiac neurons by spinal cord stimulation: implications for therapeutic use in angina pectoris. Cardiovasc Res. 2000;47:367–75.
119. Kingery WS. A critical review of controlled clinical trials for peripheral neuropathic pain and complex regional pain syndromes. Pain. 1997;73:123–39.
120. Ratti C, Nordio A, Resmini G, Murena L. Post-traumatic complex regional pain syndrome: clinical features and epidemiology. Clin Cases Miner Bone Metab. 2015;12:11–6. https://doi.org/10.11138/ccmbm/2015.12.3s.011.
121. De Rooij AM, Perez RS, Huygen FJ, van Eijs F, van Kleef M, Bauer MC, et al. Spontaneous onset of complex regional pain syndrome. Eur J Pain. 2010;14:510–3. https://doi.org/10.1016/j.ejpain.2009.08.007.
122. Birklein F, Dimova V. Complex regional pain syndrome-up-to-date. Pain Rep. 2017;2:e624. https://doi.org/10.1097/PR9.0000000000000624.
123. Bean DJ, Johnson MH, Kydd RR. The outcome of complex regional pain syndrome type 1: a systematic review. J Pain. 2014;15:677–90. https://doi.org/10.1016/j.jpain.2014.01.500.
124. Schwartzman RJ, Liu JE, Smullens SN, Hyslop T, Tahmoush AJ. Long-term outcome following sympathectomy for complex regional pain syndrome type 1 (RSD). J Neurol Sci. 1997;150:149–52.
125. Singh B, Moodley J, Shaik AS, Robbs JV. Sympathectomy for complex regional pain syndrome. J Vasc Surg. 2003;37:508–11. https://doi.org/10.1067/mva.2003.78.
126. Alkosha HM, Elkiran YM. Predictors of long-term outcome of thoracic sympathectomy in patients with complex regional pain syndrome type 2. World Neurosurg. 2016;92:74–82. https://doi.org/10.1016/j.wneu.2016.04.101.
127. Russo M, Georgius P, Santarelli DM. A new hypothesis for the pathophysiology of complex regional pain syndrome. Med Hypotheses. 2018;119:41–53. https://doi.org/10.1016/j.mehy.2018.07.026.
128. Kohr D, Tschernatsch M, Schmitz K, Singh P, Kaps M, Schäfer KH, et al. Autoantibodies in complex regional pain syndrome bind to a differentiation-dependent neuronal surface autoantigen. Pain. 2009;143:246–51. https://doi.org/10.1016/j.pain.2009.03.009.

129. Kohr D, Singh P, Tschernatsch M, Kaps M, Pouokam E, Diener M, et al. Autoimmunity against the beta2 adrenergic receptor and muscarinic-2 receptor in complex regional pain syndrome. Pain. 2011;152:2690–700. https://doi.org/10.1016/j.pain.2011.06.012.
130. Tékus V, Hajna Z, Borbély É, Markovics A, Bagoly T, Szolcsányi J, et al. A CRPS-IgG-transfer-trauma model reproducing inflammatory and positive sensory signs associated with complex regional pain syndrome. Pain. 2014;155:299–308. https://doi.org/10.1016/j.pain.2013.10.011.
131. Cannon WB, Rosenbleuth A. The supersensitivity of denervated structures. A law of denervation. New York: Macmillan; 1999.
132. Perl ER. Causalgia, pathological pain, and adrenergic receptors. Proc Natl Acad Sci U S A. 1999; 96:7664–7.
133. Chen SS, Zhang JM. Progress in sympathetically mediated pathological pain. J Anesth Perioper Med. 2015;2:216–25. https://doi.org/10.24015/JAPM.2015.0029.
134. Gori T, Fineschi M. Two coronary "orphan" diseases in search of clinical consideration: coronary syndromes x and y. Cardiovasc Ther. 2012;30:58–65. https://doi.org/10.1111/j.1755-5922.2010.00232.x.
135. Crea F, Lanza GA. Angina pectoris and normal coronary arteries: cardiac syndrome X. Heart. 2004;90:457–63.
136. Melikian N, De Bruyne B, Fearon WF, MacCarthy PA. The pathophysiology and clinical course of the normal coronary angina syndrome (cardiac syndrome X). Prog Cardiovasc Dis. 2008;50:294–310. https://doi.org/10.1016/j.pcad.2007.01.003.
137. Cannon RO 3rd, Quyyumi AA, Schenke WH, Fananapazir L, Tucker EE, Gaughan AM, et al. Abnormal cardiac sensitivity in patients with chest pain and normal coronary arteries. J Am Coll Cardiol. 1990;16:1359–66.
138. Beltrame JF. Advances in understanding the mechanisms of angina pectoris in cardiac syndrome X. Eur Heart J. 2005;26:946–8. https://doi.org/10.1093/eurheartj/ehi242.
139. Turiel M, Galassi AR, Glazier JJ, Kaski JC, Maseri A. Pain threshold and tolerance in women with syndrome X and women with stable angina pectoris. Am J Cardiol. 1987;60:503–7.
140. Falcone C, Sconocchia R, Guasti L, Codega S, Montemartini C, Specchia G. Dental pain threshold and angina pectoris in patients with coronary artery disease. J Am Coll Cardiol. 1988;12(2):348–52.
141. Legerqvist B, Sylven C, Waldenstrom A. Lower threshold for adenosine-induced chest pain in patients with angina and normal coronary angiograms. Br Heart J. 1992;68:282–5.
142. Rosen SD, Paulesu E, Wise RJ, Camici PG. Central neural contribution to the perception of chest pain in cardiac syndrome X. Heart. 2002;87:513–9.
143. Valeriani M, Sestito A, Le Pera D, De Armas L, Infusino F, Maiese T, et al. Abnormal cortical pain processing in patients with cardiac syndrome X. Eur Heart J. 2005;26:975–82. https://doi.org/10.1093/eurheartj/ehi229.
144. Agrawal S, Mehta PK, Bairey Merz CN. Cardiac Syndrome X: update 2014. Cardiol Clin. 2014;32:463–78. https://doi.org/10.1016/j.ccl.2014.04.006.
145. Madaric J, Bartunek J, Verhamme K, Penicka M, Van Schuerbeeck E, Nellens P, et al. Hyperdynamic myocardial response to beta-adrenergic stimulation in patients with chest pain and normal coronary arteries. J Am Coll Cardiol. 2005;46:1270–5. https://doi.org/10.1016/j.jacc.2005.06.052.
146. Rosano GMC, Tousoulis D, McFadden E, Clarke J, Davies GJ, Kaski JC. Effects of neuropeptideY on coronary artery vasomotion in patients with microvascular angina. Int J Cardiol. 2017;238:123–7. https://doi.org/10.1016/j.ijcard.2017.03.024.
147. Assali AR, Jabara Z, Shafer Z, Solodky A, Herz I, Sclarovsky E, et al. Insulin resistance is increased by transdermal estrogen therapy in postmenopausal women with cardiac syndrome X. Cardiology. 2001;95(1):31–4. https://doi.org/10.1159/000047340.
148. Chen YX, Luo NS, Lin YQ, Yuan WL, Xie SL, Nie RQ, Wang JF. Selective estrogen receptor modulators promising for cardiac syndrome X. J Postgrad Med. 2010;56(4):328–31. https://doi.org/10.4103/0022-3859.70936.
149. Long M, Huang Z, Zhuang X, Huang Z, Guo Y, Liao X, et al. Association of inflammation and endothelial dysfunction with coronary microvascular resistance in patients with cardiac syndrome X. Arq Bras Cardiol. 2017;109(5):397–403. https://doi.org/10.5935/abc.20170149.
150. Yue Z, Xie J, Yu AS, Stock J, Du J, Yue L. Role of TRP channels in the cardiovascular system. Am J Physiol Heart Circ Physiol. 2014;308(3):H157–82. https://doi.org/10.1152/ajpheart.00457.2014.
151. Davidson EP, Coppey LJ, Yorek MA. Activity and expression of the vanilloid receptor 1 (TRPV1) is altered by long-term diabetes in epineurial arterioles of the rat sciatic nerve. Diabetes Metab Res Rev. 2006;22:211–9. https://doi.org/10.1002/dmrr.599.
152. Shipp N, Thanigaimani S, Lau D, Brooks A, Kuklik P, Baumert M. TRPV1 down-regulation in syndrome X: its role in AF susceptibility. Heart Lung Circ. 2011;20S:S1–S155. https://doi.org/10.1016/j.hlc.2011.05.144.. Abstracts S57
153. Bratz IN, Dick GM, Tune JD, Edwards JM, Neeb ZP, Dincer UD, et al. Impaired capsaicin-induced relaxation of coronary arteries in a porcine model of the metabolic syndrome. Am J Physiol Heart Circ Physiol. 2008;294:H2489–96. https://doi.org/10.1152/ajpheart.01191.2007.
154. Guarini G, Ohanyan VA, Kmetz JG, DelloStritto DJ, Thoppil RJ, Thodeti CK, et al. Disruption of TRPV1-

mediated coupling of coronary blood flow to cardiac metabolism in diabetic mice: role of nitric oxide and BK channels. Am J Physiol Heart Circ Physiol. 2012;303(2):H216–23. https://doi.org/10.1152/ajpheart.00011.
155. Zhao JF, Ching LC, Kou YR, Lin SJ, Wei J, Shyue SK, et al. Activation of TRPV1 prevents OxLDL-induced lipid accumulation and TNF-α-induced inflammation in macrophages: role of liver X receptor α. Mediat Inflamm. 2013;925171. https://doi.org/10.1155/2013/925171.
156. Huang W, Rubinstein J, Prieto AR, Thang LV, Wang DH. Transient receptor potential vanilloid gene deletion exacerbates inflammation and atypical cardiac remodeling after myocardial infarction. Hypertension. 2009;53:243–50. https://doi.org/10.1161/HYPERTENSIONAHA.108.118349.
157. Wang HJ, Wang W, Cornish KG, Rozanski GJ, Zucker IH. Cardiac sympathetic afferent denervation attenuates cardiac remodeling and improves cardiovascular dysfunction in rats with heart failure. Hypertension. 2014;64:745–55. https://doi.org/10.1161/HYPERTENSIONAHA.114.03699.
158. Wang W, Schultz HD, Ma R. Cardiac sympathetic afferent sensitivity is enhanced in heart failure. Am J Physiol Heart Circ Physiol. 1999;277:H812–7.
159. Yoshie K, Rajendran PS, Massoud L, Kwon O, Tadimeti V, Salavatian S, et al. Cardiac vanilloid receptor-1 afferent depletion enhances stellate ganglion neuronal activity and efferent sympathetic response to cardiac stress. Am J Physiol Heart Circ Physiol. 2018;314:H954–66. https://doi.org/10.1152/ajpheart.00593.2017.
160. Leriche R, Fontaine R. L'anesthésie isolée du ganglion étoile. Sa technique, ses indications, ses résultats. Presse Med. 1934;42:849–50.
161. Gofeld M, Bhatia A, Abbas S, Ganapathy S, Johnson M. Development and validation of a new technique for ultrasound-guided stellate ganglion block. Reg Anesth Pain Med. 2009;34:475–9. https://doi.org/10.1097/AAP.0b013e3181b494de.
162. Yucel I, Demiraran Y, Ozturan K, Degirmenci E. Complex regional pain syndrome type I: efficacy of stellate ganglion blockade. J Orthop Traumatol. 2009;10:179–83. https://doi.org/10.1007/s10195-009-0071-5.
163. Hashmonai M, Kopelman D. History of sympathetic surgery. Clin Auton Res. 2003;13:I6–9. https://doi.org/10.1007/s10286-003-1103-5.
164. Hughes J. Endothoracic sympathectomy. Proc R Soc Med. 1942;35:585–6.
165. De Andrade Filho LO, Kuzniec S, Wolosker N, Yazbek G, Kauffman P, Milanez de Campos JR. Technical difficulties and complications of sympathectomy in the treatment of hyperhidrosis: an analysis of 1731 cases. Ann Vasc Surg. 2013;27:447–53. https://doi.org/10.1016/j.avsg.2012.05.026.
166. Lin TS, Kuo SJ, Chou MC. Uniportal endoscopic thoracic sympathectomy for treatment of palmar and axillary hyperhidrosis: analysis of 2000 cases. Neurosurgery. 2002;51(5 Suppl):S84–7.
167. Vannucci F, Araújo JA. Thoracic sympathectomy for hyperhidrosis: from surgical indications to clinical results. J Thorac Dis. 2017;9(Suppl 3):S178–92. https://doi.org/10.21037/jtd.2017.04.04.
168. Dai ZJ, Tu YR, Li X, et al. Expression and significance of choline acetyltransferase and vasoactive intestinal peptide in thoracic sympathetic ganglion of patients with palmar hyperhidrosis. Chin J Exp Surg. 2007;24:1017–8.
169. Chen JP, Chen RF, Peng AJ, Xu CH, Li GY. Is compensatory hyperhidrosis after thoracic sympathicotomy in palmar hyperhidrosis patients related to the excitability of thoracic sympathetic ganglions? J Thorac Dis. 2017;9(9):3069–75. https://doi.org/10.21037/jtd.2017.08.100.
170. Noppen M, Dendale P, Hagers Y, Herregodts P, Vincken W, D'Haens J. Changes in cardiocirculatory autonomic function after thoracoscopic upper dorsal sympathicolysis for essential hyperhidrosis. J Auton Nerv Syst. 1996;60(3):115–20.
171. Kardos A, Taylor DJ, Thompson C, Styles P, Hands L, Collin J, et al. Sympathetic denervation of the upper limb improves forearm exercise performance and skeletal muscle bioenergetics. Circulation. 2000;101(23):2716–20.
172. Jonnesco T. Traitement chirurgical de l'angine de poitrine par la résection du sympathique cervico-thoracique [French]. Presse Méd. 1921;20:221–30.
173. Leriche R, Fontaine R. Rôle du ganglion étoile gauche dans le déterminisme de la crise de l'angine de poitrine [French]. C R Acad Sci. 1929;188:279–80.
174. Lindgren I, Olivecrona H. Surgical treatment of angina pectoris. J Neurosurg. 1947;4:19–39.
175. Burnett CF, Evans JA. Follow-up report on resection of the anginal pathway in thirty-three patients. JAMA. 1956;162:709–12.
176. Cox WV. Influence of stellate ganglion block on angina pectoris and the post-exercise ECG. Am J Med. 1956;252:289–95.
177. Schwartz PJ. The rationale and the role of left stellectomy for the prevention of malignant arrhythmias. Ann N Y Acad Sci. 1984;427:199–221.
178. Moss AJ, McDonald J. Unilateral cervicothoracic sympathetic ganglionectomy for the treatment of long QT interval syndrome. N Engl J Med. 1971;285:903–4.
179. Schwartz PJ, Malliani A. Electrical alternation of the T wave: clinical and experimental evidence of its relationship with the sympathetic nervous system and with the long QT syndrome. Am Heart J. 1975;89:45–50.
180. Schwartz PJ, Locati EH, Moss AJ, Crampton RS, Trazzi R, Ruberti U. Left cardiac sympathetic denervation in the therapy of congenital long QT syndrome: a worldwide report. Circulation. 1991;84:503–11.

181. Schwartz PJ, Priori SG, Cerrone M, Spazzolini C, Odero A, Napolitano C, et al. Left cardiac sympathetic denervation in the management of high-risk patients affected by the long QT syndrome. Circulation. 2004;109:1826–33. https://doi.org/10.1161/01.CIR.0000125523.14403.1E.
182. Schwartz PJ, Stone HL, Brown AM. Effects of unilateral stellate ganglion blockade on the arrhythmias associated with coronary occlusion. Am Heart J. 1976;92:589–99.
183. Schwartz PJ, Billman GE, Stone HL. Autonomic mechanisms in ventricular fibrillation induced by myocardial ischemia during exercise in dogs with healed myocardial infarction: an experimental preparation for sudden cardiac death. Circulation. 1984;69:790–800.
184. Schwartz PJ. Sympathetic imbalance and cardiac arrhythmias. In: Randall WC, editor. Nervous control of cardiovascular function. New York: Oxford University Press; 1984. p. 225–52.. Ch. 10.
185. Schwartz PJ, Snebold NG, Brown AM. Effects of unilateral cardiac sympathetic denervation on the ventricular fibrillation threshold. Am J Cardiol. 1976;37:1034–40.
186. De Ferrari GM, Dusi V, Spazzolini C, Bos JM, Abrams DJ, Berul CI, et al. Clinical management of catecholaminergic polymorphic ventricular tachycardia: the role of left cardiac sympathetic denervation. Circulation. 2015;131:2185–93. https://doi.org/10.1161/CIRCULATIONAHA.115.015731.
187. Odero A, Bozzani A, De Ferrari GM, Schwartz PJ. Left cardiac sympathetic denervation for the prevention of life-threatening arrhythmias: the surgical supraclavicular approach to cervicothoracic sympathectomy. Heart Rhythm. 2010;7(8):1161–5. https://doi.org/10.1016/j.hrthm.2010.03.046.
188. Coleman MA, Bos MJ, Johnson JN, Owen HJ, Deschamps C, Moir C, et al. Videoscopic left cardiac sympathetic denervation for patients with recurrent ventricular fibrillation/malignant ventricular arrhythmia syndromes besides congenital Long-QT syndrome. Circ Arrhythm Electrophysiol. 2012;5:782–8. https://doi.org/10.1161/CIRCEP.112.971754.
189. Vaseghi M, Gima J, Kanaan C, Ajijola OA, Marmureanu A, Mahajan A, et al. Cardiac sympathetic denervation in patients with refractory ventricular arrhythmias or electrical storm: intermediate and long-term follow-up. Heart Rhythm. 2014;11:360–6. https://doi.org/10.1016/j.hrthm.2013.11.028.
190. Vaseghi M, Barwad P, Malavassi Corrales FJ, Tandri H, Mathuria N, et al. Cardiac sympathetic denervation for refractory ventricular arrhythmias. J Am Coll Cardiol. 2017;69:3070–80. https://doi.org/10.1016/j.jacc.2017.04.035.
191. Ajijola OA, Wisco JJ, Lambert HW, Mahajan A, Stark E, Fishbein MC, et al. Extracardiac neural remodeling in humans with cardiomyopathy. Circ Arrhythm Electrophysiol. 2012;5:1010–116. https://doi.org/10.1161/CIRCEP.112.972836.
192. Ajijola OA, Hoover DB, Simerly TM, Brown TC, Yanagawa J, Biniwale RM, et al. Inflammation, oxidative stress, and glial cell activation characterize stellate ganglia from humans with electrical storm. JCI Insight. 2017;2:e94715. https://doi.org/10.1172/jci.insight.94715.
193. Nguyen BL, Li H, Fishbein MC, Lin SF, Gaudio C, Chen PS, et al. Acute myocardial infarction induces bilateral stellate ganglia neural re modeling in rabbits. Cardiovasc Pathol. 2012;21:143–8. https://doi.org/10.1016/j.carpath.2011.08.001.
194. Ajijola OA, Yagishita D, Reddy NK, Yamakawa K, Vaseghi M, Downs AM, et al. Remodeling of stellate ganglion neurons after spatially targeted myocardial infarction: neuropeptide and morphologic changes. Heart Rhythm. 2015;12:1027–35. https://doi.org/10.1016/j.hrthm.2015.01.045.
195. Rizzo S, Basso C, Troost D, Aronica E, Frigo AC, Driessen AH, et al. T-cell-mediated inflammatory activity in the stellate ganglia of patients with ion-channel disease and severe ventricular arrhythmias. Circ Arrhythm Electrophysiol. 2014;7(2):224–9. https://doi.org/10.1161/CIRCEP.113.001184.
196. Atallah J, Fynn-Thompson F, Cecchin F, Di Bardino DJ, Walsh EP, Berul CI. Video-assisted thoracoscopic cardiac denervation: potential novel therapeuticoption for children with intractable ventricular arrhythmias. Ann Thorac Surg. 2008;86(5):1620–5. https://doi.org/10.1016/j.athoracsur.2008.07.006.
197. Methangkool E, Chua JH, Gopinath A, Shivkumar K, Mahajan A. Anesthetic considerations for thoracoscopic sympathetic ganglionectomy to treatventricular tachycardia storm: a single-center experience. J Cardiothorac Vasc Anesth. 2014;28(1):69–75. https://doi.org/10.1053/j.jvca.2013.08.019.
198. Gonzalez-Rivas D. Uniportal thoracoscopic surgery: from medical thoracoscopy to non-intubated uniportal video-assisted major pulmonary resections. Ann Cardiothorac Surg. 2016;5(2):85–91. https://doi.org/10.21037/acs.2016.03.07.
199. Homma T, Doki Y, Yamamoto Y, Ojima T, Shimada Y, Kitamura N, et al. Risk factors of neuropathic pain after thoracic surgery. J Thorac Dis. 2018;10(5):2898–907. https://doi.org/10.21037/jtd.2018.05.25.
200. Butler S, Jonzon B, Branting-Ekenbäck C, Wadell C, Farahmand B. Predictors of severe pain in a cohort of 5271 individuals with self-reported neuropathic pain. Pain. 2013;154:141–6. https://doi.org/10.1016/j.pain.2012.10.001.
201. Guastella V, Mick G, Soriano C, Vallet L, Escande G, Dubray C, et al. A prospective study of neuropathic pain induced by thoracotomy: incidence, clinical description, and diagnosis. Pain. 2011;152(1):74–81. https://doi.org/10.1016/j.pain.2010.09.004.
202. Litwin MS. Post sympathectomy neuralgia. Arch Surg. 1962;84(5):591–5. https://doi.org/10.1001/archsurg.1962.01300230107022.

203. Antiel RM, Bos JM, Joyce DD, Owen HJ, Roskos PL, Moir C, et al. Quality of life after videoscopic left cardiac sympathetic denervation in patients with potentially life-threatening cardiac channelopathies/cardiomyopathies. Heart Rhythm. 2016;13:62–9. https://doi.org/10.1016/j.hrthm.2015.09.001.
204. Schwartz PJ, De Ferrari GM, Pugliese L. Cardiac sympathetic denervation 100 years later: Jonnesco would have never believed it. Int J Cardiol. 2017;237:25–8. https://doi.org/10.1016/j.ijcard.2017.03.020.
205. Dusi V, Pugliese L, Castelletti S, Dagradi F, Crotti L, Mori A, et al. Cardiac sympathetic denervation: evolving technique, expanding indications. Eur Heart J. 2018;39(Suppl):4748.
206. Keegan JJ, Garrett FD. The segmental distribution of the cutaneous nerves in the limbs of man. Anat Rec. 1948;102:409–37.
207. O'Halloran KD, Perl ER. Effects of partial nerve injury on the responses of C-fiber polymodal nociceptors to adrenergic agonists. Brain Res. 1997;759:233–40.
208. Sato J, Perl ER. Adrenergic excitation of cutaneous pain receptors induced by peripheral nerve injury. Science. 1991;251:1608–10.
209. Bossut DF, Perl ER. Effects of nerve injury on sympathetic excitation of a delta mechanical nociceptors. J Neurophysiol. 1995;73:1721–3.
210. Bossut DF, Shea V, Perl ER. Sympathectomy induces adrenergic excitability of cutaneous C-fiber nociceptors. J Neurophysiol. 1996;75:514–7. https://doi.org/10.1152/jn.1996.75.1.514.
211. La Rovere MT, Bigger JT, Marcus FI, Mortara A, Schwartz PJ. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) investigators. Lancet. 1998;351:478–84. https://doi.org/10.1016/S0140-6736(97)11144-8.
212. Cohn JN, Levine TB, Olivari MT, Garberg V, Lura D, Francis GS, et al. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. N Engl J Med. 1984;311:819–23. https://doi.org/10.1056/NEJM198409273111303.
213. Schwartz PJ, Motolese M, Pollavini G, Lotto A, Ruberti U, Trazzi R, et al. Prevention of sudden cardiac death after a first myocardial infarction by pharmacologic or surgical antiadrenergic interventions. J Cardiovasc Electrophysiol. 1992;3:2–6.
214. Dusi V, De Ferrari GM, Pugliese L, Schwartz PJ. Cardiac Sympathetic Denervation in Channelopathies. Front Cardiovasc Med. 2019;26;6:27. https://doi.org/10.3389/fcvm.2019.00027.
215. Dusi V, Sorg JM, Gornbein J, Gima J, Yanagawa J, Lee JM, et al. Prognostic impact of atrial rhythm and dimension in patients with structural heart disease undergoing cardiac sympathetic denervation for ventricular arrhythmias. Heart Rhythm 2019. https://doi.org/10.1016/j.hrthm.2019.12.007.
216. Kaski JC. Pathophysiology and management of patients with chest pain and normal coronary arteriograms (Cardiac Syndrome X). Circulation. 2004;109:568-72. https://doi.org/10.1161/01.CIR.0000116601.58103.62.

8 The Role of Emotions, Stress, and Mental State in Inflammatory Processes Perturbing Brain-Heart Dialogue

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*,
https://doi.org/10.1007/978-3-030-28008-6_11

Abstract

Emotions and stress have a great impact on mental states and well-being, and the mind-body problem has historically been conceived as a continuum from dualism to physicalism. Stress and emotions are undoubtedly defined by the physical underpinnings but cannot be reduced to them. Mental states, such as beliefs, goals, or values, play also an essential role. Moreover, despite stressful events are constitutive part of our everyday, when personal resources are not enough to deal with the situation, the physical homeostasis can be seriously threatened. An important point is to explore possible pathways connecting entities like emotion and stress with the physical body, and neuroinflammation seems to be an important candidate.

This chapter aims to address the relationship between stress, emotions, and mental states in those inflammatory processes affecting cardiovascular system. In particular, the interaction of sympathetic nervous system and cholinergic anti-inflammatory pathway in modulate inflammation during stressful events or mental disorders will be described.

Keywords

Emotions · Stress · Mental state · Neuroinflammation · Psychoneuroimmunity

Introduction

The fact that the brain and heart are connected has begun to be increasingly understood in the biomedical scientific community in the last years [1]. Nevertheless, it cannot be stated the same regarding the complex emergence of mental states related to the undoubted interaction of diverse physiological structures and processes. Indeed, one of the most challenging and long-lasting metaphysical questions revolves around the connection between mind and body. Simply put, the mind-body problem has historically been conceived as a continuum from dualism to physicalism. That is, the existence of mind and brain as independent substances in the case of dualistic stances or matter and physical properties as the only real substance in the case of physicalism. The former position is wholly implausible from a scientific perspective. The latter neglects the existence of mental states. A number of standpoints in between the two extremes tried to explain how body and mind are connected giving entity to the both aspects [2].

This chapter aims to address the relationship between stress, emotions, and mental states in inflammatory processes. The reader could then rightfully ask why to begin with a paragraph focused on the core aspect of philosophy of mind. It is not our goal to unravel such an intricate issue but we do need to start from claiming that if emotions, stress, and mental states are considered, a non-reductive position should be adopted in order to concede them an ontological status as causal entities. What specific stance to take is out of the scope of this chapter. However, first and foremost, it is essential to incorporate an embodied perspective in order to grasp the idea that the whole body contributes to what we conceive as mental states. Besides, despite the existing dispute regarding the ontological status of psychological properties (with solid arguments for and against), we assume that mental states are not either reducible to physical properties. In this sense, stress and emotions are undoubtedly defined by the physical underpinnings but cannot be reduced to them. Mental states, such as beliefs, goals, or values, play also an essential role. This does not necessarily mean to adopt a

constructivist perspective but rather the necessity to take into account the different positions in order to adopt a perspective as integrated as possible.

Emotions

There are different positions regarding the ontological status of emotions, ranging from constructivist positions to innate perspectives. There are three main conceptualizations throughout the history regarding emotions: one that sees emotions primarily as experiences, a second one as evaluations, and a third one as motivations. It could be possible to say that one is the correct position, and all have their strong arguments in favor and against.

Among the different positions, there are perspectives that hold the existence of emotions that are innate or basic and thus transversal to all the humans regardless the cultural specificities. In the opposite pole, there are positions that claim the cultural determination of emotions. Likewise, there is a long-standing controversy whether they are better grasped as discrete categories (e.g., sadness, fear, surprise) or as dimensions (principally in a circumplex model with arousal and valence as axes) [3].

However, there are some undisputable points that have reached a consensus among the different stances. For instance, it is widely agreed that emotion episodes entail certain physiological underpinning, evaluations, expressions, subjective experience, and finally mental processes and behavioral dispositions. Besides, it is also fully shared the fact that emotions have intentionality and variability.

In between, there are more or less integrative perspectives, such as the one stated by Damasio who describes that an emotion is the set of changes produced in the body and connected to certain mental content, process that in turn trigger automatic responses in the body [4]. The process by which the person takes into account different options in a certain scenario makes him/her evoke past emotions that were experienced in similar contexts. These are the memories that elicit the so-called somatic markers and help the person decide in an intuitive way whether a situation is positive or negative, for example, fearless or fearful.

Additionally, emotions constitute the most embodied of all the existing mental states. Perceiving and thinking emotions is defined by a set of specified corporal instantiations, which are intrinsic parts of the phenomenon [5]. In this vein, mental states constitute an essential element in the information processing that we deploy (intra- and interpersonally) and they are inseparable from the physiological processes.

Stress

There are very divergent pathways that we take in order to appraise certain stimuli depending on the contextual factors and our perception in regards to the resources that we have and we believe we have to cope with the demands. Whether we perceive control or not is determinant to elicit determinant physiological responses, such as stress. The key aspect is related to the situations in which stress appears. In a generic way, it is possible to say that it is commonly a phenomenon that occurs when a person evaluates that the contextual demands exceed the resources that she or he has to deal with them [6].

From the beginning of our days and throughout our entire lives, we are faced to obstacles, hassles, challenges, and problems to be faced. Hence, stressful events are constitutive part of our everyday, and despite the fact that there are some objective factors (e.g., death of a love one or moving from one country to a new one), the subjective factors are determinant to explain the appearance of a stressful event. Indeed, regarding the objective nature of stress is namely related to the stressors; while the subjective aspect has to do with the appraisal that a person does judging a certain situation and the resources that she or he has to cope with it. As a result, a stressful situation can be understood as those situations in which an individual perceives the own resources are not enough to deal with the situation [7]. More eloquently, Hans Selye already in 1956 defined that stress as anything that seriously threatens homeostasis [8].

The classical perspective of homeostasis, originally stated by Cannon [9], consists in the ongoing maintenance and defense of vital physiological processes. That is, in order to survive, a system needs to be in a certain balance. However, nowadays, it is widely agreed that the stability is achieved through constant change (allostasis).

Extensive research has focused on the mechanisms that people implement in order to alleviate the physical and cognitive burden associated with that perceived stress. Coping styles, stress management techniques, self-regulation or emotion regulation techniques are different traditions of research but in all cases refer to the way people implement certain behavioral, cognitive, or emotional strategies to maintain allostatic load [10]. In other words, every living organism needs to vary among plasticity and stability in order to survive. Human beings are not the exception to the rule and the complex system that conforms every single subject redound in the necessity of reaching a constant level of regulation that permits to the individuals to pursuit their goals.

As stated by Logan and Barksdale [11]:

> Frequent or chronic challenges produce dysregulation of several major physiological systems, including the hypothalamic–pituitary–adrenal (HPA) axis, the sympathetic nervous system and the immune system.
>
> Repeated and cumulative allostasis over time causes allostatic load, and this overexpose to neural, endocrine, and immune stress mediators results in various organ diseases. For example, blood pressure (one allostasis biomarker) is continuously rising and falling during the day according to physical and emotional status [12]. However, repeated elevated blood pressure (allostatic load) may increase atherosclerotic plaques and stiffness of large arteries leading to greater risk for cardiovascular disease.

Although the relationship between stress and emotions is undisputable, the distinction between them remains blurry. Stressful events unequivocally elicit emotional responses, which in turn may constitute a way to be prepared to cope with the difficulties that the situation has presented. This may be the case with both negative and positive emotions.

Our appraisal may be biased or not, but in case we constantly are under stressful events, there will be a certain moment in which the body will not have the capacity anymore to support the contextual demands, and this is the moment in which an overload can be the reason of the appearance of chronic stress or mental disorders, such as emotional disorders. Indeed, the same responses that may be adaptive at a certain extent, if deployed chronically, may become highly detrimental in terms of health consequences. In particular, there can be a suppression of different vital systems. Research has largely indicated that exposure to stressful situations in life is linked to the appearance and maintenance of a vast array of clinical conditions throughout the whole life span. Illustrative examples are posttraumatic stress disorder [13] or major depression [14].

One process that has shown to play an instrumental role in the moderation and mediation between stress and health is emotion regulation (ER). Emotion generation and emotion regulation are essential processes that all persons deploy. All emotions are useful if they are deployed at the right moment and with the right intensity and duration. The capacity to implicitly or explicitly manipulate emotional states plays an instrumental role to create adaptive responses to cope with stressful situations. When the person does not have developed skills and constantly deploy maladaptive strategies to regulate the emotion, then the individual elicits negative psychological and physiological health outcomes (e.g., depression and stress-induced cardiomyopathy) [15–18].

This process has an undeniable biological process. Experienced stressful events trigger the activation of the nervous system, both the central and autonomous system. With regard to the peripheral activity, it was Walter Cannon at the dawn of the twentieth century who introduced the concept of fight-or-flight response as the behavioral consequence of experiencing acute stress. Indeed, there are pure biological definitions of stress, such as the one that states that it is any stimulus that derives in the activation of the HPA system, releasing ACTH and adrenal glucocorticoids as well as the activation of the SAM system, releasing adrenaline and noradrenaline [19].

It is precisely the parasympathetic activity the process that better explains the relationship between mind, brain, and heart. The respiratory sinus arrhythmia and the high frequency of heart rate variability are the most reliable indexes of control vagal control, which in turn constitutes the best available correlate of emotion regulation. The vagal regulation of the heart is fostered through the myelinated pathways that are originated in the nucleus ambiguous. The vagal tone is considered as a break that is inhibited or disinhibited depending on the contextual demands [20]. If the environment is perceived as a threat, the sympathetic system is activated and accordingly the vagal brake inhibited. On the contrary, if the context is considered as safe, there takes place a process called visceral homeostasis that enables restoration through a slow activity of the heart, an inhibition of the previously mentioned fight-or-flight response as well as reducing the production of the HPA axis. In other words, vagal withdrawal constitutes a fundamental process when stress responses are elicited [21].

The neurovisceral theory is another principal systematic explanation of how self-regulation processes work. In words of Thayer and Lane [22] this

> theory describes a common reciprocal inhibitory neural circuit associated with self-regulation processes in which subcortical structures underpinning defensive behavior (e.g. the amygdala) are under tonic inhibitory control of prefrontal cortical regions. In case of threat or stress, the prefrontal cortex becomes hypoactive, leading to parasympathetic withdrawal and disinhibition of the sympathoexcitatory circuits that activate the organism to respond to the threatening event.

The most relevant aspect of these two theories is how they solidly integrate brain and heart and in turn how these systems affect and are affected by emotional and stressful states. Indeed, there is a long-standing tradition connecting cardiovascular and emotional states. In particular, mental stress and emotional arousal have shown to be potential triggers of acute myocardial infarction among other cardiac problems [23, 24].

Although the multifaceted characterization of emotions and stress, when it comes to find markers to distinguish adaptive from maladaptive processes, the parasympathetic system, in particular the cardiac activity, arises as a key process. In particular, the cardiac vagal control (CVC) constitutes the most reliable indicator of the efficiency of the parasympathetic activity [20, 22].

From the existing indexes of CVC, certain indexes of heart rate variability (HRV), in particular the high frequency (HRV-HF) of the spectral analysis, has gathered ample evidence as the most reliable one. Specifically, its combination with the respiratory sinus arrhythmia (RSA) has been suggested as the best indicators of CVC and therefore is considered transdiagnostic markers of psychopathology as well as cardiovascular diseases [25–27].

The role of RSA and HF-HRV as peripheral markers of parasympathetic regulation is primarily supported by polyvagal and neurovisceral integration theories. In particular, the rationale is that high resting RSA or HRV-HF amplitude as well as a high withdrawal during stressors and recovery after the stressor represents a more adaptive response to any contextual demand. On the contrary, low resting RSA or HRV-HF and a reduced withdrawal during a stressful situation is associated with maladaptive responses to situational challenges. In this vein, it is consistent to grasp why literature has consistently shown that people with mental disorders like depression or anxiety disorders present particular maladaptive patterns of RSA and HRV-HF reactivity [28–30].

HRV-HF both at the reactivity and resting state has shown to be regulated by cortical activity and to impact on and be impacted by mental states. In this sense, it is difficult to ascertain which, if there is some, structure that is at the core of the final observable behavior. The link is principally defined in the sense that brain activity is fed by oxygen that naturally is transported in the blood. In this sense, all changes in blood affect the brain activity and in MRI this can be seen in the oscillations of blood oxygen level dependent (BOLD). High values of HRV-HF cannot be explained just by a simple random variability but as a consequence of the heart activity in response to oscillatory signals, specially blood pressure feedback or breathing. When the breathing and baroreflex

feedback loop can be synchronized at the same frequency, resonance is generated [1]. In turn, this synchronization impels high amplitude physiological oscillation activity in the brain.

Respiratory Sinus Arrhythmia (RSA) as a Predictor

Apart from constituting a solid indicator of physiological regulation, RSA has gathered mounting evidence in regards to the capability of RSA functioning in the prediction of different psychopathological conditions, principally in depression and its trajectory [31–34]. RSA has been even founded to be important as a predictor of outcome in different treatments, like psychotherapy for social anxiety disorder [35] or panic disorder with agoraphobia [36]. For depression, the emerging literature suggests that RSA could constitute an endophenotype in this clinical condition [37] and the fact that RSA predicts the onset of the disease is one of the criteria.

Stress and Emotion Regulation

Given that avoiding stressful situation is not possible in life, the way individuals can cope with affective responses that those situations elicit is fundamental to explain the appearance of maladaptive responses which in turn can lead to the development of mental disorders and physical diseases [38]. The whole process by which the individuals aim to influence the emotional reactions involved both after stressful and non-stressful events is denominated emotion regulation [39]. Stress and emotion regulation are related due to a physiological underpinning. The activation of the HPA previously described is also found to be important in emotion regulation, in particular for children as a predictor in the cortisol response.

Different brain regions have consistently been found connected between stress and emotion regulation, such as the prefrontal cortex, the anterior cingulate cortex, or the amygdala. There are some brain regions that are shared by emotion regulation and HRV, reason for which both processes have been linked in an intrinsic way. In particular, HRV presents activation in the regional cerebral blood flow in ventromedial prefrontal cortex and the amygdala, regions that are also consistently identified with emotion regulation in ample evidence [1, 40].

Stress and Perseverative Thinking

Perseverative thinking, including rumination and worry, is considered a transdiagnostic factor for a wide range of psychopathological conditions, such as depression and anxiety [41]. There is a large body of evidence showing that the difference between more adaptive and less adaptive people is not principally determined by the number of stressful events but rather due to the personal disposition to processes like suppression, worry, and rumination. In this sense, individuals who usually deploy maladaptive ER strategies are more prone to present stronger affective responses and a blunt reaction in the cortisol system, all of which is considered to depict the vulnerability to health problems [42].

It is precisely perseverative thinking one of the processes that has gathered more evidence to explain the heart-brain interaction. The most relevant concept is that perseverative thinking represents a form of cognitive inflexibility, which is represented both in the body and the brain. While the bodily component is primarily constituted by the rigidity of the autonomic activity which has shown specific patterns of heart rate variability [43], the brain is principally defined by the prefrontal-amygdala functional activity [44]. Indeed, there is a specific rumination form identified that is called stress-reactive rumination. This kind of rumination is principally defined by the connection of the ruminative thinking with a specific stressor [45].

There is also evidence showing between specific markers of stress like cortisol and rumination [46–48]. Specifically, a repetitive thinking over stressful events is associated with increased levels of cortisol and activation of the cardiovascular system.

Stress and Cognitive Reappraisal

Reappraisal is one of the most researched strategies among the emotion regulation literature. It is defined as changing how think about a situation with the aim of exerting influence on the way we feel. Every time an individual reaches to manage a particular emotional episode through the reconfiguration of the environmental conditions, both changing the perspective or the interpretation of the events, it is called cognitive reappraisal [49].

The relationship between reappraisal and stress has been shown through different studies, arising important findings such as the fact that reappraisal is associated with heightened neuroendocrine reactivity to acute stress, despite the fact that in the long run (such as reduction of negative affect), it is suggested as a more efficacious emotion regulation strategy [50].

Interventions in Emotion Regulation to Target Chronic Stress

Taken together, all the previous research largely indicates the importance of intervening at a psychological and psychophysiological level in an integrated way. In the next section, an overview of some of the available evidence-based treatments that there exist to increase the levels of emotion regulation in clinical and nonclinical populations will be presented.

Emotion regulation training/stress management are quite similar approaches in which it is sought that the person increases the abilities, capacities, and disposition to cope with emotional processes and stressful situations. There are specific trainings with the aim of creating more flexible patterns regarding these strategies and all of them are comprised under the family of psychotherapies.

Likewise, as previously described, there are physiological underpinnings in the process of responding in a maladaptive way to stressors, principally certain brain regions as well as the cardiac vagal control. Biofeedback training both on the neural parts involved in the inflexibility of the vagal control as well as RSA and HF-HRV are effective, improving the indexes of emotion regulation and thus improving also the clinical condition of a range of different mental disorders [51].

Biofeedback

Biofeedback is a well-known technique allowing an individual to use own psychophysiological signals to be visualized in order to change them indirectly trying to manipulate their visual expression and thus learning a set of implicit techniques to manipulate own internal states.

Numerous studies have yielded evidence that biofeedback can be an important treatment for a wide range of clinical conditions, and although scant research has particularly focused on emotion regulation, it is consistent to assume that an enhancement in emotion regulation constitutes a mechanism of change that fosters the clinical change. This is consistently from a theoretical: HRV biofeedback constitutes a way of enhancing emotion regulation due to the possibility, as previously stated, of synchronizing the baroreflex and respiration cycle.

Heart Rate Variability Biofeedback

Heart rate variability (HRV) biofeedback is supposed to work on respiration and a specific technique to change indirectly the variability in heart rate for improving emotional regulation and other psychological processes starting from the physiological correlates.

Heart rate variability entails a chaotic structure with superimposed oscillation frequencies, which do not follow a linear relation between each other, known as negative feedback loops.

There is meta-analytic evidence that biofeedback works for anxiety and stress-related disorders [52].

Psychotherapy

Psychotherapy has emerged in the twentieth century as a scientific tool in order to help people dealing with their behavior problems, their severe subjective discomfort, their experiential disorganization, or their interpersonal problems, among the many core targets. As a consequence of these

enumerated issues, and given a complex interaction with genetic and environmental factors, different symptoms may arise. When these symptoms are organized in certain ways, specific identified syndromes or what has been proposed as mental disorders may emerge [54].

Initially rooted in a medical tradition, medicine was then the main scientific field from which psychotherapeutic practice was enriched. Freud, in fact, was a neurologist who develop what he denominated *talking cure*, and psychiatrists were for many years the authorized professionals to deliver psychotherapy. So, the psychoanalytical tradition primarily comes from a medical origin.

Inflammatory Reactions Associated with Stress, Mental State, and Emotions-Possible Role in Cardiovascular Disease

Clinical Clues

In an interesting work, Hänsel and colleagues presented several evidence of the role of inflammation as a biomarker in chronic psychosocial stress [55]. The hypothalamic–pituitary–adrenal (HPA) axis is one of the well-known pathways of the stress-related biological responses, and it was demonstrated that chronic stress-related continuous stimulation of HPA axis leads to a diminishing vagal activity with a consequent increase of inflammatory processes [56, 57]. Interestingly, Cuffee and colleagues [58] link psychological factors with hypertension, identifying specific situation (e.g., occupational stress) in which human body-mind system reacts to chronic stress with a maladaptive response affecting cardiovascular system. Notably, hypertension is one of the mayor risk factors for heart disease, stroke, diabetes, and heart failure [59–61], and is strongly associated with inflammation and neuroinflammatory pathways [57]. Moreover, psychological stress has been proposed as one of the main contributors to the progression of cardiovascular disease, through sympathetic-adrenal-medullary axis, with catecholamine release and heart rate and blood pressure elevation [62]. Of note, sympathetic activation and catecholamine release are known to be pro-inflammatory factors, and chronic sympathetic stimulation is considered a cause of systemic inflammation [57]. Remarkably, psychosocial stress is associated with systemic low-grade inflammation stimulation [63], especially in work-related stress where IL-6 and CRP content increased in unemployed subjects respect to workers. Even in burnout condition, there is a CRP and TNF alpha increase, and in case of low socioeconomic status, a significantly higher levels in CRP over a 13-year period were detected with respect to the controls [63].

A very interesting work connecting psychological stress with inflammation and cardiovascular disease is a review published in 2002 by Black and Garbutt [64]. They presented data showing that chronic psychological stress or repeated acute stress episodes can lead to inflammatory activation followed by atherosclerosis both in humans and in animal models.

Since the early 2000s, several investigations showed correlations between psychological state and immune system activation in humans [55, 65–67]; in particular, it was reported cytokines levels association with emotions and with stress. The main finding was the description of neuro-immune pathways, activated by psychological distress, as mechanisms likely underlying several cardiovascular diseases. In this section, these association will be described.

Emotions and Inflammation

In 2019, a group of investigators explored the problem of increased risk of cardiovascular disease and premature mortality in people suffering recent bereavement due to the spouse death [68]. They found that bereaved individuals who met or exceeded the grief cut point (established for identifying "syndromal" levels of grief) had higher levels of the proinflammatory cytokines Interleukin-6 (IL-6), TNF-α, and IFN-γ, among the plasma cytokines analyzed (IL-6, TNF-α, IFN-γ, IL17-A, and IL-2). In the depression analyses, bereaved individual also suffering major

depressive disorder exhibited greater elevations in the cytokines IL-6, TNF-α, IFN-γ, and IL17-A (the latter being strongly associated with hypertension [57]).

Low socioeconomic status or social resources were associated with hypothalamic–pituitary–adrenal (HPA) axis dysregulation in pregnancy [69]. As previously reported, HPA axis is the system modulating stress and inflammatory responses which was found to be involved in stress-related hypertension [57]. Three years later, Mitchell and colleagues correlated low socioeconomic status (SES) and serum cytokine levels in 67 pregnant women [70] finding that greater meaning in life was associated with higher levels of the anti-inflammatory cytokine IL-4 and negative thinking was negatively associated with IL-4. One of the cardiovascular complications in pregnant women can be preeclampsia, and, in this study, lower levels of IL-4 were found among the seven women who had gestational hypertension or preeclampsia.

Other studies on inflammation in fear and anxiety-based disorders indicate that pro-inflammatory markers can directly modulate affective behavior. In particular, high levels of cytokines and C-reactive protein (CRP) have been described in posttraumatic stress disorder (PTSD), in generalized anxiety disorder (GAD), in panic disorder (PD), and in phobias (agoraphobia, social phobia, etc.). CRP is a molecule strongly associated with increased risk of diabetes and cardiovascular disease, with depression, anxiety, and stress [71]. Nevertheless, also gender, comorbid conditions, types of trauma exposure, and behavioral sources of inflammation resulted to be important factors in the maintenance of these disorders. Dysregulation of the stress-axis and of the sympathetic/parasympathetic tone, typical of anxiety disorders, could further increase inflammation and cardiovascular risk [72].

Finally, in a regression model, emotion dysregulation was significantly associated with higher C-reactive protein (hCRP) in women with type 2 diabetes mellitus [73].

Interestingly, positive thoughts and emotions and social cohesion enhance resilience and have beneficial effects on cardiovascular diseases, in particular by protecting against incident heart failure after a cardiac event [74].

Alexander Lowen, a physician and psychotherapist, former student of Wilhelm Reich, wrote that purely verbal therapies may "help a person to become conscious of his tendencies to deny, project, blame, or rationalize, [but] this conscious awareness rarely affects the muscular tensions or releases the suppressed feelings." At the same time, a purely physical treatment of "body work as massage and yoga exercises has a positive value, but is not specifically therapeutic in itself." Lowen developed a series of physical exercises combined with breath and emotional release, called "bioenergetics," as a tool of self-discovery and therapy. Bioenergetics explores the link between the body and the mind integrating "a work with the body, with the patient's interpersonal relationships, and with his mental processes; each of which is correlated and interpreted in terms of the others" [75, 76].

This particular form of therapy is described as successful in most cases, nevertheless, so far, data on inflammatory parameters in the blood before and after exercise are still lacking. Considering the close relationship existing among emotions, their expression, and the HPA axis, it is plausible to hypothesize a neuro-immune modulation activated by bioenergetics and its influence on the body.

Stress and Inflammation

Das reported a study about the correlation between inflammation and psychosocial distress, describing analyses for linkages of CRP [71]. Observational studies reported that people suffering schizophrenia, bipolar disorder, and major depressive disorder have an increased risk of developing cardiovascular diseases respect to control patients and, in 2014, American Heart Association remarked the strong relationship between high depressive symptoms and poor prognosis after acute myocardial infarction [77–80].

Chronic depression is now listed as one of the important cardiovascular risk factors for poor

prognosis among patients with myocardial infarction, and low-grade chronic inflammation was found to strongly correlate with higher incidence of depression [71, 81–83].

Furthermore, clinical evidence of stress-related inflammation are reported by studies describing an association between IL-6, TNF-alpha, and CRP in individuals with work-related stress and burnout [63] and between IL-6 and caregiver stress [55].

The neurobiology of stress consists in impulses which arise from high cortical centers of the brain and are transmitted to the hypothalamus in the so-called hypothalamic–pituitary–adrenal axis. In this axis, hypothalamic cells, activated by norepinephrine, serotonin, and acetylcholine, produce corticotropin-releasing hormone which activates a cascade producing adrenocorticotropic hormone (ACTH). The subsequent production of corticosteroids, of glucagon, of growth hormone, and of catecholamine and neuropeptides by the sympathetic nervous system (SNS) mediate prompt response to stress insult [64]. In chronic stress conditions, continuous activation of HPA-axis triggers shear-stress and cytokines production [55, 66] which can impair endothelial function leading, for example, to atherosclerosis and hypertension, the latter being a major risk factor for cardiovascular disease and dementia [66] (Fig. 1).

Stress, Cognitive Reappraisal, and Cardiovascular Inflammation

Cognitive reappraisal may be adaptive when stressors are uncontrollable, for example, an accident or chronic disease of a family member, but maladaptive when stressors can be controlled, as the case of relationships or conflicts at workplace [87].

An interesting work of Gianaros and colleagues [88] described an inflammatory pathway linking atherosclerotic cardiovascular disease risk to neural activity evoked by maladaptive cognitive reappraisal. In particular, they showed that elevated reappraisal-related activity in several sections of anterior cingulate cortex, prefrontal cortex, and anterior insula covaried with elevated IL-6, an inflammatory cytokine strongly involved in cardiovascular disease including atherosclerosis [89, 90].

Moreover, it also covaried with greater preclinical atherosclerosis, as reflected by carotid intima-media thickness and inter-adventitial diameter, which are arterial measures predicting cardiovascular outcomes. Finally, IL-6 mediated the association between reappraisal-related activity in the dorsal anterior cingulate cortex and preclinical atherosclerosis [88].

Another work [65] described adaptive and maladaptive emotion regulation (reappraisal and suppression) in relation to CRP, the inflammatory molecule strongly correlated with cardiovascular disease. Authors showed that adaptive reappraisal was associated with lower CRP when compared with maladaptive suppression, associated with higher levels of CRP.

A Neuro-immune Hypothesis

In a mouse model of chronic psychological stress, Ataka and colleagues demonstrated that bone-marrow derived microglia (BMDM) infiltrated brain paraventricular nucleus by crossing blood–brain barrier (BBB), with a mechanism involving the CCR2-CCL2 axis [91]. About in the same period, the group of Raizada and colleagues discovered that BMDM infiltrating rat brain could cause neurogenic hypertension. The mechanism started with sympathetic activation followed by CXCL12 decrease in the BM and subsequent peripheral inflammatory cells increased with extravasation into the brain [92, 93].

These preclinical evidence suggest a possible mechanism of action of psychological distress-related cardiovascular disease, where BM peripheral organs and brain have a key role through their reciprocal crosstalk. In particular, psychological distress, through sympathetic nervous system activation, might stimulate stem cells egression from BM to blood stream where they can differentiate in inflammatory cells and infiltrate the brain becoming BMDM. When BMDM affect brain cardiovascular regulatory areas, the

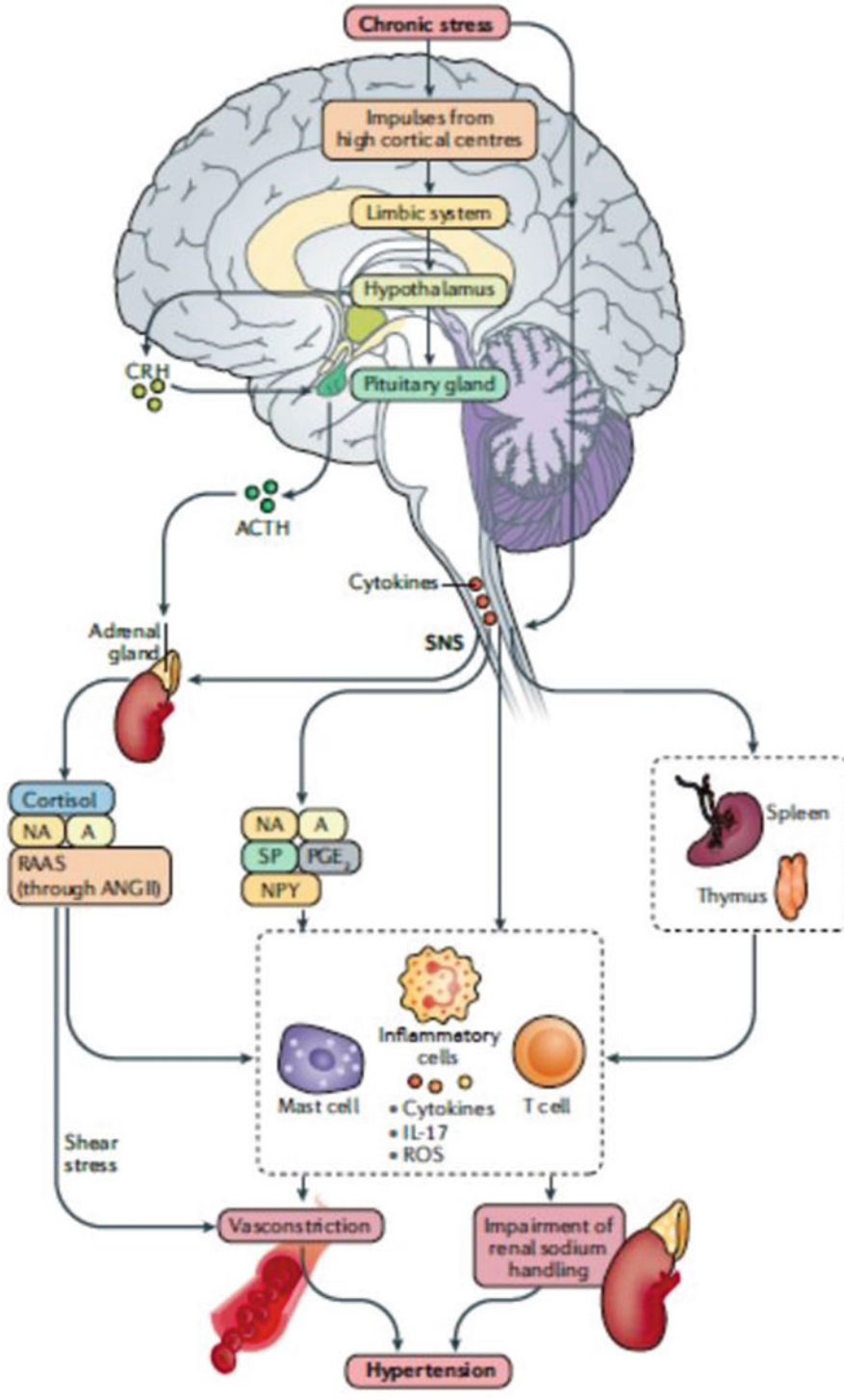

Fig. 1 Example of possible pathways connecting emotion and stress with cardiovascular system. Autonomic nervous system modulates inflammation during chronic stressful events leading to hypertension, a major risk factor for coronary artery disease, stroke, heart failure, atrial fibrillation, peripheral vascular disease, vision loss, chronic kidney disease, and dementia. *CRH* corticotropin-releasing hormone, *ACTH* adrenocorticotropic hormone, *ROS* reactive oxygen species. (Courtesy from Calvillo et al. [57])

subsequent neuroinflammation might lead to cardiovascular disease [57]. The preclinical evidence observed in mice and rats [91, 93] could not so far be reproduced in humans due to the difficulty of detecting BMDM in the brain of patients, but a partial confirmation of this pathway comes from a small clinical study where diabetic obese hypertensive subjects suffering diabetic retinopathy, in addition to diet to decrease body weight, were treated with the antibiotic minocycline for 10 months [94]. All patients reported improving in both BMI and visual acuity, and a significant decrease in BP values. Authors suggested that, alongside the beneficial effect of the weight loss, the mechanisms underlying the remarkable outcomes observed might be due to minocycline anti-inflammatory actions on the brain. In fact, minocycline freely crosses the BBB, is neuroprotective and inhibits microglial activation and inflammatory cytokines in the brain [94]. These evidence from hypertension research suggest a common neuroinflammatory pathway underlying the observed phenomena of psychological distress-related cardiovascular disease. In particular, the role of microglia in modulating neuroinflammatory processes in cardiovascular homeostasis has been highlighted by the work of Kapoor and colleagues [95–97] who discovered that changes in blood pressure can induce morphological transformations in microglia. In fact, following 6 h of acute hypertension, the number of synapses of cardiovascular neurons in contact with microglia increased by 30% in both regions of the brainstem involved in cardiovascular regulation. Conversely, acute hypotension for 6 h causes microglia to reduce the number of synaptic contacts by >20%. Analysis of morphology revealed the "alert" state thus suggesting an active cooperation with brainstem cardiovascular neurons to maintain a healthy and receptive state [97]. Microglia are proving to be "sensors," not only of inflammatory stimuli from environment but also of the activity level of synapses, being in constant communication with neurons, thanks to the presence on their surface of receptors for several peptides and neurotransmitters, including those important in cardiovascular homeostasis (Fig. 2) [98].

What might occur to this fine-tuned communication in case of an increased stress load? If, as described above, chronic psychological stress in mice stimulated neuroinflammation in paraventricular nucleus (in contact, among others, with afferents carrying information on plasma Angiotensin II content and heart function), then psychological state might deeply affect synaptic activity and trigger a neuroinflammatory state also in humans, even in the absence of a commonly recognized stimulus acting as a first triggering spark in cardiovascular disease. The complexity of human behavioral and emotional aspects, the combination of genetic factors together with environmental and psychophysiological factors could thus represent a complex stimulus interacting with the BM-microglia-neuro-immune network (Figs. 1 and 2).

Cholinergic Anti-inflammatory Pathway

In this complex scenario, parasympathetic activity seems to be the likely process that better explains the relationship between mind, brain, and heart. In the beginning of twenty-first century, the neurosurgeon Kevin Tracey demonstrated the role of the vagus nerve in controlling the immune system [56], discovering that alpha 7 nicotinic acetylcholine receptor (α7nAChR) is expressed on macrophage membrane and that its stimulation inhibits TNF-alpha release from the macrophage itself. In the following years, several groups showed that also endothelial cells and many leukocytes expressed α7nAChR, and that this stimulation decreases apoptosis, stimulates angiogenesis, protects mitochondria, and in general has beneficial anti-inflammatory effects [99–101].

In the last two decades, investigators demonstrated the protective role of cholinergic anti-inflammatory pathway in several cardiovascular diseases including myocardial ischemia, reperfusion injury, and heart failure [99, 100, 102], and it is now clear that vagal nerve stimulation causes a decreased inflammatory activity in most of the organs whose cells express α7nAChR [103]. It is thus plausible to speculate that those situations, like psychological distress, shifting the

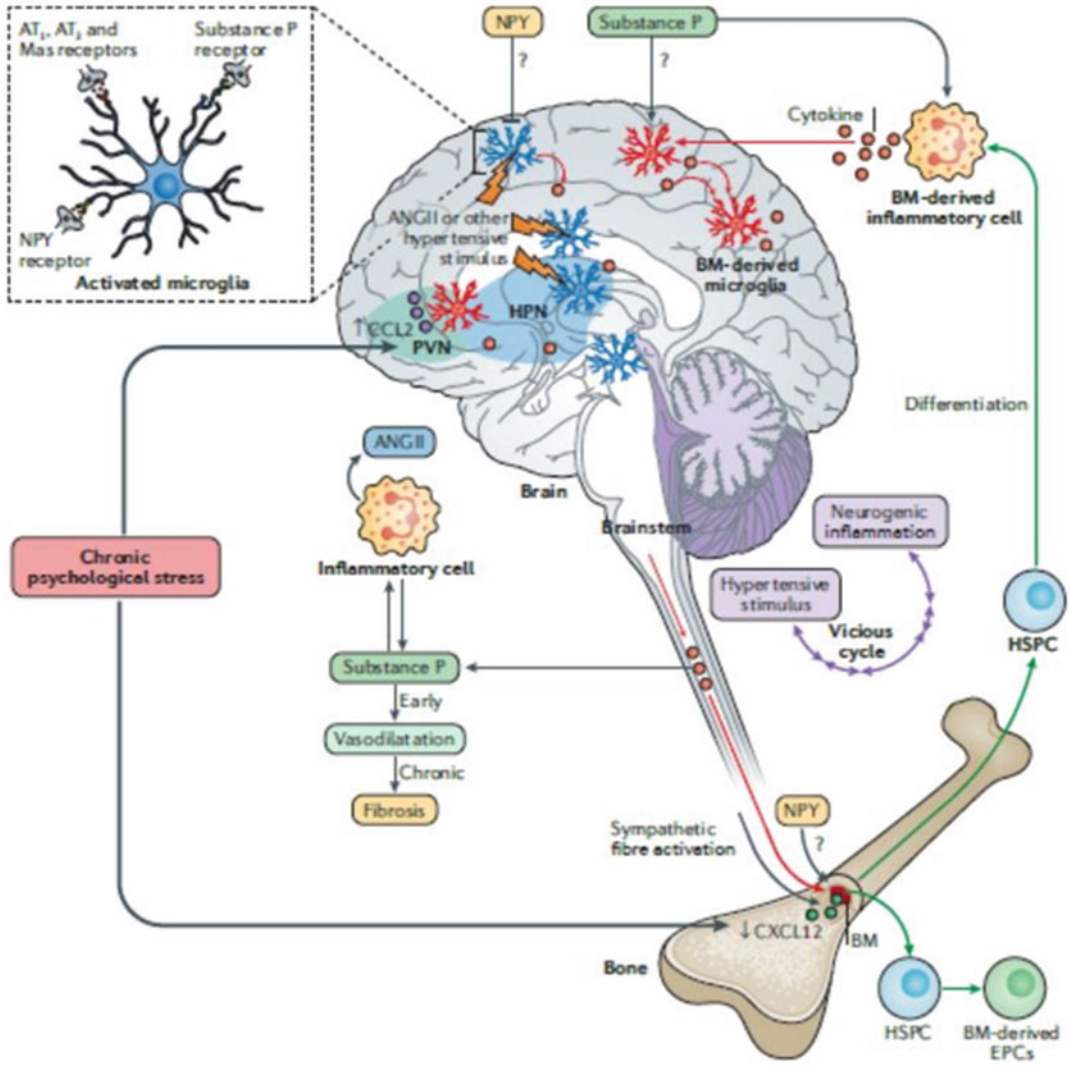

Fig. 2 Proposed involvement of microglia in stress-induced cardiovascular disease. Example from hypertension research. *SP* substance P, *NPY* neuropeptide Y, *CCL2* CC-chemokine ligand 2 (also known as MCP-1), *CXCL12* CXC-chemokine ligand 12 (also known as SDF-1), *HPN* hypothalamic paraventricular nucleus. (Courtesy from Calvillo et al. [57])

sympathovagal balance toward a reduced vagal tone, might inhibit a physiological protective system which is probably designed to maintain the immune system homeostasis. A decreased vagal tone due to stressful situations might thus affect not only cardiovascular system but also the other organs protected by vagal nerve function. Interestingly, Tracey himself indicated cholinergic anti-inflammatory pathway as a possible target of therapies like biofeedback, conditioning, and meditation [56], which are part of psychological strategies aimed to improved psychological and mental state of patients.

Conclusion

In conclusion, the strong connection between heart and brain is also confirmed when emotions and stress influence the mental state. Immune

system has proved to be one of the most important biological tools able to modulate allostasis of these two organs, during their reciprocal crosstalk. This evidence opens the way to further study on the complexity of psycho-neuro-immune system and provides new cues of reflection for possible therapeutic strategies.

References

1. Mather M, Thayer JF. How heart rate variability affects emotion regulation brain networks. Curr Opin Behav Sci. 2018;19:98–104.
2. Matthews E. Mental disorder: can Merleau-Ponty take us beyond the "mind–brain" problem? In: Fulford KWM, Davies M, Gipps RGT, Graham G, Sadler JZ, Stanghellini G, et al., editors. The Oxford handbook of philosophy and psychiatry. Oxford: Oxford University Press; 2013.
3. Hamann S. Mapping discrete and dimensional emotions onto the brain. Trends Cogn Sci. 2012;16(9): 458–66.
4. Damasio H, Grabowski T, Frank R, Galaburda AM, Damasio AR. The return brain from of Phineas Gage: clues about the brain from the skull of a famous patient. Science (80–). 1994;264(5162):1102–5.
5. Niedenthal PM. Embodying emotion. Science (80–). 2007;316(5827):1002–5.
6. Olino TM, Mennies RJ, Wojcieszak ZK. Personality-stress vulnerability models. In: The Oxford handbook of stress and mental health. Oxford: Oxford University Press; 2018. p. 1–33.
7. Ellis BJ, Del Giudice M. Developmental adaptation to stress: an evolutionary perspective. Annu Rev Psychol. 2018;70(1):111–39.
8. Selye H. The stress of life. New York: McGraw-Hill; 1956. p. xvi, 324.
9. Cannon WB. The wisdom of the body. 2nd ed. Oxford, UK: W. W. Norton; 1939.
10. McEwen BS. Stressed or stressed out: what is the difference? J Psychiatry Neurosci. 2005;30(5):315–8.
11. Logan JG, Barksdale DJ. Allostasis and allostatic load: expanding the discourse on stress and cardiovascular disease. J Clin Nurs. 2008;17(7b):201–8.
12. Sterling P, Eyer J. Allostasis: a new paradigm to explain arousal pathology. In: Handbook of life stress, cognition and health. New York: Wiley; 1988. p. 629–47.
13. Dohrenwend BP, Turner JB, Turse NA, Adams BG, Koenen KC, Marshall R. The psychological risks of Vietnam for U.S. veterans: a revisit with new data and methods. Science. 2006;743:979–82.
14. Kendler KS, Karkowski LM, Prescott CA. Causal relationship between stressful life events and the onset of major depression. Am J Psychiatry. 1999;156:837–41.
15. Boyes ME, Hasking PA, Martin G. Adverse life experience and psychological distress in adolescence: moderating and mediating effects of emotion regulation and rumination. Stress Health. 2016;32(4): 402–10.
16. Richardson CME. Emotion regulation in the context of daily stress: impact on daily affect. Personal Individ Differ. 2017;112:150–6.
17. Lewis EJ, Yoon KL, Joormann J. Emotion regulation and biological stress responding: associations with worry, rumination, and reappraisal. Cognit Emot. 2018;32(7):1487–98.
18. Martin RC, Dahlen ER. Cognitive emotion regulation in the prediction of depression, anxiety, stress, and anger. Personal Individ Differ. 2005;39(7): 1249–60.
19. Fink G. In: Fink G, editor. Stress: concepts, cognition, emotion, and behavior. Handbook of stress series, vol. 1. Cambridge, MA: Academic; 2016.
20. Porges SW. The polyvagal perspective. Biol Psychol. 2007;74(2):116–43.
21. Reed SF, Ohel G, David R, Porges SW. A neural explanation of fetal heart rate patterns: a test of the polyvagal theory. Dev Psychobiol. 1999;35(2): 108–18.
22. Thayer JF, Lane RD. A model of neurovisceral integration in emotion regulation and dysregulation. J Affect Disord. 2000;61(3):201–16.
23. Singh RB, Kartik C, Otsuka K, Pella D, Pella J. Brain-heart connection and the risk of heart attack. Biomed Pharmacother. 2002;56(Suppl 2):257s–65s.
24. Grippo AJ, Johnson AK. Stress, depression and cardiovascular dysregulation: a review of neurobiological mechanisms and the integration of research from preclinical disease models. Stress Int J Biol Stress. 2009;12(1):1–21.
25. Beauchaine TP, Bell ZE. Respiratory sinus arrhythmia as a transdiagnostic biomarker of emotion dysregulation. In: Oxford handbook of emotion dysregulation. New York: Oxford University Press; 2018. p. 1–26.
26. Beauchaine TP, Thayer JF. Heart rate variability as a transdiagnostic biomarker of psychopathology. Int J Psychophysiol. 2015;98:338–50.
27. Beauchaine T. Vagal tone, development, and Gray's motivational theory: toward an integrated model of autonomic nervous system functioning in psychopathology. Dev Psychopathol. 2001;13(2): 183–214.
28. Yaptangco M, Crowell SE, Baucom BR, Bride DL, Hansen EJ. Examining the relation between respiratory sinus arrhythmia and depressive symptoms in emerging adults: a longitudinal study. Biol Psychol. 2015;110:34–41.
29. Kidwell M, Ellenbroek BA. Heart and soul: heart rate variability and major depression. Behav Pharmacol. 1998;2018(29):152–64.
30. Kemp AH, Quintana DS. The relationship between mental and physical health: insights from the study

of heart rate variability. Int J Psychophysiol. 2013; 89(3):288–96.
31. Yaroslavsky I, Rottenberg J, Bylsma LM, Jennings JR, George C, Baji I, et al. Parasympathetic nervous system activity predicts mood repair use and its effectiveness among adolescents with and without histories of major depression. J Abnorm Psychol. 2016;125(3):323–36.
32. Kovacs M, Yaroslavsky I, Rottenberg J, George CJ, Kiss E, Halas K, et al. Maladaptive mood repair, atypical respiratory sinus arrhythmia, and risk of a recurrent major depressive episode among adolescents with prior major depression. Psychol Med. 2016;46(10):2109–19.
33. Vazquez L, Blood JD, Wu J, Chaplin TM, Hommer RE, Rutherford HJ, et al. High frequency heart-rate variability predicts adolescent depressive symptoms, particularly anhedonia, across one year. J Affect Disord. 2016;196:243–7.
34. Rottenberg J, Salomon K, Gross JJ, Gotlib IH. Vagal withdrawal to a sad film predicts subsequent recovery from depression. Psychophysiology. 2005;42(3): 277–81.
35. Mathewson KJ, Schmidt LA, Miskovic V, Santesso DL, Duku E, McCabe RE, et al. Does respiratory sinus arrhythmia (RSA) predict anxiety reduction during cognitive behavioral therapy (CBT) for social anxiety disorder (SAD)? Int J Psychophysiol. 2013;88(2):171–81.
36. Wendt J, Hamm AO, Pane-Farre CA, Thayer JF, Gerlach A, Gloster AT, et al. Pretreatment cardiac vagal tone predicts dropout from and residual symptoms after exposure therapy in patients with panic disorder and agoraphobia. Psychother Psychosom. 2018;87(3):187–9.
37. Yaroslavsky I, Rottenberg J, Kovacs M. Atypical patterns of respiratory sinus arrhythmia index an endophenotype for depression. Dev Psychopathol. 2014;26(4):1337–52.
38. Brosschot JF, Gerin W, Thayer JF. The perseverative cognition hypothesis: a review of worry, prolonged stress-related physiological activation, and health. J Psychosom Res. 2006;60(2):113–24.
39. Gross JJ. The emerging field of emotion regulation: an integrative review. Rev Gen Psychol. 1998;2(3): 271–99.
40. Zilverstand A, Parvaz MA, Goldstein RZ. Neuroimaging cognitive reappraisal in clinical populations to define neural targets for enhancing emotion regulation. A systematic review. Neuroimage. 2017;151:105–16.
41. Topper M, Emmelkamp PMG, Watkins E, Ehring T. Prevention of anxiety disorders and depression by targeting excessive worry and rumination in adolescents and young adults: a randomized controlled trial. Behav Res Ther. 2017;90:123–36.
42. Krkovic K, Clamor A, Lincoln TM. Emotion regulation as a predictor of the endocrine, autonomic, affective, and symptomatic stress response and recovery. Psychoneuroendocrinology. 2018;94:112–20.
43. Ottaviani C, Thayer JF, Verkuil B, Lonigro A, Medea B, Couyoumdjian A, et al. Physiological concomitants of perseverative cognition: a systematic review and meta-analysis. Psychol Bull. 2016;142: 231.
44. Ottaviani C. Brain-heart interaction in perseverative cognition. Psychophysiology. 2018;55(7):1–14.
45. Rood L, Roelofs J, Bögels SM, Meesters C. Stress-reactive rumination, negative cognitive style, and stressors in relationship to depressive symptoms in non-clinical youth. J Youth Adolesc. 2012;41(4): 414–25.
46. Lam S, Dickerson SS, Zoccola PM, Zaldivar F. Emotion regulation and cortisol reactivity to a social-evaluative speech task. Psychoneuroendocrinology. 2009;34(9):1355–62.
47. Roger D, Najarian B. The relationship between emotional rumination and cortisol secretion under stress. Personal Individ Differ. 1998;24(4):531–8.
48. Zoccola PM, Dickerson SS. Assessing the relationship between rumination and cortisol: a review. J Psychosom Res. 2012;73(1):1–9.
49. Mcrae K. ScienceDirect. Cognitive emotion regulation: a review of theory and scientific findings. Curr Opin Behav Sci. 2016;10:119.
50. Denson TF, Creswell JD, Terides MD, Blundell K. Cognitive reappraisal increases neuroendocrine reactivity to acute social stress and physical pain. Psychoneuroendocrinology. 2014;49(1):69–78.
51. Schoenberg PLA, David AS. Biofeedback for psychiatric disorders: a systematic review. Appl Psychophysiol Biofeedback. 2014;39(2):109–35.
52. Goessl VC, Curtiss JE, Hofmann SG. The effect of heart rate variability biofeedback training on stress and anxiety: a meta-analysis. Psychol Med. 2017; 47(15):2578–86.
53. Remue J, Vanderhasselt MA, Baeken C, Rossi V, Tullo J, De Raedt R. The effect of a single HF-rTMS session over the left DLPFC on the physiological stress response as measured by heart rate variability. Neuropsychology. 2016;30(6):756–66. https://doi.org/10.1037/neu0000255. Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L607178732%0A
54. Wampold BE, Imel ZE. The great psychotherapy debate: the evidence for what makes psychotherapy work. 2nd ed. New York: Routledge/Taylor & Francis Group; 2015. p. x, 323. (Counseling and psychotherapy).
55. Hänsel A, Hong S, Cámara RJA, von Känel R. Inflammation as a psychophysiological biomarker in chronic psychosocial stress. Neurosci Biobehav Rev. 2010;35(1):115–21.
56. Tracey KJ. The inflammatory reflex. Nature. 2002;420(6917):853–9.
57. Calvillo L, Gironacci MM, Crotti L, Meroni PL, Parati G. Neuroimmune crosstalk in the pathophysiology of hypertension. Nat Rev Cardiol. 2019; 16(8):476–90.

58. Cuffee Y, Ogedegbe C, Williams NJ, Ogedegbe G, Schoenthaler A. Psychosocial risk factors for hypertension: an update of the literature. Curr Hypertens Rep. 2014;16(10):1–18.
59. Parati G. Antihypertensive therapy in 2014: linking pathophysiology to antihypertensive treatment. Nat Rev Cardiol. 2015;12(2):77–9. Available from: http://www.nature.com/doifinder/10.1038/nrcardio.2014.221
60. Zanchetti A, Thomopoulos C, Parati G. Randomized controlled trials of blood pressure lowering in hypertension: a critical reappraisal. Circ Res. 2015;116(6):1058–73.
61. Kim MJ, Lim NK, Choi SJ, Park HY. Hypertension is an independent risk factor for type 2 diabetes: the Korean genome and epidemiology study. Hypertens Res. 2015;38(11):783–9. https://doi.org/10.1038/hr.2015.72.
62. Huang CJ, Webb HE, Zourdos MC, Acevedo EO. Cardiovascular reactivity, stress, and physical activity. Front Physiol. 2013;4:1–13.
63. Rohleder N. Stimulation of systemic low-grade inflammation by psychosocial stress. Psychosom Med. 2014;76(3):181–9.
64. Black PH, Garbutt LD. Stress, inflammation and cardiovascular disease. J Psychosom Res. 2002;52(1):1–23.
65. Appleton AA, Buka SL, Loucks EB, Gilman E, Kubzansky LD. Divergent associations of adaptive and maladaptive emotion regulation strategies with inflammation. Health Psychol. 2013;32(7):748–56.
66. Munakata M. Clinical significance of stress-related increase in blood pressure: current evidence in office and out-of-office settings. Hypertens Res. 2018;41(8):553–69.
67. Dantzer R, Connor JCO, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat Rev Neurosci. 2008;9(1):46–56.
68. Fagundes CP, Brown RL, Chen MA, Murdock KW, Saucedo L, LeRoy A, et al. Grief, depressive symptoms, and inflammation in the spousally bereaved. Psychoneuroendocrinology. 2019;100:190–7. https://doi.org/10.1016/j.psyneuen.2018.10.006.
69. Bublitz MH, Vergara-Lopez C, Treter MOR, Stroud LR. Association of lower socioeconomic position in pregnancy with lower diurnal cortisol production and lower birthweight in male infants. Clin Ther. 2016;38:265–74.
70. Mitchell AM, Christian LM. Repetitive negative thinking, meaning in life, and serum cytokine levels in pregnant women: varying associations by socioeconomic status. J Behav Med. 2019. https://doi.org/10.1007/s10865-019-00023-6.
71. Das A. Psychosocial distress and inflammation: which way does causality flow? Soc Sci Med. 2016;170:1–8.
72. Michopoulos V, Powers A, Gillespie CF, Ressler KJ, Jovanovic T. Inflammation in fear- and anxiety-based disorders: PTSD, GAD, and beyond. Neuropsychopharmacology. 2017;42(1):254–70. https://doi.org/10.1038/npp.2016.146.
73. Powers A, Michopoulos V, Conneely K, Gluck R, Dixon H, Wilson J, et al. Emotion dysregulation and inflammation in African-American women with type 2 diabetes. Neural Plast. 2016;2016(Article ID 8926840):1–10. Available from: http://www.hindawi.com/journals/np/2016/8926840/
74. Kim ES, Smith J, Kubzansky LD. Prospective study of the association between dispositional optimism and incident heart failure. Circulation. 2014;7(3):394–400.
75. Lowen A. Bioenergetics: the revolutionary therapy that uses the language of the body to heal the problems of the mind. New edition. London: Penguin Books Ltd; 1994. Available from: https://www.bookdepository.com/Bioenergetics-Alexander-Lowen/9780140194715
76. Lowen, A. (1958). Physical dynamics of character structure: Bodily form and movement in analytic therapy. Grune & Stratton open library publisher. https://openlibrary.org/publishers/Grune_&_Stratton.
77. De Hert M, Detraux J, Vancampfort D. The intriguing relationship between coronary heart disease and mental disorders. Dialogues Clin Neurosci. 2018;20:31–40.
78. Lichtman JH, Froelicher ES, Blumenthal JA, Carney RM, Doering LV, Frasure-Smith N, et al. Depression as a risk factor for poor prognosis among patients with acute coronary syndrome: systematic review and recommendations: a scientific statement from the American Heart Association. Circulation. 2014;129:1350–69.
79. Cohen BE, Edmondson D, Kronish IM. State of the art review: depression, stress, anxiety, and cardiovascular disease. Am J Hypertens. 2015;28:1295–302.
80. Penninx BW. Depression and cardiovascular disease: epidemiological evidence on their linking mechanisms. Neurosci Biobehav Rev. 2017;74:277–86. https://doi.org/10.1016/j.neubiorev.2016.07.003.
81. Danesh J, Wheeler JG, Hirschfield GM, Eda S, Eiriksdottir G, et al. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. N Engl J Med. 2004;350(14):1387–97.
82. Fioranelli M, Bottaccioli AG, Bottaccioli F, Bianchi M, Rovesti M, Roccia MG. Stress and inflammation in coronary artery disease: a review psychoneuroendocrineimmunology-based. Front Immunol. 2018;9:2031.
83. Liu H, Luiten PGM, Eisel ULM, Dejongste MJL, Schoemaker RG. Depression after myocardial infarction: TNF-α-induced alterations of the blood-brain barrier and its putative therapeutic implications. Neurosci Biobehav Rev. 2013;37(4):561–72. https://doi.org/10.1016/j.neubiorev.2013.02.004.
84. Lackland DT, Weber MA. Global burden of cardiovascular disease and stroke: hypertension at the core. Can J Cardiol. 2015;31(5):659–71.

85. Lau DH, Nattel S, Kalman JM, Sanders P. Modifiable risk factors and atrial fibrillation. Circulation. 2017;136(6):583–96.
86. Hernandorena I, Duron E, Vidal JS, Hanon O. Treatment options and considerations for hypertensive patients to prevent dementia. Expert Opin Pharmacother. 2017;18(10):989–1000.
87. Troy AS, Shallcross AJ, Mauss IB. A person-by-situation approach to emotion regulation: cognitive reappraisal can either help or hurt, depending on the context. Psychol Sci. 2013;24(12):2505–14.
88. Gianaros PJ, Marsland AL, Kuan DC, Schirda BL, Jennings JR, Sheu LK, et al. An inflammatory pathway links atherosclerotic cardiovascular disease risk to neural activity evoked by the cognitive regulation of emotion. Biol Psychiatry. 2014;75(9):738–45.
89. Ridker PM, Rifai N, Stampfer MJ, Hennekens CH. Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men. Circulation. 2000;101(15):1767–72.
90. Dusi V, Ghidoni A, Ravera A, De Ferrari GM, Calvillo L. Chemokines and heart disease: a network connecting cardiovascular biology to immune and autonomic nervous systems. Mediat Inflamm. 2016; 2016:Article ID 5902947.
91. Ataka K, Asakawa A, Nagaishi K, Kaimoto K, Sawada A, Hayakawa Y, et al. Bone marrow-derived microglia infiltrate into the paraventricular nucleus of chronic psychological stress-loaded mice. PLoS One. 2013;8(11):1–14.
92. Zubcevic J, Santisteban MM, Pitts T, Baekey DM, Perez PD, Bolser DC, et al. Functional neural-bone marrow pathways: implications in hypertension and cardiovascular disease. Hypertension. 2014;63(6): 129–40.
93. Santisteban MM, Ahmari N, Carvajal JM, Zingler MB, Qi Y, Kim S, et al. Involvement of bone marrow cells and neuroinflammation in hypertension. Circ Res. 2015;117:178–91.
94. Yellowlees Douglas J, Bhatwadekar AD, Li Calzi S, Shaw LC, Carnegie D, Caballero S, et al. Bone marrow-CNS connections: implications in the pathogenesis of diabetic retinopathy. Prog Retin Eye Res. 2012;31(5):481–94. https://doi.org/10.1016/j.preteyeres.2012.04.005.
95. Kapoor K, Bhandare AM, Farnham MMJ, Pilowsky PM. Alerted microglia and the sympathetic nervous system: a novel form of microglia in the development of hypertension. Respir Physiol Neurobiol. 2016;226:51–62.
96. Kapoor K, Bhandare AM, Mohammed S, Farnham MMJ, Pilowsky PM. Microglial number is related to the number of tyrosine hydroxylase neurons in SHR and normotensive rats. Auton Neurosci. 2016;198:10–8. https://doi.org/10.1016/j.autneu.2016.05.005.
97. Kapoor K, Bhandare AM, Nedoboy PE, Mohammed S, Farnham MMJ, Pilowsky PM. Dynamic changes in the relationship of microglia to cardiovascular neurons in response to increases and decreases in blood pressure. Neuroscience. 2016;329:12–29. https://doi.org/10.1016/j.neuroscience.2016. 04.044.
98. Pocock JM, Kettenmann H. Neurotransmitter receptors on microglia. Trends Neurosci. 2007; 30(10):527–35.
99. Calvillo L, Vanoli E, Andreoli E, Besana A, Omodeo E, Gnecchi M, et al. Vagal stimulation, through its nicotinic action, limits infarct size and the inflammatory response to myocardial ischemia and reperfusion. J Cardiovasc Pharmacol. 2011; 58(5):500–7.
100. Li M, Zheng C, Sato T, Kawada T, Sugimachi M, Sunagawa K. Vagal nerve stimulation markedly improves long-term survival after chronic heart failure in rats. Circulation. 2004;109(1):120–4.
101. Kakinuma Y, Ando M, Kuwabara M, Katare RG, Okudela K, Kobayashi M, et al. Acetylcholine from vagal stimulation protects cardiomyocytes against ischemia and hypoxia involving additive non-hypoxic induction of HIF-1α. FEBS Lett. 2005; 579(10):2111–8.
102. Uitterdijk A, Yetgin T, te Lintel Hekkert M, Sneep S, Krabbendam-Peters I, van Beusekom HM, et al. Vagal nerve stimulation started just prior to reperfusion limits infarct size and no-reflow. Basic Res Cardiol. 2015;110(5):1–14.
103. Huston JM, Tracey KJ. The pulse of inflammation: heart rate variability, the cholinergic anti-inflammatory pathway and implications for therapy. J Intern Med. 2011;269(1):45–53.

Part III

Emotional Processes and How They May Influence Cardiovascular Activity, Disease Onset, Outcomes, and Quality of Life

Biofeedback

9

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Contents

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*,
https://doi.org/10.1007/978-3-030-28008-6_17

Abstract

This chapter presents the basic biofeedback training paradigm, introduces commonly used biofeedback modalities, and describes the physiological processes measured by each. In addition, the chapter describes common applications for each of the biofeedback modalities used in everyday practice, the importance of evidence-based practice, and the role of the Biofeedback Certification International Alliance (BCIA) in setting international training and practice standards.

Keywords

Biofeedback · Psychophysiology · Self-regulation · Mindfulness · Self-quantification · Evidence-based practice · Certification

Introduction: The Biofeedback Paradigm

Biofeedback is a learning process that is analogous to instruction to improve range of motion or stability. A biofeedback professional functions like a personal trainer. In this revolutionary paradigm, an individual performs an action (such as breathing slowly), observes the physiological consequences (heart rate swings increase), and practices this skill throughout the day across diverse situations.

Biofeedback is a "psychophysiological mirror" that teaches individuals to monitor, understand, and change their physiology in order to treat symptoms and improve performance [1]. The goal of biofeedback training is to teach *self-regulation* (control of behavior without external feedback). While biofeedback is not inherently relaxing (an elevated blood pressure could be upsetting), clients can combine biofeedback with relaxation exercises (*biofeedback-assisted relaxation*) to reduce autonomic overactivation.

For example, a biofeedback practitioner can provide a biofeedback display to show clients their own breathing process, and the biofeedback display will guide them to breathe more slowly, evenly, and smoothly, with less sighing and breath holding. When clients have practiced sufficiently to achieve relaxed, slow breathing without feedback, this shows that they have achieved self-regulation. Biofeedback training is a bridge to self-regulation. While biofeedback training is a powerful evidence-based intervention in clinical disorders, it is increasingly used to promote optimal performance [2].

Biofeedback can involve no-technology (observing your posture in a mirror), low-technology (alcohol thermometer), or high-technology (computerized data acquisition systems). Biofeedback is defined by the learning process and not by the hardware used in training. The most complex biofeedback systems follow the simple paradigm described earlier. If we can monitor a physiological process and feed back this information in real time, an individual can gain awareness of and control over that process.

Our colleague, Eric Willmarth, says that "Biofeedback is like teaching a deaf person to sing" [3]. Biofeedback training provides an external feedback loop when healthy internal self-regulation no longer functions. Biofeedback often assists the restoration of healthy self-regulation

of physiology, emotion, and overall adaptation. In optimal performance applications, biofeedback instrumentation augments normal body awareness and enables higher levels of performance and resilience. Gaining a sense of control over a simple bodily process such as muscle tension often generalizes into a broader sense of personal confidence in gaining control over one's life, health, and problems. The result is enhanced self-efficacy throughout an individual's life.

The Synergy Between Biofeedback and Mindfulness

Biofeedback training may be more effective when instruction promotes mindfulness. There has always been an element of mindfulness in biofeedback training. Biofeedback practitioners guide patients to focus on their body, deepening awareness of processes usually outside of awareness, and to cultivate relaxed attention without striving. Explicit instruction in a *mindfulness approach* teaches clients to more systematically focus on their immediate feelings, cognitions, and sensations, in an accepting and nonjudgmental way, to distinguish between what can and cannot be changed, and to change the things they can [4]. This enhances traditional biofeedback training by helping clients disengage from an unhelpful struggle with their thoughts and emotions and encouraging them to use biofeedback as a healthy way of responding to distress and suffering.

Definitions of Biofeedback and Neurofeedback Therapy

A task force of professionals from the major organizations in the biofeedback field developed an official definition of biofeedback in 2008:

> Biofeedback is a process that enables an individual to learn how to change physiological activity for the purposes of improving health and performance. Precise instruments measure physiological activity such as brainwaves, heart function, breathing, muscle activity, and skin temperature. These instruments rapidly and accurately 'feed back' information to the user. The presentation of this information — often in conjunction with changes in thinking, emotions, and behavior — supports desired physiological changes. Over time, these changes can endure without continued use of an instrument. [5] (p90)

The main elements of this definition are that (1) biofeedback is a learning process that teaches individuals to control their physiological activity, (2) the aim of biofeedback training is to improve health and performance, (3) instruments rapidly monitor an individuals' performance and display it back to them, (4) individuals use this feedback to produce physiological changes, (5) changes in thinking, emotions, and behavior often accompany and reinforce physiological changes, and (6) these changes become independent of external feedback from instruments.

The International Society for Neurofeedback and Research [6] proposed that:

> Like other forms of biofeedback, neurofeedback training uses monitoring devices to provide moment-to-moment information to an individual on the state of their physiological functioning. The characteristic that distinguishes neurofeedback training from other biofeedback is a focus on the central nervous system and the brain. Neurofeedback training has its foundations in basic and applied neuroscience as well as data-based clinical practice. It takes into account behavioral, cognitive, and subjective aspects as well as brain activity.

Physiological Monitoring and Modulation Are Not Biofeedback

Physiological monitoring, detecting biological activity like blood pressure, is only one component of biofeedback. When nurses measure your blood pressure, this is physiological monitoring. Nurses provide biofeedback when they report these values to you, because this provides you with information about your performance. Their announcing that your blood pressure was 120/70 closes the loop and allows you to refine your self-awareness and control of your physiology.

Physiological monitoring often serves as an adjunct to psychotherapy. For example, the therapist can watch the display and observe when abrupt changes in skin conductance, heart rate, heart rate variability, or EEG indicate emotional reactivity to the subject under discussion at that moment. The client is not receiving feedback or engaging in training for self-regulation in that session, but the monitoring is informing the psychotherapy process. If the therapist makes the display visible to the client, it becomes *biofeedback*, potentially guiding the client toward enhanced self-regulation.

Likewise, *modulation*, stimulating the nervous system to produce psychophysiological change, is not biofeedback because it acts on your body instead of providing you with information about its performance. For example, a physical therapist might treat low back pain through a modality called *muscle stimulation*. An electrical current delivered to postural muscles fatigues them so that they cannot produce painful spasms. After muscle stimulation brings spasms under control, a physical therapist can initiate surface electromyographic (SEMG) biofeedback to teach the patient to increase awareness and control of postural muscle contraction.

Biofeedback Modalities

Any physiological signal that can be monitored can be trained. However, research is necessary to determine whether biofeedback training can produce sufficient change to be clinically and practically relevant. We know, for example, that the direct training of blood pressure can reduce blood pressure, yet the changes are often insufficient to normalize elevated blood pressure. Instead, current evidence supports a combination of lifestyle changes (e.g., weight loss and low salt diet) and feedback of heart rate variability (the fluctuation in the time intervals between adjacent heartbeats), skeletal muscle electrical activity, and skin temperature.

A variety of biofeedback instruments are now available, and a number of research studies have demonstrated that feedback learning can produce improved awareness of and control over several physiological systems. Table 1 [7] shows each biofeedback modality, the abbreviation for the modality, the physiological signal measured, the type of sensor used, and the measurement unit commonly used to designate the magnitude of the signal.

The principal modalities employed in clinical and optimal performance practice include the

Table 1 Commonly used biofeedback modalities

Modality	Abbreviation	Physiological signal	Sensor	Measurement unit
Capnometer	CAP	End-tidal CO2	Infrared detector	pCO2 or torr
Electrocardiograph	ECG	Cardiac electrical activity, heart rate, heart rate variability	Precious metal	Beats per minute
Electrodermograph	EDA, GSR, SCL, SPL	Eccrine sweat gland-mediated changes in skin electrical potential	Zinc or precious metal	Kohms, microsiemens, millivolts
Electroencephalograph	EEG	Cortical postsynaptic potentials	Precious metal	Microvolts, picowatts
Electromyograph	EMG, SEMG	Muscle action potentials	Precious metal	Microvolts
Feedback thermometer	TEMP	Peripheral blood flow	Thermistor	Degrees F or C
Photoplethysmograph	PPG	Peripheral blood flow, heart rate, heart rate variability	Infrared detector	Arbitrary units, beats per minute
Respirometer	RESP	Abdominal/chest movement	Strain gauge	Arbitrary units, breaths per minute

pCO2 percentage of carbon dioxide in exhaled air, *torr, Kohms* thousands of ohms, *microsiemens* millionths of a siemen; *millivolts* thousandths of a volt, *microvolts* millionths of a volt, *picowatts* billionths of a watt

capnometer, electrocardiograph, electrodermograph, electroencephalograph, electromyograph, feedback thermometer, photoplethysmograph, and respirometer (see Table 1).

Capnometer

A *capnometer* provides continuous information about end-tidal CO_2, which is the percentage of CO_2 in exhaled air at the end of exhalation. An optical sensor analyzes the composition of air collected by a nasal cannula. The goal of training is to increase end-tidal CO_2 values to between 35 and 45 mmHg (or torr). A reading of 36 mmHg corresponds to about 5% CO_2 in exhaled air [8]. Clinicians use capnometric biofeedback to treat anxiety and panic, hyperventilation, overbreathing, and posttraumatic stress disorder by teaching clients to normalize blood CO_2 levels via breathing training.

Electrocardiograph

An *electrocardiograph* (ECG/EKG) measures the electrical activity of the heart and provides information about cardiac conduction, heart rate, and heart rate variability (HRV). For biofeedback, assemblies with two active and one reference electrode are positioned on the wrists or torso to detect the R-spike in the QRS complex, which is associated with depolarization of the ventricles (lower chambers) and repolarization of the atria (upper chambers) of the heart.

Heart rate is the number of heartbeats per minute. Normal resting heart rate values fall between 60 and 80 beats per minute [12].

Heart rate variability (HRV) consists of the beat-to-beat changes in the time intervals between adjacent beats. Greater HRV is associated with health and resilience; reduced HRV is associated with aging, illness, and diminished performance. We can characterize HRV using time domain, frequency domain, and nonlinear measurements. *Time domain* indices quantify the amount of variability in measurements of the interbeat interval (IBI), which is the time period between successive heartbeats. *Frequency domain* indices quantify the temporal distribution of absolute or relative power into four frequency bands. Finally, *nonlinear* indices quantify the unpredictability of a time series, which results from the complexity of the mechanisms that regulate heart rate variability.

The goal of HRV biofeedback is to increase time domain measurements like SDNN (the standard deviation of the interbeat interval between successive heart beats) and *RMSSD* (the root mean square of successive differences between normal heartbeats) and increase power in the *low-frequency band* (0.04–0.15 Hz) when breathing between 4.5 and 6.5 breaths per minute guided by displays of heart rate and respiration signals. Clinicians may integrate HRV biofeedback with training in diaphragmatic breathing, emotional self-regulation, mindfulness, and stress management.

Biofeedback therapists use HRV biofeedback when treating patients diagnosed with anxiety disorders, asthma, cardiovascular disease, chronic obstructive pulmonary disease (COPD), depression, diabetes, essential hypertension, irritable bowel syndrome, and post-concussion syndrome [4, 9–11].

Electrodermograph

An *electrodermograph* measures fluctuations in skin electrical activity generated by eccrine sweat glands. An electrodermograph measures skin electrical activity directly (skin conductance and skin potential) and indirectly (skin resistance) using electrodes placed over the second phalange of the digits or over the palmar surface of the hand and wrist. Eccrine sweat gland activity increases can be produced by sympathetic arousal, cognitive activity, orienting responses to unexpected stimuli, and worry.

Skin conductance (SC) is monitored by applying an imperceptible current across the skin and measuring how easily it moves through the skin. As the level of sweat in a sweat duct rises, conductance increases. Skin conductance is measured in microsiemens (millionths of a siemen) and normal resting values using finger snaps fall below 5 μS per cm^2 [12].

Skin potential (SP) is generated by the difference in the electrical charge between an active site (e.g., the palmar surface of the hand) and an inactive site (e.g., the forearm). Typical values range from +10 to −70 millivolts (thousands of a volt) referenced to the inactive electrode.

Skin resistance (SR), also called galvanic skin response (GSR), is monitored by applying a current to the skin and measuring tissue opposition to its passage in Kohms (thousands of ohms). Typical values run from 10 to 500 Kohms per cm^2 [13].

All three recording methods produce comparable results and share a 1–3 s latency between a stimulus and an electrodermal response [14]. The goal of electrodermal biofeedback is to restore normal autonomic regulation of sweat gland function. While we want to reduce disproportionate and chronic autonomic activation, we want clients to appropriately engage the electrodermal system in response to sudden or threatening stimuli.

Biofeedback therapists use electrodermal biofeedback when treating anxiety disorders, hyperhidrosis (excessive sweating), motion sickness, and stress [15]. Electrodermal biofeedback is also frequently used as an adjunct to psychotherapy. Patients in psychotherapy who deny the presence of negative emotion or anxiety often become more aware and attuned to their emotions after they have observed their skin electrical activity increase each time they discuss a troubled work setting or relationship [16, 17]. Clinicians also use electrodermal biofeedback to monitor the effectiveness of other biofeedback interventions such as neurofeedback since it can indicate distress.

Electroencephalograph

An *electroencephalograph* (EEG) monitors fast cortical potentials (0.5–100 Hz or cycles per second) and slow cortical potentials (300 milliseconds to several seconds). *Fast cortical potentials* range from 0.5 to 100 Hz. The main frequency ranges include delta, theta, alpha, sensorimotor rhythm, and beta (see Table 2). *Slow cortical potentials* (SCPs) are gradual changes in the membrane potentials of cortical dendrites. These potentials include the contingent negative variation (CNV), readiness potential, movement-related potentials (MRPs), and P300 and N400 potentials and exclude event-related potentials (ERPS) [18].

The EEG uses precious metal electrodes to detect a voltage between at least two electrodes located on the scalp. The EEG records both excitatory postsynaptic potentials (EPSPs) and inhibitory postsynaptic potentials (IPSPs) that largely occur in the dendrites of pyramidal cells in the upper cortical layers. Neurons work in partnership with glial cells, which produce slow cortical potentials. There are multiple generators of the EEG rhythms that are studied and shaped by neurofeedback professionals. Intracellular and extracellular studies provide evidence of a corticothalamic network that is responsible for multiple EEG rhythms. These waveforms appear to be grouped by slow cortical potentials.

The EEG shows the amplitude (strength) of electrical activity at each cortical site, the amplitude and relative power of various waveforms at each site, and the degree to which each cortical

Table 2 Common EEG frequencies

EEG frequency	Frequency range	Activity
Delta rhythm	0.5–3.5 Hz	Sleep, traumatic brain injury, tumor
Theta rhythm	4–7 Hz	Daydreaming, drowsiness, imagery, inattention, memory formation and retrieval, network communication
Alpha rhythm	8–13 Hz	Resting state rhythm, meditation, receptiveness
Sensorimotor rhythm (SMR)	12–15 Hz	Inhibition of movement, resting state of the sensorimotor cortex
Low beta rhythm	13–21 Hz	Activation, focused thinking, localized information processing
High beta rhythm	20–32 Hz	Anxiety, hypervigilance, panic, optimum performance, worry
Gamma rhythm	36–44 Hz	Perception of meaning, meditative awareness

site communicates with other sites (coherence and co-modulation).

EEG rhythms possess frequency and amplitude. *Frequency* is the number of cycles completed each second. The higher the frequency, the shorter the wavelength. *Amplitude* is the energy or power contained within the EEG signal and is measured in microvolts (millionths of a volt) or picowatts (billionths of a watt). High amplitude means that a large number of neurons are depolarizing and hyperpolarizing at the same time.

The majority of EEG power or signal energy falls within the 0–20 Hz frequency range. The *dominant frequency* (frequency with the greatest amplitude) during an adult's waking consciousness is 10 Hz with eyes closed and at least 13 Hz with eyes open.

Based on assessment and training goals, clinicians select surface electrode configurations called *montages* to detect localized or global EEG activity [19]. The electrode sites are located using the 21-electrode International 10–20 system or the 75-electrode modified expanded International 10–20 system, which is also called the 10–10 system. They may monitor a single electrode site or a montage of 19, 72, or more sites. The *Quantitative EEG (QEEG)* calculates average EEG voltages within selected frequency bands. Clinicians may reference patient values to a digital database to aid diagnosis and to guide Z-score-based training.

The goal of neurofeedback is to normalize the EEG. A *performance-based approach* uses tasks and neurofeedback training to correct symptoms and improve performance. This approach, which is often called "amplitude training," compares clients to themselves and not a normative database. In contrast, *Z-score training* attempts to normalize brain function with respect to mean values in a normative database. EEG amplitudes that are two or more standard deviations above or below the database means are down-trained or uptrained to treat symptoms and improve performance.

Either method may be accomplished using one or more strategies. *Frequency protocols* uptrain (increase signal power) and/or down-train (decrease signal power) specific frequencies at targeted sites on the scalp. *Connectivity protocols* correct deficient or excessive communication between two brain sites as measured by indices like coherence and co-modulation. *Slow cortical potential protocols* teach clients to increase positive shifts and reduce negative shifts to reduce cortical hyperexcitability in disorders like epilepsy and migraine. There are currently insufficient data to compare the efficacy of these approaches and protocols for specific disorders or optimal performance applications.

Clinicians use neurofeedback to treat anxiety disorders (including worry, obsessive-compulsive and posttraumatic stress disorder), attention deficit hyperactivity disorder (ADHD), autism spectrum disorders (ASD), depression, generalized seizures, adult headache, learning disability, mild closed head injuries and traumatic brain injury, and substance use disorders [2].

Electromyograph

The *electromyograph (EMG)* uses electrodes to detect *muscle action potentials* from underlying skeletal muscles. Since clinical biofeedback places sensors on the skin instead of inside skeletal muscles, this instrument is called the surface electromyography (SEMG).

At least two and usually three electrodes, made out of precious metals such as silver/silver chloride or gold, are needed to measure the EMG signal. Disposable versions of EMG electrodes are widely used today to reduce potential infection coming from reuse. They typically utilize hypoallergenic materials and are pre-gelled for ease of use.

Like the EEG, we designate active and reference electrodes according to their placement site. Clinicians must know sufficient muscle anatomy and kinesiology to correctly position the active and reference electrodes. They place the *active electrode(s)* over a target muscle and the *reference electrode* over a less electrically active site. Since the electrodes should detect different amounts of EMG activity (the active electrodes should detect more energy), a voltage should develop between them.

The EMG signal is measured in microvolts (millionths of a volt). The frequency range for surface recording is 2–1000 Hz. The greatest concentration of power in a resting muscle lies between 10 and 150 Hz [20]. During a resting baseline in which clients receive no feedback, normal values lie below 3 μV for small-to-moderate-sized muscles and below 5 μV for large muscles [12].

In applications such as stroke and low back pain, therapists monitor and train patients' paired muscles, such as the masseter and upper trapezius, bilaterally because achieving more symmetrical muscle activity may be critical to symptomatic improvement. In neuromuscular rehabilitation, therapists monitor flexors and extensors located at the same joint to prevent interference and enhance muscle cooperation in functional movement. SEMG-assisted physical therapy attempts to restore muscle function lost due to motor nerve injury or stroke or to correct dysfunctional muscle use due to congenital conditions like cerebral palsy.

Important innovations in biofeedback-assisted rehabilitation include Steven Wolf's teaching patients to engage in problem-solving to reacquire functional movement and Jeffrey Bolek's *quantitative surface electromyography (QSEMG)* approach [21] that teaches functional movement patterns by providing feedback from multiple muscle sites.

The goal of SEMG biofeedback-assisted rehabilitation is to down-train excessive SEMG activity, uptrain deficient SEMG activity, and restore symmetrical muscle recruitment patterns, range of motion, and functional activity.

Therapists may use portable electromyographs and EMG Bluetooth telemetry systems to dynamically monitor muscle activity during training to correct gait, posture, and athletic and musical performance [22, 23]. Patients often use portable electromyographs at work or home to correct dysfunctional muscle use patterns in their natural setting (e.g., monitoring wrist flexors and extensors in repetitive strain). This is a valuable intervention for reducing computer-related disorder (CRD) at worksites [24].

Biofeedback therapists use EMG biofeedback when treating anxiety and worry, cerebral palsy, essential hypertension, fibromyalgia, headache (migraine and tension-type), low back pain, stroke, and temporomandibular muscle and joint disorder [2, 25].

Feedback Thermometer

A *feedback thermometer* detects skin temperature with a *thermistor* (a temperature-sensitive resistor) that is usually attached to a finger or toe. Thermistors function like valves that adjust the flow of electricity from the feedback thermometer in response to changes in skin temperature. As warming skin heats the probe, the valve opens and more current flows. As cooling skin chills the probe, the valve closes and current flow is reduced [14]. Skin temperature is a sluggish autonomic index of peripheral blood flow that can take 20–30 s to reflect the impact of a stressor.

Skin temperature mainly reflects *arteriole* (small muscular artery) diameter. Hand-warming and hand-cooling are produced by separate mechanisms, and their regulation involves different skills. Increased sympathetic activation associated with anxiety and hypervigilance can produce vasoconstriction and hand-cooling. In turn, increased parasympathetic activation indirectly dilates the arterioles and warms the fingers and hands through the release of vasodilating agents like nitric oxide, epinephrine, and atrial natriuretic hormone [26]. In temperature biofeedback, a patient watches temperature displays with at least one-tenth of a degree resolution that are updated at least every few seconds. Clinicians may train clients to achieve bidirectional control in which they master voluntary hand-cooling and hand-warming.

Normal finger temperatures exceed 88 °F (31 °C), and toe temperatures reach about 85 °F (29 °C) in 74 °F (23 °C) rooms. Clinicians can uptrain finger temperature to 95 °F (35 °C) and toe temperature to 93 °F (34 °C) [12].

The goal of temperature biofeedback is to teach clients to improve thermoregulation so that they

can maintain normal digital temperatures during stressful situations. Indirectly, temperature biofeedback enhances autonomic nervous regulation as well as circulation.

Biofeedback therapists use temperature biofeedback when treating anxiety, chronic pain, edema, essential hypertension, headache (migraine and tension), Raynaud's disease, and stress [7, 12].

Photoplethysmograph

Blood volume is the amount of blood contained in an area. This measure mainly reflects venous tone. *Blood volume pulse (BVP)* indexes rapid changes in blood flow. It is calculated as the vertical distance between the minimum value of one pulse wave and the maximum value of the next.

Blood volume pulse is detected using a *photoplethysmograph (PPG)* which measures the relative amount of blood flow through tissue using a photoelectric transducer. An infrared (7000–9000°A) light source is transmitted through or reflected off the tissue. Clinicians often place PPG sensors on a digit or earlobe and may simultaneously monitor blood volume pulse, blood volume amplitude (relative volume of blood), heart rate, and respiration during training to increase heart rate variability. A PPG can reflect the impact of a stressor in 0.5–2 s and display large-scale (>50%) changes in amplitude.

When the PPG is used to increase peripheral blood flow, the goal of biofeedback is to increase BVP amplitude so that more blood perfuses a digit. Like temperature biofeedback, BVP feedback training also enhances autonomic regulation.

Biofeedback therapists use the PPG for the same applications as temperature biofeedback. When temperature increases plateau, clinicians can switch from a feedback thermometer to the PPG for higher-resolution feedback as long as the digits are not very cold. In addition, professionals often prefer PPG sensors over ECG sensors during HRV biofeedback training. While ECG sensors more accurately detect the heartbeat, they may require skin preparation, disposable supplies, and the partial removal of clothing.

Respirometer

A *respirometer* is a flexible sensor band placed around the chest, abdomen, or both that monitors respiration effort, pattern, and rate. A respirometer measures changes in expansion by detecting changes in electrical resistance [27]. Normal resting respiration rates range from 12 to 14 breaths per minute [12].

Respirometer biofeedback has two limitations: measurements are in relative units and breathing mechanics can look correct, while end-tidal CO_2 and heart rate variability are reduced due to excessive effort. Two identical respiration curves can be associated with very different patterns of heart rate variability. For this reason, clinicians may also monitor breathing using a capnometer and SEMG sensors placed on breathing accessory muscles like the trapezius and scalene.

The goal of respiratory biofeedback is to teach clients to breathe effortlessly so that the diaphragm muscle does most of the work. This breathing pattern can increase end-tidal CO_2, optimize oxygen delivery to the tissues, and increase heart rate variability when clients breathe at rates between 4.5 and 6.5 breaths per minute that maximally stimulate their baroreceptor (blood pressure control) system.

Biofeedback therapists use respiratory biofeedback with patients diagnosed with anxiety disorders, asthma, chronic pulmonary obstructive disorder (COPD), essential hypertension, panic, and stress [2].

The Importance of Evidence-Based Practice

Best practice in biofeedback and neurofeedback must be based on the objective and systematic evaluation of outcome research. The Association for Applied Psychophysiology and Biofeedback

(AAPB) has published authoritative reviews of these interventions since 2004 based on guidelines recommended by a joint Task Force and adopted by the Boards of Directors of the Association for Applied Psychophysiology and Biofeedback (AAPB) and the International Society for Neuronal Regulation (ISNR) [28].

The efficacy standards that served as the basis for the latest guide, *Evidence-Based Practice in Biofeedback and Neurofeedback* (third ed.) [2], progress through five levels based on experimental design, sample size, and independent replication:

Level 1 – Not empirically supported (complex regional pain syndromes)
Level 2 – Possibly efficacious (cerebral palsy and stroke)
Level 3 – Probably efficacious (autism and traumatic brain injury)
Level 4 – Efficacious (adult headache and anxiety)
Level 5 – Efficacious and specific (attention deficit hyperactivity disorder)

Current Applications of Biofeedback and Neurofeedback

Since biofeedback and neurofeedback emerged in the late 1960s and 1970s, a steady stream of research studies has explored the effectiveness of biofeedback for treating medical and emotional disorders. As instrumentation has advanced, new treatment protocols have proliferated [29]. *Evidence-Based Practice in Biofeedback and Neurofeedback* (third ed.) reviews 40 disorders and problems that have been treated with biofeedback and neurofeedback and assesses the clinical efficacy of each. Fifteen applications earned the two highest ratings, efficacious or efficacious and specific. These applications, ranging from anxiety and attention deficit hyperactivity disorder to depressive disorders and diabetes mellitus to Raynaud's disease and temporomandibular joint disorders, can be considered well documented by research. Applications with the probably efficacious rating have moderate amounts of research support and can be effective for many patients. Applications with the lowest two ratings have not yet been well documented in research, but may be worth considering when the patient has failed to respond to more established treatment and after the patient has been fully informed of the relatively meager research support. Table 3 shows the current efficacy ratings for all 40 applications in the *Evidence-Based Practice in Biofeedback and Neurofeedback* [2].

Trends in Biofeedback

Consumers are increasingly incorporating biofeedback into their lives through activity trackers, smartphones, and personal training devices. Activity trackers can measure exercise type, speed, distance, duration, intensity, calories burned, heart rate, and respiration rate. They can monitor sleep duration during light sleep, REM sleep, and deep sleep, and time awake. They can also nag us when we have been inactive for too long.

Smartwatches like the Apple Watch® can perform the functions of activity trackers; can provide blood pressure, glucose, ECG, EMG, HRV, posture, skin conductance, temperature, and weight biofeedback with specialized sensors; and can now alert individuals to undetected cardiac arrhythmias like atrial fibrillation before they suffer complications like stroke.

Finally, inexpensive stand-alone devices are now available for personal HRV biofeedback, sleep biofeedback, and respiratory biofeedback.

Emerging biofeedback technology promotes *self-quantification*, in which consumers measure their inputs (steps walked), states (mood), and performance (heart rate) to increase awareness of their health and fitness and improve lifestyle choices.

BCIA Certification Sets International Standards for Education and Practice

The Biofeedback Certification International Alliance (BCIA), formerly the Biofeedback Certification Institute of America, was created in 1981 with

Table 3 Biofeedback and neurofeedback efficacy ratings

Application	Rating	Application	Rating
Adult headache	4	Functional/recurrent abdominal pain	2
Alcohol and substance abuse disorders	3	Hyperhidrosis	2
Anxiety and anxiety disorders	4	Hypertension	4
Attention deficit hyperactivity disorder (ADHD)	5	Immune function	2
Arthritis	3	Insomnia	3
Asthma	3	Irritable bowel syndrome (IBS)	4
Autism	3	Motion sickness	3
Cerebral palsy	2	Performance enhancement	3
Chemobrain	3	Preeclampsia	4
Chronic pain	1–4	Posttraumatic stress disorder (PTSD)	3
Chronic obstructive pulmonary disease (COPD)	2	Raynaud's disease	4
Constipation	4	Repetitive strain injury (RSI)	2
Coronary artery disease	2	Stroke	2
Depressive disorders	4	Temporomandibular muscle and joint disorder	4
Diabetes mellitus	2–4	Tinnitus	2
Epilepsy	4	Traumatic brain injury (TBI)	3
Erectile dysfunction	4	Urinary incontinence: children	3
Facial palsy	3	Urinary incontinence: men	3
Fecal incontinence	4	Urinary incontinence: women	3
Fibromyalgia	3	Vasovagal syncope	2

Level 1, not empirically supported; level 2, possibly efficacious; level 3, probably efficacious; level 4, efficacious; level 5, efficacious and specific

the primary mission to certify individuals who meet education, training, and ethical standards in biofeedback and neurofeedback and progressively recertify those who advance their knowledge through continuing education. In March of 2010, BCIA adopted a new name to reflect its global identity and became the Biofeedback Certification International Alliance. BCIA currently certifies professionals in 37 countries and has affiliates in Australia/New Zealand and Mexico-Hispano-América.

Professional certification is not a license to practice. BCIA Board Certification does not authorize professionals to provide services that they could not legally offer before certification [30]. Certification is a voluntary process. In contrast, licensure for specific professions is mandatory and means that a government agency has authorized an individual to use a professional designation, like psychologist, and provide treatment for diagnosed disorders within their scope of practice.

Board certification establishes that an individual has met entry-level training requirements for the practice of biofeedback. Candidates for certification who do not hold a professional license or its equivalent must stipulate that they practice under the supervision of a licensed provider when treating a medical or psychological disorder.

BCIA offers four certification programs: Biofeedback, Heart Rate Variability Biofeedback, Neurofeedback, and Pelvic Muscle Dysfunction Biofeedback. BCIA also offers a Certificate of Completion in Heart Rate Variability Biofeedback that attests to the successful completion of an accredited didactic workshop based on BCIA's blueprint, ethics coursework, and passing an exam over its content.

Summary

Biofeedback uses electronic instruments to measure physiological signals and display these signals in real time to the human subject. The trainee uses an audiovisual display to enhance self-awareness of physiological processes and to increase voluntary control over these bodily processes. Any

physiological process that can be measured and fed back to the subject can be trained. However, the levels of control achieved vary for specific physiological processes, and not all such training is clinically or educationally useful. Fortunately, several biofeedback modalities, each measuring specific physiological signals, have proven useful in medical, educational, and optimum performance settings. The most common instruments in general use are the surface EMG biofeedback measuring muscle activity, thermal biofeedback measuring peripheral temperature, electrodermal biofeedback measuring variations in skin electrical activity, EEG biofeedback measuring electrical activity in the brain, the respirometer and capnometer measuring breathing patterns, and the ECG and PPG measuring heart rate and heart rate variability. Rigorous efficacy standards provide the foundation for evidence-based practice in biofeedback and neurofeedback. The Biofeedback Certification International Alliance (BCIA) offers four certifications and one certificate of completion to promote science-based education and ethical evidence-based practice.

Cross-References

- ▶ Psychological and Cardiovascular Effects of Meditation and Yoga
- ▶ The Relationship Between Psychological Distress and Bio-behavioral Processes in Cardiovascular Disease

References

1. Peper E, Shumay DM, Moss D. Change illness beliefs with biofeedback and somatic feedback. Biofeedback. 2012;40(4):154–9.
2. Tan G, Shaffer F, Lyle R, Teo I, editors. Evidence-based treatment in biofeedback and neurofeedback. 3rd ed. Wheat Ridge: Association for Applied Psychophysiology and Biofeedback; 2016.
3. Willmarth E. Oral communication, 8 Apr 2018.
4. Khazan IZ. The clinical handbook of biofeedback: a step-by-step guide for training and practice with mindfulness. Oxford: Wiley; 2013.
5. Schwartz MS. A new improved universally accepted definition of biofeedback: where did it come from? Why? Who did it? Who is it for? What's next? Biofeedback. 2010;38(3):88–90.
6. International Society for Neurofeedback and Research. Definition of neurofeedback. 2010 [cited 15 June 2018]. Available from: https://www.isnr.org/neurofeedback-introduction
7. Shaffer F, Moss D. Biofeedback. In: Yuan C-S, Bieber EJ, Bauer BA, editors. Textbook of complementary and alternative medicine. 2nd ed. Abingdon: Informa Healthcare; 2006.
8. Gilbert C. Pulse oximetry. Biofeedback. 2012;40(4):137–41.
9. Gilbert C, Moss D. Biofeedback and biological monitoring. In: Moss D, McGrady A, Davies T, Wickramaskera I, editors. Handbook of mind-body medicine in primary care: behavioral and physiological tools. Thousand Oaks: Sage; 2003.
10. Lehrer P. Biofeedback training to increase heart rate variability. In: Lehrer PM, Woolfolk RL, Sime WE, editors. Principles and practice of stress management. 3rd ed. New York: Guilford; 2007.
11. Wheat AL, Larkin KT. A critical review. Appl Psychophysiol Biofeedback. 2010;35(3):229–42.
12. Khazan I. A guide to normal values in biofeedback. In: Moss D, Shaffer F, editors. Physiological recording technology and applications in biofeedback and neurofeedback. Wheat Ridge: Association for Applied Psychophysiology and Biofeedback; 2019.
13. Hassett JA. A primer of psychophysiology. San Francisco: W. H. Freeman; 1978.
14. Peek CJ. A primer of traditional biofeedback instrumentation. In: Schwartz MS, Andrasik F, editors. Biofeedback: a practitioner's guide. 3rd ed. New York: The Guilford Press; 2016.
15. Moss D. The anxiety disorders. In: Moss D, McGrady A, Davies T, Wickramaskera I, editors. |Handbook of mind-body medicine in primary care: behavioral and physiological tools. Thousand Oaks: Sage; 2003.
16. Toomim M, Toomim H. GSR biofeedback in psychotherapy: some clinical observations. Psychother Theory Res Pract. 1975;12(1):33–8.
17. Moss D. Psychophysiological psychotherapy: the use of biofeedback, biological monitoring, and stress management principles in psychotherapy. Psychophysiology today: the magazine for mind-body. Medicine. 1975;2(1):14–8.
18. Andreassi JL. Psychophysiology: human behavior and physiological response. 5th ed. Mahwah: Erlbaum; 2007.
19. Thompson M, Thompson L. The neurofeedback book: an introduction to basic concepts in applied psychophysiology. 2nd ed. Wheat Ridge: Association for Applied Psychophysiology and Biofeedback; 2016.
20. Stern RM, Ray WJ, Quigley WS. Psychophysiological recording. New York: Oxford University Press; 2001.
21. Bolek J. Motor learning made possible using a tool of applied psychophysiology: quantitative surface electromyography. Biofeedback. 2016;44(1):24–7.
22. Arena JG. Future directions in surface electromyography. Biofeedback. 2010;38(2):78–82.
23. Arena J, Whitfield JL. Telehealth applications of psychophysiological interventions for chronic pain disorders. In: Columbus AM, editor. Advances in

psychology research, vol. 51. Hauppauge: Nova Science Publishers; 2010.
24. Peper E, Gibney JH. Healthy computing with muscle biofeedback. New York: Mosaic Press; 2000.
25. Nestoriuc Y, Rief W, Martin A. Meta-analysis of biofeedback for tension type headache: efficacy, specificity, and treatment moderators. J Consult Clin Psychol. 2008;76(3):379–96.
26. Widmaier EP, Raff H, Stang KT. Vander's human physiology: the mechanisms of body function. Boston: McGraw-Hill; 2016.
27. Shaffer F, Combatalade D. Don't add or miss a beat: a guide to cleaner heart variability recordings. Biofeedback. 2013;41(3):121–30.
28. LaVaque TJ, Hammond DC, Trudeau D, Monastra V, Perry J, Lehrer P, Matheson D, Sherman R. Template for developing guidelines for the evaluation of the clinical efficacy of psychophysiological evaluations. Appl Psychophysiol Biofeedback. 2002;27(4):273–81.
29. Moss D, Shaffer F. Introduction: technology and advances in applied psychophysiology. In: Moss D, Shaffer F, editors. Physiological recording technology and applications in biofeedback and neurofeedback. Wheat Ridge: Association for Applied Psychophysiology and Biofeedback; 2019.
30. Shaffer F, Crawford J, Moss D. What is BCIA really? Biofeedback. 2012;40(4):133–6.

Distinguishing Cardiac from Psychological Somatic Symptoms

10

Alessandro Rodolico and Ludovico Mineo

Contents

Abstract

Chest pain is not always a matter of serious concern. It is not necessarily life-threatening as it recognizes multiple potential benign causes. However, it is often followed by psychogenic symptoms that may interfere with the diagnostic process and the therapeutic approach. A reciprocal relationship between cardiac symptoms and psychopathology has long been described. Once heart-related causes have been ruled out, physicians refer to cardialgic syndrome as non-cardiac chest pain (NCCP). Currently it is commonly described as the occurrence of chest pain, generally associated

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*,
https://doi.org/10.1007/978-3-030-28008-6_16

with other neurovegetative symptoms, in the absence of ischemia signs on functional non-invasive testing or obstructive lesions/abnormalities at coronary angiography. Thus, this clinical diagnosis should be posed only after a careful clinical and instrumental assessment aimed at excluding any possible underlying cardiovascular factor. Clearly, to successfully perform this diagnostic pathway strictly depends on the willingness of a physician to investigate and on the setting where she works. In order to facilitate the differential diagnosis, all possible causes of the pain, their risk factors, and their prognosis should be previously considered so that the best decision for the patient can be made. This chapter focuses on the differential diagnosis of NCCP mainly dwelling upon thoracic manifestations of psychogenic origin.

Keywords

NCCP · Non-cardiac chest pain · Heart · MUS · Medically unexplained symptoms · Somatization

What Causes NCCP?

First clinical pictures resembling NCCP were described by cardiologists in the mid nineteenth century. The frequent observation of cardiovascular symptoms in traumatized soldiers during the American Civil War was reported by surgeon Jacob Mendes da Costa who described a syndrome characterized by left-sided chest pain, palpitations, breathlessness, and fatigue in response to exertion [1]. Da Costa's syndrome was the first example of a series of similar syndromes, later described with various denominations such as "circulatory neurasthenia," "irritable heart," "soldier's heart," or "effort syndrome," but all classifiable as "cardiac neuroses." The common denominator of these clinical entities was represented by the occurrence of cardiovascular symptoms, without the finding of any organic or physiopathological abnormality, in individuals who had been undergoing severe stressful events.

While many authors tried to elucidate the physiopathology of these cardialgic syndromes, at least Paul Wood in his Goulstonian Lectures in 1941 suggested that the origin of the NCCP had to be detected in emotional mechanisms [2]. Since it is evident that several factors contribute to the occurrence of NCCP, an integrated approach that considers biopsychosocial factors is needed.

Given that the most frequent underlying causes of NCCP are represented by non-cardiac conditions such as gastroesophageal reflux, musculoskeletal problems, or psychiatric disorders, cardiologists and general practitioners should ideally be supported by other specialists.

In the evaluation of chest pain, it should also be considered that somatic symptoms are related to an emotional background and they influence each other. It is common that a subject who already experienced a myocardial infarction (MI) tends to misinterpret a harmless pain, attributing it to a cardiac cause and increasing his levels of vigilance toward pain-related symptoms.

At the same time, to overlook the treatment for symptoms deriving from other etiologies might result in a persistent distress [3] interfering with domestic, social, and occupational activities. Furthermore, individual functioning might be compromised by some psychological processes such as catastrophisation and avoidance behavior. These are cognitive distortions related to the belief that the heart is the source of the pain [4] and that those symptoms are uncontrollable [4].

Epidemiology

Admissions for Cardiac Versus Non-cardiac Chest Pain

Reliable data on the epidemiology of NCCP around the world are still limited also because the available studies present significant differences concerning several aspects, such as NCCP definition, sample size, sampling order, geography, and ethnic disparities. In the United States, each year over 7 million visits to the emergency department (ED) [5] and more than 27 million office visits [5] are due to chest pain, while the lifetime population prevalence of angina [6] is

much lower than the cases of non-cardiac chest pain. Prevalence of NCCP would be equally distributed between the genders, although females with NCCP tend to self-refer to ED and to consult healthcare providers more frequently compared to males. It has been observed as a decreased prevalence of NCCP with increasing age after 25 with a second peak of incidence occurring in women between 45 and 55. Compared to patients presenting an ischemic heart disease, those complaining NCCP are younger, consume greater amount of tobacco and alcohol, and are more likely to suffer from an anxiety disorder [7].

Up to date few studies have specifically investigated the natural course of NCCP. In a recent prospective observational study examining the follow-up history for adult patients referred to a Dutch emergency department with chest pain, it was found that more than 60% of the 1239 patients were discharged with NCCP diagnosis. Furthermore, the study showed that the all-cause 1-year mortality rate of patients with NCCP was 2.3% compared with 7.2% in patients with cardiac chest pain, while the occurrence of major adverse cardiac events was 5.1% versus 8.3%, respectively. Although patients with cardiac chest pain (CCP) had a higher utilization of medical resources compared to patients with NCCP, the duration of the rehospitalizations of these latter at the cardiology department was however similar to that of patients with CCP. Moreover, a proportion of 13.7% of patients with NCCP re-presented at the ED [8]. Among NCCP patients, those with NCCP of unknown origin had a longer duration of the first hospitalization, more representations at the ED, more rehospitalization in general, more outpatient department visits, more noninvasive interventions such as CT-scans, SPECT, or MRIs, and more consultations by phone and a longer outpatient department monitoring compared to the patients with NCCP of known origin, namely, patients who were discharged from the index admission with a clear non-cardiac diagnosis for their chest pain, such as pneumonia, pneumothorax, and severe gastrointestinal disorders and also benign conditions such as gastroesophageal reflux disease, musculoskeletal disorders, and psychological disorders.

Surprisingly, there are controversial data on long-term morbidity and mortality of NCCP patients. A systematic review of the literature on NCCP prognosis found mixed findings between the studies taken into account. Among the 41 studies selected, 16 supported worse outcomes in relation to cardiac morbidity and mortality, while 25 supported good outcome. These contrasting conclusions may be attributed to the heterogeneity of the study populations: studies indicating worse outcome had longer follow-up and tended to include patients of higher age and with high pre-existing cardiac risk factors; conversely articles supporting good cardiovascular outcome included young adults presenting less cardiac risk factors. One possible explanation could be that age $\geq$55 years, together with increased cardiac risk factors, could be associated with a long-term worse cardiovascular outcome compared to NCCP patients between 45 and 50 years of age with less risk factors. More studies are warranted to investigate if this risk is higher than in the general population aged $\geq$55 years without NCCP. However, all studies converged in finding a persistence of chest pain for many years in patients receiving a diagnosis of NCCP and a high prevalence of Axis I psychiatric disorders [9].

Quality of Life and Socioeconomic Burden

NCCP entails a severe reduction in quality of life, even greater in certain parameters, if compared to patients with cardiac chest pain, with a remarkable socioeconomic burden. Many NCCP patients report frequent doctors' consults and chronic intake of cardiology drugs, despite no evidence for a cardiac cause. Although only few studies have been conducted to evaluate the economic impact of NCCP, its related costs are estimated to be very high. In a Swedish study [10] aimed at presenting a detailed description of the costs of patients with NCCP (direct healthcare costs and indirect costs), the NCCP patients' annual societal cost was still lower compared to acute myocardial infarction (AMI) and angina pectoris (AP) patients (€10,068 vs. €15,989 and €14,737 per person, respectively). However, considering the high prevalence of NCCP and symptoms persistence, the cumulative annual national cost of these patients may be more burdensome.

Organic Causes of NCCP

In recent years, as a consequence of preventive care, acute coronary syndromes (ACS) are less frequent. Indeed, the percentage of patients in the emergency department (ED) with ACS has declined considerably in the United States from 23.6% in 1999–2000 to 13.0% in 2007–2008. An ACS can be ruled out for 60–90% of patients referring to an ED with chest pain, after an accurate diagnostic workup has been conducted. However, the burden of symptoms potentially suggesting ACS is high. Indeed, those symptoms are threefolds higher than other ones (abdominal, pelvic) in emergency departments [11]. Patients reporting NCCP can be subdivided in patients with and without a detectable underlying cause. It has been estimated that up to 70% of patients discharged from the ED have an underlying esophageal disease or a musculoskeletal disease or a psychiatric disorder, although in most of cases the diagnostic pathway is limited to exclude the cardiac etiology or other potential life-threatening conditions, neglecting other ones like:

- **Gastrointestinal causes**: gastroesophageal reflux disease (GERD) is very common and constitutes many episodes of NCCP. Its most common manifestation is pyrosis (burning substernal discomfort) [7]. Another less common clinical condition is esophageal hypersensitivity that generally has a functional etiology [12]. NCCP may be also due to gastritis, peptic ulcer, or diseases of gallbladder and biliary tree.
- **Pulmonary causes**: most distressing and scaring symptom suggesting a pulmonary etiology of NCCP is dyspnea that might be a sign of acute cardiac failure. Pulmonary causes of NCCP include pleuritis, pneumonia, intrathoracic masses, pneumothorax, and pulmonary embolism.
- **Musculoskeletal causes**: they are very common representing nearly half of all non-emergent cases of chest pain [13]. The most frequent musculoskeletal causes of NCCP are represented by costochondritis and rheumatic diseases such as fibromyalgia, rheumatoid arthritis, and polychondritis. Less frequently, musculoskeletal chest pain may be caused by relatively rare conditions like lower rib pain syndrome, xiphoidalgia, Tietze's syndrome, and stress fractures.
- **Systemic and miscellaneous causes:** other possible causes of NCCP include drug-induced pain, sickle cell diseases, herpes zoster, and neoplasms.

Other candidate causes that should be considered in differential diagnosis of non-cardiac chest pain are listed in Table 1.

Nonorganic Causes of NCCP

Misdiagnosis and Impact on Economic Resource Consumption

Economic resource consumption by subject affected by NCCP is high [14]. It has been estimated that the overall cost to assess and exclude life-threatening causes in these patients range between $315 million and $1.8 billion per year [15]. Even if cardiologists know that the risk linked to NCCP and myocardial infarction or premature death is close to zero [16], an inaccurate diagnosis might determine a chronicization of the disease [17] with a heavy burden on everyday patient socio-professional functioning that might determine lost workdays [16]. Patients affected by NCCP reach poor scores in QoL questionnaires as well as patient with coronary heart disease (CAD) [18]. Among the factors underpinning poor quality of life in NCCP patients are social withdrawal, avoidance of activities that can elicit or exacerbate symptomatology, and the presence of comorbid psychiatric conditions such as anxiety and depression. Additionally the pain might become the main focus of the life of these patients, continuously looking for a diagnosis of an organic disease [19], while the cause is often a psychogenic condition such as anxiety. Other psychiatric conditions that might lead to chest-related suffering are somatic delusions that can be present in psychotic depression and in schizophrenia.

Table 1 Other causes of NCCP

Musculoskeletal	Gastrointestinal	Pulmonary	Miscellaneous
Costochondritis	Pancreatic	Lung cancer	Pulmonary hypertension
Tietze's syndrome	Biliary tree	Pneumonia	Pericarditis and myocarditis
Precordial catch syndrome	Gastric	Pneumothorax and pneumomediastinum	Aortic disorders
Fibromyalgia	Intra-abdominal masses (benign and malignant)	Sarcoidosis	Drug-induced pain
Slipping rib syndrome		Intrathoracic masses (benign and malignant)	Herpes zoster
			Psychological disorders
		Pleural effusions	Sickle cell crisis
		Pulmonary embolus	

Anxiety and the Body

In its clinical presentation, anxiety is followed and maintained by fear and anguish. On the basis of the intensity of these feelings, the anxious subject relates himself with the world. It should be clear that anxiety and fear are different; indeed the latter is a useful feeling designed to fight against something really harmful, while this beneficial function cannot be recognized in the former. When the subject tries to challenge anxiety, this often leads to persistent ruminations, without overcoming the problem. The body of the phobic person is often the first target of these pathologic cognitive and emotional issues. The contact with the body is persistent and inescapable, and this might be the reason for the strict connection between anxiety-related diseases and thoracic pain.

In the light of the exceptional nature of the event, it is very common that a patient suffering from a myocardial infarction experiences anxiety during the episode; nevertheless it resolves spontaneously. If the disorder is mainly psychogenic, it might persist with various degrees of intensity and duration.

Cardiac Manifestations and Generalized Anxiety Disorder

There is some literature that investigated the comorbidity between generalized anxiety disorder (GAD) and NCCP that found a spread range of co-prevalence from 5.7% to over 30% [20, 21]. A recent work investigated a candidate biological cause of NCCP in subjects also affected by anxiety. The authors [22] found that in presence of anxiety and NCCP, vitamin D levels are reduced, suggesting to consider this aspect in presence of this condition. On the other hand, GAD is often accompanied by panic disorder [23], whose painful symptoms often concern thoracic areas.

Cardiac Symptoms in Panic Disorder

Panic is an extreme form of fear. A panic attack is quantitatively and qualitatively different from anxiety. It is described as an overwhelming and vague sense of imminent death or doom. According to the definition of the DSM-5, panic disorder is characterized by more than one unexpected panic attacks for more than a month, followed by a significant maladaptive behavior related to the attacks (such as avoidance of exercise or other anxiogenic situation). Panic disorder (PD) may be a trigger of NCCP. Chest pain, associated with difficulty to breath properly, is a very common complaint among PD patients [24]. Indeed, between a percentage ranging from 25% to 60% of NCCP cases result to be a manifestation of a panic attack [25]. However it should be noted that PD per se might increase the risk of coronary heart disease (CHD) and myocardial infarction, while it is not demonstrated in the contrary [26]. Atypical quality of chest pain, female gender, younger age, high levels of self-reported anxiety, and the absence of known CAD are among the

factors orientating the diagnosis toward a panic attack [27].

Cardiac Symptoms in Post-traumatic Stress Disorder

Despite its relocation from anxiety disorder section in DSM-IV-TR (Text Revision) to trauma- and stressor-related disorders section of the DSM-5, anxiety is a common and severe symptom in subjects affected by post-traumatic stress disorder (PTSD). This psychopathological condition is the consequence of the exposure to a terrible traumatic event, where patient life had been in danger. It is accompanied by physiologic arousal that induces a sympathetic activation that determines an increase in cardiac activity. Poor data from literature is available on comorbidity between PTSD and NCCP. It is acquired that there is a reciprocity between PTSD and heart-related pain syndromes like coronary heart disease (CHD) development [28].

Thus, the manifestation of PTSD symptoms and ACS is close and might be challenging to differentiate them. As a consequence, it is essential to assess if the occurrence of chest pain might be related to a hyperarousal state triggered by a stimulus resembling aspects of the past traumatic event.

Major Depressive Disorder

The term melancholia was used by ancient Greeks to define an excess of "dark bile" that was one of the four humors (also including blood, yellow bile, and phlegm). Nowadays it is used to describe a particular way of feeling of the depressed patient, marked by the loss of affective resonance. Those patients often describe an altered way of experience of the body whose vitality is lost. In this context, somatic symptoms including chest pain are often part of the depressive syndrome. Indeed, the onset of a major depressive disorder may be associated with the exacerbation of a pre-existing physical complaint or with the occurrence of a new unexplained somatic symptom. Conversely, the prevalence of depressive symptoms in NCCP patients ranges from 9% to 40% [29], suggesting a bidirectional and mutual association between these conditions. Anyway, frequency and severity of depressive symptoms are higher and roughly similar in patients affected by both cardiac and non-cardiac chest pain compared to healthy individuals.

Somatic Symptoms

If not related to another mental disorder, psychogenic NCCP may be correctly considered as a type of medically unexplained symptoms (MUS) that is theoretically and clinically part of the broader concept of somatization. The terms MUS and somatization refer to somatic symptoms that cannot be fully explained by an underlying physiopathological process. These terms can also be used when symptom burden is excessive commensurate to the underpinning organic condition.

The presence of MUS still represents a key feature of somatic symptom disorder (SSD) diagnosis of the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5), although new DSM-5 criteria for SSD no longer require that somatic symptoms must be medically unexplained [30] (as it was for the diagnosis of somatization disorder in DSM IV-TR) [31]. The emphasis is instead posed on how much the severity of symptoms is out of proportion to what expected. It is common in ambulatorial clinical practice to encounter this patient recurrently. They often exhibit their malaise in a dramatic way, partially as a consequence of the need of complaining their suffering to others.

The prevalence of somatic symptoms and related disorders in the general population is only 1–3% [32]; however, it is probably underestimated. As an illustration, one large epidemiological study of chronic pain in the United States found a prevalence of 15% [33]. The percentage of NCCP cases attributable to somatic symptom and related disorders has not been formally estimated, but clinical experience suggests that it is not insignificant.

Illness Anxiety Disorder

The differential diagnosis between somatic symptom disorder and illness anxiety disorder (IAD) is based on the actual presence of symptoms versus the preoccupation of developing an illness, respectively. It is difficult to reassure these patients, and they quickly lose faith on what has been told them. Patients affected by IAD usually present a variety of somatic preoccupations affecting multiple organ systems. Some patients focus their worries on the occurrence of cardiac clinical manifestations. However, the prevalence of IAD in NCCP is unknown.

Among illness anxiety disorder spectrum, "cardiophobia" is the fear of having a cardiac problem with a consequential overestimation of heart-related symptoms like palpitations or transient thoracic pain [34]. Subjects tend to avoid physical activities because of their apprehension toward somatosensory and cardiopulmonary sensations that are interpreted as potential signs of a major coronary heart disease [35]. Individuals affected by this disorder tend to reject any psychosocial explanation of their condition, and this behavior tends to postpone and even compromise an appropriate treatment [36]. In order to asses symptoms linked to cardiophobia and other heart-focused anxiety, the Cardiac Anxiety Questionnaire (CAQ) has been created [37]. Patients affected by psychogenic conditions have higher scores in the questionnaire than health population [38]. Not receiving a cardiac diagnosis can heighten worry about chest pain and possibly contributing to weaken quality of life.

Schizophrenia Spectrum Disorders

Differential diagnosis might be challenging in some psychotic patients who are affected by body-image disturbances and somatic delusions. Even though hypochondriacal delusion is more common in psychotic depression, some acute and chronic schizophrenic patients might experience these symptoms [39]. As it has been shown by the Australian national survey of psychosis in 2010, this issue is relevant because this subgroup of patients often has a heavy burden of CVD risk factors [40] and is twice as likely to have coronary heart disease. Among those factors a very common one is dyslipidemia, which is linked to the illness courses and to some second-generation antipsychotics (SGAs), especially olanzapine, risperidone, and paliperidone. These drugs indeed increase triglycerides and reduce high-density lipoprotein cholesterol (HDL-C), whose dose changes are well-known risk modifiers of CVD. Moreover, use of SGAs has a well-established hyperglycemic effect that might be responsible for microvascular damage at the coronary level. The heart-related hypochondriacal delusions have not been investigated, neither differential diagnosis with cardiac chest pain. It might be useful to dedicate attention to the topic, taking into account the potential consequences of a misdiagnosis in these high-risk patients.

Psychological Perspective

The high occurrence of NCCP in anxiety and somatoform disorders led to refer to the empirically supported models of these conditions in the building of a theoretical model for NCCP. A seminal contribution to the psychological perspective of NCCP is represented by early works by G.H. Eifert on cardiophobia [41], described as a syndrome characterized by repeated complaints of chest pain, heart palpitations, and other somatic sensations accompanied by fears of having a heart attack and of dying. People suffering from this condition tend to focus attention on their heart in stressful situations. They show a phobic attitude in perceiving and interpreting the function of their heart and persist in believing that they are affected by an organic disease, engaging into ruminations and avoidance behaviors. Therefore, Eifert considered cardiophobia as a particular type of anxiety disorder and proposed an integrative and complex psychobiological model in which previous learning conditions related to experiences of separation and cardiac disease lead to particular deficits in basic behavioral patterns. Deficient and inappropriate personality repertoires would result in a psychological vulnerability for the development and maintenance of cardiophobia since they

affect future behaviors and responses to life stressors, in particular separation or loss experiences (actual or potential), current or recent illness of self or close others, overwork, and work conflicts. Furthermore, a significant role in mediating the impact of such stressors would be also mediated and exacerbated by biological vulnerability factors including chronic hyperarousal, hyperventilatory breathing, mild coronary spasm, and acquired changes in the perception and processing of pain stimuli (nociception) of the chest intercostal muscles. Thus, both psychological and biological factors would mutually interact in determining the clinical features of cardiophobia, as triggering stressors occur. Symptoms of cardiophobia were grouped by Eifert in three clusters:

1. Physiological symptoms encompassing chest pain, heart palpitations, and respiratory symptoms (dyspnea, hyper-ventilatory breathing)
2. Affective-cognitive symptoms encompassing intense fear of heart attack or dying, obsessive belief of suffering from a heart disease, and anxious apprehension
3. Behavioral consequences encompassing compulsive reassurance and help seeking, excessive medical consults, and avoidance behaviors (Fig. 1)

Drawing partially upon Eifert's works, Richard Mayou formulated an etiological model for cardiac functional symptoms but potentially applicable to all functional somatic symptoms [42]. A key component of this conceptualization is represented by an abnormal interpretation of bodily sensations with a tendency to the catastrophization of relatively benign symptoms. One of the psychological factors underlying and maintaining this cognitive distortion is anxiety sensitivity, a dispositional variable distinguishable from trait anxiety. It consists in the specific attitude to fear anxiety-related physiological sensations since they are believed to signal impeding harm [43]. People with high anxiety sensitivity tend to attribute a harmful meaning to certain bodily sensations, probably also because of a higher interoceptive sensitivity [44]. Consequently, coherently with this model, individuals with NCCP may consider heart palpitations or a transient harmless thoracic pain as an imminent catastrophic heart attack, while people with low anxiety sensitivity will probably consider these sensations as simply disturbing. Several studies have shown that NCCP patients fear cardiopulmonary symptoms as much as cardiopathic patients. Moreover, the severity of their cardiac complaints is strictly correlated with the level of heart-related fears [45]. From an affective-cognitive perspective, the relation between fears of cardiac problems and physical complaints may be established by this sequence of processes:

1. Labelling: whenever a patient feels a thoracic pain, it is interpreted as an approaching heart attack. This label is a source of fear able to elicit in turn a physical symptom.
2. Anticipation: even in absence of any complaint, these may be anticipated, provoking a feeling of anxiety. Consequently, any feeling induced by this anticipation could be labelled as a thoracic complaint.
3. Attention: labelling and anticipation processes may lead the patients to focus on specific parts of the body. Perception threshold is decreased, and a large number of interoceptive sensations become perceptible. This relation can be strengthened and maintained by hyperventilation [46].

Another psychological factor putatively involved in NCCP etiology is alexithymia. Alexithymia is a personality construct characterized by deficits in identifying, discriminating, and describing emotions [47]. Since individuals with alexithymia present a marked dysfunction in emotional processing and have not a full awareness of the well-established relationship between affective states and physiological neurovegetative alterations, they tend to experience these latter not as bodily emotional responses but as undifferentiated, disturbing, and unexplainable physical sensations. In a second step, these physical sensations may be misinterpreted as symptoms of an organic condition [48]. Thus, this inappropriate attribution may make individuals with alexithymia more likely to complain NCCP and to seek medical

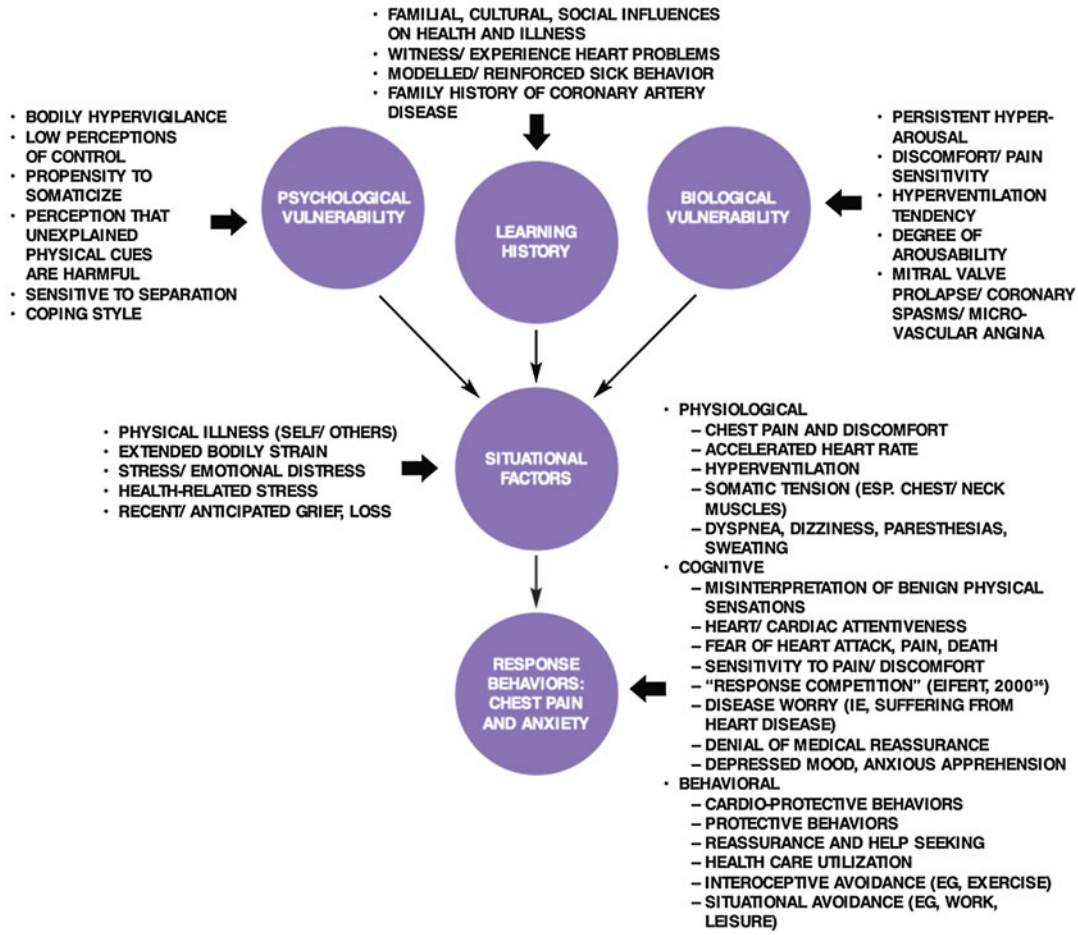

Fig. 1 Factors of non-cardiac chest pain, with permission of Kamila S. White [74]

evaluation. Indeed, the few studies that investigated the contribution of alexithymia [49] to NCCP reported high alexithymia scores in NCCP patients [50]. Although alexithymia and anxiety sensitivity have in common a misinterpretation of benign physical sensations (tendency to concentrate on physical alterations tied to emotional arousal, in alexithymia; tendency to focus on anxiety-related symptoms on the basis of beliefs on their harmfulness, in anxiety sensitivity) with a following attribution of their origin to a putative organic illness, they are two distinct constructs, only moderately correlated [51]. They act as unique but related psychological vulnerability factors for recurrent pain in patients with NCCP. In particular it has been hypothesized that anxiety sensitivity may be associated with secondary alexithymia, defined as a coping mechanism against highly emotional events [52] and consisting in a drastic reduction of emotional range. Indeed, the fear of anxiety-related sensations may lead to an emotional restriction intended as a coping mechanism.

The psychodynamic understanding of medically unexplained symptoms finds its roots in Jean-Martin Charcot's studies conducted in the nineteenth century in the Hôpital universitaire Pitié-Salpêtrière, where the neurologist used the term hysteria. Then, the topic had been investigated by the father of psych*o*analysis, Sigmund Freud, who hypothesized that somatic symptoms

might derive from a conflict between desire and reality activating a conversive "defense mechanism." In this sense the physical manifestation substitutes a repressed feeling, and the complained symptom is endowed with a symbolic meaning related to the psychodynamic conflict. Janet in the early twentieth century used the term dissociation to refer to unintegrated experiences. According to the theory proposed by Janet, the somatic manifestation represented the way to express unexplainable emotions linked to a traumatic event. The term that is now commonly used, somatization, was coined by Wilhelm Stekel, a psychoanalyst and Freud's pupil, in 1924. Thus, according to the psychodynamic perspective, somatoform disturbances might be attributed to a mental conflict, to a structure deficit, or both. The weakness of "structure" is referred to the personality of a subject, who is not adequately able to cope with environment requests. The conflict may be experienced physically as pain, even if there is not an underlying biological basis behind it. Psychodynamic interpretation of cardiophobia has not been enough investigated. Among the authors who studied the cardiophobia, Ermann [53] proposed a model based on the disproportion between the personal ambitions and their achievability. The subject might experience anxiety that he will probably regret, and, as a consequence, he might feel guilty when the pursuit is prohibited by his own conscience. The consequence of this inner contrast is self-punishment like cognitive distortions about cardiac health. In addition, according to the author, the patients' feeling of blameworthiness might also result from the conflict between the desire of independence from the mother and the persisting need of maternal protection. During the therapeutic process, the psychotherapist helps the patient to make a connection between their somatizations and their removed feelings and desires.

Contributions of Personality

It has been hypothesized that some personality traits, such as aggressiveness, social inhibition, and neuroticism, may play a role in cardiovascular health and in persistent chest pain. A correlation between personality structure and cardiovascular risk was for the first time theorized in the late 1950s by American cardiologists Meyer Friedman and Ray Rosenman. They argued that a particular type of personality, called type A behavior pattern (TABP) – characteristic of highly competitive, ambitious, and aggressive individuals – could represent a risk factor for coronary heart disease (CHD) [54]. However, the first positive findings supporting this correlation [55] have not been replicated, and many subsequent reviews have rejected the hypothesis that TABP may be causally linked with CHD onset or outcome [56]. Although some studies have found that type A cardiac patients tend to exhibit a complaining behavior and report a more severe chest pain compared to patients with similar coronary disease [57], the relationship between NCCP and TABP has not been adequately investigated.

In more recent times, the potential contribution of personality to cardiac health has been widely emphasized by several works suggesting a correlation between "type D" (distressed) personality – characterized by the combination of the tendency to experience negative emotions (negative affectivity) and the tendency to inhibit self-expression in social interaction (social inhibition) – and worse cardiac outcomes together with an impaired self-reported physical and mental health [58]. Nevertheless, these findings have not been replicated in larger studies. With specific regard to NCCP, a recent observational study, conducted on a large sample of patients without CAD derived from the TweeSteden Mild Stenosis study cohort, found a significant association between persistent chest pain and type D personality in patients with non-obstructive CAD [59].

The differences in personality and psychological profile of subjects with NCCP and CAD were investigated in a cross-sectional study involving patients requiring cardiac consultation for persistent chest pain. Looking at personality profiles, explored in accordance to the Big 5 model, the only significant data was a reduced score of NCCP patients on the emotional control subscale [60].

Further studies of possible associations between personality traits and NCCP are warranted.

Implication of Psychogenic Symptoms on Chest Pain Diagnosis and Treatment Guidelines

In Emergency Setting

The undeferrable priority in patients referring to the ED with chest pain must first be centered on monitoring the hemodynamic situation and excluding potentially fatal causes. In the presence of unstable vital parameters, an assessment of respiratory and cardiocirculatory function should be carried out immediately after an early hemodynamic stabilization. The clinical presentation of the patient should orientate the diagnostic algorithm and the sequence of instrumental investigations (e.g., electrocardiogram ECG, echocardiogram, chest x-ray CXR,) in order to identify life-threatening conditions such as acute coronary syndromes, aortic dissection, acute myocarditis, pericarditis, pulmonary embolism, tension pneumothorax, and, less frequently, Boerhaave's syndrome. In a patient with stable hemodynamic parameters, in addition to the evaluation of the clinical history and a detailed physical examination, the most accredited diagnostic algorithms recommend a resting 12-lead ECG, dosage of cardiac and coagulation markers. Chest x-ray or chest computed tomography (CT) should be performed in order to exclude other diagnosis if recommended workup for myocardial ischemia has been negative. In summary, in front of a patient with acute chest pain, unstable vital parameters, an abnormal ECG pattern, or other signs and symptoms suggestive of a coronary syndrome (e.g., escalating chest pain, diaphoresis) warrant referral as an emergency. Otherwise, ECG and potential further checks should be reserved to patients reporting new onset or worsening chest pain without any evident cause [61, 62]. Differentiating angina from NCCP on the sole basis of clinical and semeiological features is challenging. Patients with NCCP usually describe a typology of pain and a pattern of pain irradiation which are indistinguishable from cardiac-related chest pain. This is complicated by the fact that patients with history of coronary artery disease (CAD) may also experience NCCP. Consequently, a first cardiological evaluation is non-delayable. Recently some doubts emerged over the utility of troponin test in the diagnostic algorithm of cardiac chest pain. A recent retrospective study found that most of elevated troponin test results were found in absence of electrocardiographic changes or chest pain, leading the authors to conclude that this marker has no clinical utility and it results in costly increased downstream evaluations. Thus, this marker might be elevated also in NCCP.

However, some slight differences have been observed in the patients' attitude during an episode of chest pain. NCCP patients tend to report a higher rate of chest pain occurrence and a more severe pain intensity. Furthermore, NCCP is commonly associated with a thoracic respiratory pattern characterized by overt hyperpnea ("hyperventilation"), generally precipitated by psychophysiological processes such as panic or stress arousal. It has also been reported that NCCP patients usually describe their current critical situation using more sensory and affective words, compared to patients with ischemic heart disease [7].

It is worth highlighting that emergency physicians often have a negative attitude toward psychiatric patients presenting to an emergency department reporting physical symptoms [63]. This prejudice could lead to a summary patient's assessment with a premature but harmful closure of the differential diagnosis, since psychiatric comorbidity represents well-established risk factors for several medical illnesses, including cardiovascular diseases.

In Non-emergency Setting

After a cardiac disease or a life-threatening condition has been excluded, a clinical challenge is represented by the choice of the appropriate diagnostic test to apply in order to discriminate patients with non-specific chest pain and other underlying diseases, including NCCP as possible manifestation. As previously mentioned, almost 90% of patients discharged from the ED with NCCP diagnosis complain persistent and recurring thoracic pain, and up to 80% of them had

consulted a healthcare provider (generally a general practitioner) in the year previous to the ED admission [64]. A recent US-based survey showed that almost 50% of the patients diagnosed with NCCP in the ED consult at least a cardiologist in the subsequent months. Of those NCCP patients who were referred, 45.9% were sent back to the general practitioner, only 29.3% to a gastroenterologist, and less than 10% to a psychiatrist or a clinical psychologist [65].

Management of patients with chronic persistent NCCP may be particularly difficult, time- and resources-consuming, also because of the absence of specific diagnostic and therapeutic guidelines. A multidisciplinary team-based approach to the evaluation and treatment of this class of patients represents a feasible and potentially effective care model.

Implementation of this organizational protocol within the context of pre-existing "rapid access chest pain clinics" – already active in United Kingdom and originally developed to manage new-onset angina – has been proposed by Marks and colleagues [66], promoting the need of a biopsychological approach. According to this view, biological, psychological, and social factors are strictly mutually interrelated, requiring a holistic attitude, as each one contributes to patients' clinical presentation [67].

Thus, based on this biopsychosocial theoretical framework, they planned a stepped-care management program for NCCP patients combining [68]:

- Preliminary cardiological evaluation
- Evaluation for other potential causes of persistent non-acute chest pain (pulmonary, gastrointestinal, musculoskeletal, rheumatological) by multiple medical specialists
- Systematic evaluation for potential psychiatric disorders in comorbidity using specific screening and assessment tools (Table 2)
- Psychological consult with possible referral to cognitive behavioral therapy (CBT) if considered as appropriate

Reassuring patients constitutes a crucial step of this management program, regardless of the actual presence of underlying medical causes. Indeed, in some cases psychological factors may shape the intensity and features of pain perception, while in others psychological dynamics are predominant without evidence of a medical condition. Reassurance should be given adopting a biopsychosocial formulation: timing and method of delivery represent significant factors in order to strengthen its efficacy [69]. Providing patients with clear explanation of symptoms, plausible clarifications of the likely determinants, and possible outcomes appears to lessen patients' preconceived concerns

Table 2 Screening and assessment tools for psychiatric conditions

Instrument	Format	Lenght
General psychiatric screening		
Brief symptom inventory (BSI)	Self-report	53 items
Hospital Anxiety and Depression Scale (HADS)	Self-report	14 items
Health-related quality of life (short form SF-36)	Self-report	20 items
Brief Psychiatric Rating Scale-expanded (BPRS)	Self-report, interview	18 items, variable
Brief cognitive screening		
Mini-mental state examination-modified	Interview	12 min
Neurobehavioral Cognitive Status Examination (CSE)	Interview	45 min
Affective and anxiety disorders		
Beck anxiety inventory	Self-report	21 items
Beck depression inventory-II	Self-report	25 items
Primary care evaluation of mental disorders (PRIME-MD)	Self-report, Interview	10 min
Anxiety disorders interview schedule for DSM-IV (ADIS-IV)	Interview	≈60 min
Structured clinical interview for DSM-IV (SCID-IV)	Interview	≈60 min

and catastrophic thoughts regarding the origin of the chest pain [70]. It is recommendable to use well-accepted and comfortable words [71, 72], not to minimize patients' worries and anguish about the nature of symptoms, explicitly recognizing that their condition is real and disabling.

Schematically, after the assessment phase and an adequate "reassuring comfort," management of these patients should include:

- Prescription of appropriate medications if an organic cause other than cardiac ones has been detected
- Deep breathing exercises and techniques for stress relief [73]
- Addressing cognitive distortions by means of CBT
- Referral to specialist mental health services

Conclusions

Non-Cardiac Chest Pain is a common condition. Its correct interpretation is essential not only to exclude more severe clinical outcomes but also to help patients properly. The approach of Medically Unexplained Syndromes offers a practical framework to support the clinician in prognostic pathways. Similarly, it is remarkable the effort of psychodynamic authors to identify the core aspects of somatization that they used to contextualize clinical pictures similar to NCCP. Regardless of the theoretical reference framework, this research area should be better investigated to increase diagnostic and therapeutic evidence.

References

1. Da Costa JM. On irritable heart. Am J Med. 2004;11(5):559–67. [Internet]. Available from: https://www.sciencedirect.com/science/article/pii/0002934351900381
2. Wood P. Da Costa's syndrome (or effort syndrome). Lecture I. Br Med J. 1941;1(4194):767–72. [Internet]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20783672
3. Bass C, Wade C, Hand D, Jackson G. Patients with angina with normal and near normal coronary arteries: clinical and psychosocial state 12 months after angiography. Br Med J (Clin Res Ed). 1983;287(6404):1505–8. [Internet]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/6416475
4. Dumville JC, MacPherson H, Griffith K, Miles JNV, Lewin RJ. Non-cardiac chest pain: a retrospective cohort study of patients who attended a rapid access chest pain clinic. Fam Pract. 2007;24(2):152–7. [Internet]. Available from: https://academic.oup.com/fampra/article-lookup/doi/10.1093/fampra/cmm002
5. Meguire P. Discovering boundary algebra: a simple notation for Boolean algebra and the truth functions. Int J Gen Syst. 2003;32(1):25–87. [Internet]. Available from: http://www.cdc.gov/nchs/data/ahcd/2015_NHAMCS_AS_PRF_Sample_Card.pdf
6. Hemingway H, Langenberg C, Damant J, Frost C, Pyörälä K, Barrett-Connor E. Prevalence of angina in women versus men. Circulation. 2008;117(12):1526–36. [Internet]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18347213
7. Fass R, Achem SR. Noncardiac chest pain: epidemiology, natural course and pathogenesis. J Neurogastroenterol Motil. 2011;17(2):110–23. [Internet]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21602987
8. Mol KA, Smoczynska A, Rahel BM, Meeder JG, Janssen L, Doevendans PA, et al. Non-cardiac chest pain: prognosis and secondary healthcare utilisation. Open Heart. 2018;5(2):e000859. [Internet]. Available from: http://openheart.bmj.com/lookup/doi/10.1136/openhrt-2018-000859
9. Meresh E, Piletz J, Halaris A. Noncardiac chest pain: systematic review of the literature on prognosis. Res Rep Clin Cardiol. 2018;9:1–9. [Internet]. Available from: https://www.dovepress.com/noncardiac-chest-pain-systematic-review-of-the-literature-on-prognosis-peer-reviewed-article-RRCC
10. Mourad G, Alwin J, Strömberg A, Jaarsma T. Societal costs of non-cardiac chest pain compared with ischemic heart disease – a longitudinal study. BMC Health Serv Res. 2013;13(1):403.
11. Bhuiya FA, Pitts SR, McCaig LF. Emergency department visits for chest pain and abdominal pain: United States, 1999–2008. NCHS Data Brief. 2010;(43):1–8. [Internet]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20854746
12. Park SH, Choi JY, Park EJ, Lee JJ, Lee S, Na JO, et al. Prevalence of gastrointestinal diseases and treatment status in noncardiac chest pain patients. Korean Circ J. 2015;45(6):469–72. [Internet]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26617648
13. Svavarsdóttir AE, Jónasson MR, Gudmundsson GH, Fjeldsted K. Chest pain in family practice. Diagnosis and long-term outcome in a community setting. Can Fam Physician. 1996;42:1122–8. [Internet]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8704488
14. Leise MD, Locke GR, Dierkhising RA, Zinsmeister AR, Reeder GS, Talley NJ. Patients dismissed from the hospital with a diagnosis of noncardiac chest pain: cardiac outcomes and health care utilization. Mayo Clin Proc. 2010;85(4):323–30. [Internet]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20194143

15. Wilhelmsen L, Rosengren A, Hagman M, Lappas G. "Nonspecific" chest pain associated with high long-term mortality: results from the primary prevention study in Goteborg, Sweden. Clin Cardiol. 1998;21(7):477–82. [Internet]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9669056
16. Fagring AJ, Lappas G, Kjellgren KI, Welin C, Manhem K, Rosengren A. Twenty-year trends in incidence and 1-year mortality in Swedish patients hospitalised with non-AMI chest pain. Data from 1987-2006 from the Swedish hospital and death registries. Heart. 2010;96(13):1043–9. [Internet]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20483906
17. Chambers J, Christopher B. Chest pain with normal coronary anatomy: a review of natural history and possible etiologic factors. Prog Cardiovasc Dis. 1990;33:161–84. [Internet]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2236564
18. Ortiz-Garrido O, Ortiz-Olvera NX, González-Martínez M, Morán-Villota S, Vargas-López G, Dehesa-Violante M, et al. Clinical assessment and health-related quality of life in patients with non-cardiac chest pain. Rev Gastroenterol Méx. 2015;80(2):121–9. English Ed [Internet]. Available from: http://linkinghub.elsevier.com/retrieve/pii/S2255534X15000493
19. Shelby RA, Somers TJ, Keefe FJ, Silva SG, McKee DC, She L, et al. Pain catastrophizing in patients with noncardiac chest pain: relationships with pain, anxiety, and disability. Psychosom Med. 2009;71(8):861–8. [Internet]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19737857
20. Al-Ani M, Winchester DE. Prevalence and overlap of noncardiac conditions in the evaluation of low-risk acute chest pain patients. In: Critical pathways in cardiology [Internet]. 2015. p. 97–102. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26214812
21. Hocaoglu C, Gulec MY, Durmus I. Psychiatric comorbidity in patients with chest pain without a cardiac etiology. Isr J Psychiatry Relat Sci. 2008;45(1):49–54. [Internet]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18587169
22. Alkhatatbeh MJ, Abdul-Razzak KK, Amara NA, Al-Jarrah M. Non-cardiac chest pain and anxiety: a possible link to vitamin D and calcium. J Clin Psychol Med Settings. 2018;0(0):0. [Internet]. Available from: https://doi.org/10.1007/s10880-018-9579-2
23. Carter CS, Servan-Schreiber D, Perlstein WM. Anxiety disorders and the syndrome of chest pain with normal coronary arteries: prevalence and pathophysiology. J Clin Psychiatry. 1997;58(Suppl 3):70–3; discussion 74–5. [Internet]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9133495
24. Barlow DH, Vermilyea J, Blanchard EB, Vermilyea BB, Di Nardo PA, Cerny JA. The phenomenon of panic. J Abnorm Psychol. 1985;94(3):320–8. [Internet]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/4031229
25. Dammen T, Arnesen H, Ekeberg O, Husebye T, Friis S. Panic disorder in chest pain patients referred for cardiological outpatient investigation. J Intern Med. 1999;245(5):497–507. [Internet]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10363751
26. Tully PJ, Turnbull DA, Beltrame J, Horowitz J, Cosh S, Baumeister H, et al. Panic disorder and incident coronary heart disease: a systematic review and meta-regression in 1 131 612 persons and 58 111 cardiac events. Psychol Med. 2015;45(14):2909–20. [Internet]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26027689
27. Huffman JC, Pollack MH. Predicting panic disorder among patients with chest pain: an analysis of the literature. Psychosomatics. 2003;44(3):222–36. [Internet]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12724504
28. Edmondson D, Kronish IM, Shaffer JA, Falzon L, Burg MM. Posttraumatic stress disorder and risk for coronary heart disease: a meta-analytic review. Am Heart J. 2013;166(5):806–14. [Internet]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24176435
29. Webster R, Norman P, Goodacre S, Thompson A. The prevalence and correlates of psychological outcomes in patients with acute non-cardiac chest pain: a systematic review. Emerg Med J. 2012;29(4):267–73. [Internet]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22034535
30. American Psychiatric Association. DSM-5. Diagnostic and statistical manual of mental disorders. 2013. 4–5 p. Arlington, VA: Author
31. American Psychiatric Association. DSM-IV. Diagnostic and statistical manual of mental disorders 4th edition TR. 2000. p. 210, 373–374. Arlington, VA: Author
32. Boone K. Somatoform disorders, factitious disorder, and malingering. In: The little black book of neuropsychology [Internet]. Boston: Springer US; 2011. p. 551–66. Available from: http://link.springer.com/10.1007/978-0-387-76978-3_18
33. Hamilton JC, Eger M, Razzak S, Feldman MD, Hallmark N, Cheek S. Somatoform, factitious, and related diagnoses in the national hospital discharge survey: addressing the proposed DSM-5 revision. Psychosomatics. 2013;54(2):142–8. [Internet]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23274011
34. Zvolensky MJ, Feldner MT, Eifert GH, Vujanovic AA, Solomon SE. Cardiophobia: a critical analysis. Transcult Psychiatry. 2008;45(2):230–52. [Internet]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18562494
35. Hadlandsmyth K, White KS, Krone RJ. Quality of life in patients with non-CAD chest pain: associations to fear of pain and psychiatric disorder severity. J Clin Psychol Med Settings. 2013;20(3):284–93. [Internet]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23338745
36. Barsky AJ. Clinical practice. The patient with hypochondriasis. N Engl J Med. 2001;345(19):1395–9. [Internet]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11794173

37. Eifert GH, Thompson RN, Zvolensky MJ, Edwards K, Frazer NL, Haddad JW, et al. The cardiac anxiety questionnaire: development and preliminary validity. Behav Res Ther. 2000;38(10):1039–53. [Internet]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11004742
38. Marker CD, Carmin CN, Ownby RL. Cardiac anxiety in people with and without coronary atherosclerosis. Depress Anxiety. 2008;25(10):824–31. [Internet]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17597101
39. McGilchrist I, Cutting J. Somatic delusions in schizophrenia and the affective psychoses. Br J Psychiatry 1995;167(SEPT.):350–361.
40. Sweeting J, Duflou J, Semsarian C. Postmortem analysis of cardiovascular deaths in schizophrenia: a 10-year review. Schizophr Res. 2013;150(2–3):398–403.
41. Eifert GH. Cardiophobia: a paradigmatic behavioural model of heart-focused anxiety and non-anginal chest pain. Behav Res Ther. 1992;30:329–45.
42. Mayou R, Bryant B, Forfar C, Clark D. Non-cardiac chest pain and benign palpitations in the cardiac clinic. Br Heart J. 1994;72(6):548–53. [Internet]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7857738
43. Deacon B, Abramowitz J. Anxiety sensitivity and its dimensions across the anxiety disorders. J Anxiety Disord. 2006;20:837–57.
44. White KS, Barlow DH. Panic disorder and agoraphobia. In: Anxiety and its disorders: the nature and treatment of anxiety and panic, 2nd ed. New York: Guilford; 2002. p. 328–379.
45. McNally RJ. Anxiety sensitivity and panic disorder. Biol Psychiatry. 2002;52:938–46.
46. Beunderman R, Duyvis DJ. Myocardial infarction patients during the prodromal and acute phase: a comparison with patients with a diagnosis of "non-cardiac chest pain". Psychother Psychosom. 1983;40:129–36.
47. Sifneos PE. The prevalence of "Alexithymic" characteristics in psychosomatic patients. Psychother Psychosom. 1973;22(2–6):255–62. [Internet]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/4770536
48. Lumley MA, Stettner L, Wehmer F. How are alexithymia and physical illness linked? A review and critique of pathways. J Psychosom Res. 1996;41(6):505–18. [Internet]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9032714
49. White KS, McDonnell CJ, Gervino EV. Alexithymia and anxiety sensitivity in patients with non-cardiac chest pain. J Behav Ther Exp Psychiatry. 2011;42(4):432–9. [Internet]. Available from. https://doi.org/10.1016/j.jbtep.2011.04.001.
50. Zincir SB, Sunbul M, Sunbul EA, Dalkilic B, Cengiz F, Kivrak T, et al. Evaluation of alexithymia, somatosensory sensitivity, and health anxiety levels in patients with noncardiac chest pain. Biomed Res Int. 2014;2014:896183. [Internet]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24967410
51. Zahradnik M, Stewart SH, Marshall GN, Schell TL, Jaycox LH. Anxiety sensitivity and aspects of alexithymia are independently and uniquely associated with posttraumatic distress. J Trauma Stress. 2009;22:131–8.
52. Messina A, Beadle JN, Paradiso S. Towards a classification of alexithymia: primary, secondary and organic. J Psychopathol. 2014;20:38–49.
53. Ermann M. Herz und Seele: Psychosomatik am Beispiel des Herzens. Kohlhammer; 2005.
54. Friedman HS, Booth-Kewley S. Personality, type A behavior, and coronary heart disease: the role of emotional expression. J Pers Soc Psychol. 1987;53:783–92.
55. Jenkins CD, Rosenman RH, Zyzanski SJ. Prediction of clinical coronary heart disease by a test for the coronary-prone behavior pattern. N Engl J Med. 2010;290(23):1271–5. [Internet]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/4827626
56. Kuper H, Marmot M, Hemingway H. Systematic review of prospective cohort studies of psychosocial factors in the etiology and prognosis of coronary heart disease. Semin Vasc Med. 2002;02(3):267–314. [Internet]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16222620
57. Bass C. Type A behaviour in patients with chest pain: test-retest reliability and psychometric correlates of Bortner scale. J Psychosom Res. 1984;28(4):289–300. [Internet]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/6481663
58. Versteeg H, Spek V, Pedersen SS, Denollet J. Type D personality and health status in cardiovascular disease populations: a meta-analysis of prospective studies. Eur J Prev Cardiol. 2012;19(6):1373–80. [Internet]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21965518
59. Mommersteeg PMC, Widdershoven JW, Aarnoudse W, Denollet J. Personality subtypes and chest pain in patients with nonobstructive coronary artery disease from the TweeSteden Mild Stenosis study: mediating effect of anxiety and depression. Eur J Pain. 2016;20(3):427–37. [Internet]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26105088
60. García-Campayo J, Rosel F, Serrano P, Santed MA, Andrés E, Roca M, et al. Different psychological profiles in non-cardiac chest pain and coronary artery disease: a controlled study. Rev Esp Cardiol. 2010;63(3):357–61. English Ed [Internet].Available from: http://linkinghub.elsevier.com/retrieve/pii/S1885585710700700
61. Swap CJ, Nagurney JT. Value and limitations of chest pain history in the evaluation of patients with suspected acute coronary syndromes. J Am Med Assoc. 2005;294:2623–9. [Internet]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16304077
62. Smeeth L, Skinner JS, Ashcroft J, Hemingway H, Timmis A. NICE clinical guideline: chest pain of recent onset. Br J Gen Pract. 2010;60:607–10.
63. Zun L. Care of psychiatric patients: the challenge to emergency physicians. West J Emerg Med. 2016;17(2):173–6. [Internet]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26973743
64. Wertli MM, Dangma TD, Müller SE, Gort LM, Klauser BS, Melzer L, et al. Non-cardiac chest pain patients in the emergency department: Do physicians have a plan

how to diagnose and treat them? A retrospective study. PLoS One. 2019;14(2):e0211615. Serra R, editor. [Internet]. Available from:. https://doi.org/10.1371/journal.pone.0211615.
65. Wong WM, Risner-Adler S, Beeler J, Habib S, Bautista J, Goldman S, et al. Noncardiac chest pain: the role of the cardiologist – a national survey. J Clin Gastroenterol. 2005;39:858–62. [Internet]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16208108
66. Marks EM, Chambers JB, Russell V, Bryan L, Hunter MS. The rapid access chest pain clinic: unmet distress and disability. QJM. 2014;107(6):429–34. [Internet]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24448381
67. Chambers JB, Marks EM, Russell V, Hunter MS. A multidisciplinary, biopsychosocial treatment for non-cardiac chest pain. Int J Clin Pract. 2015;69(9):922–7. [Internet]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25363358
68. NHS. Medically unexplained symptoms positive practice guide. 2008 October.
69. Drossman DA, Dumitrascu DL. Rome III: new standard for functional gastrointestinal disorders. J Gastrointest Liver Dis. 2006;15(3):237–41. [Internet]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17013448
70. Stone J, Carson A, Sharpe M. Functional symptoms in neurology: management [Internet]. Vol. 76, Neurology in practice. BMJ Publishing Group; 2005. p. i13–21. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15718216
71. Stone J, Wojcik W, Durrance D, Carson A, Lewis S, MacKenzie L, et al. What should we say to patients with symptoms unexplained by disease? The "number needed to offend". BMJ. 2002;325(7378):1449–50. [Internet]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12493661
72. Marks EM, Hunter MS. Medically unexplained symptoms: an acceptable term? Br J Pain. 2015;9(2):109–14. [Internet]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26516565
73. Potts SG, Lewin R, Fox KA, Johnstone EC. Group psychological treatment for chest pain with normal coronary arteries. QJM. 1999;92(2):81–6. [Internet]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10209659
74. White BKS, Raffa SD. Anxiety and other emotional factors in noncardiac chest pain. 2004;(October).

Consequences of Altered Cardiac Activity on Brain Activity

11

Enrico Baldi and Simone Savastano

Contents

Abstract

Many heart diseases can affect brain activity and the most common are atrial fibrillation, arterial hypertension, heart failure, ischemic heart disease, valvular heart disease, pulmonary arterial hypertension, and sudden cardiac arrest. The mechanisms underlying the brain dysfunction and the cognitive impairment can be different depending on the heart disease, but the decreased blood perfusion, silent cerebral infarctions due to cardioembolism, and cerebral white matter hyperintensities are the most commonly involved pathogenetic mechanisms, although also genetics seems to play a role in many diseases. Another important aspect to be considered is the presence of depression, which is common in many heart

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*,
https://doi.org/10.1007/978-3-030-28008-6_13

diseases and can affect not only the quality of life but also the outcome. Considering the importance of brain dysfunction on outcome, it is evident from the literature, how important it is to correctly identify patients who develop this type of problem in order to optimize their treatment and improve their outcome.

Keywords

Heart diseases · Brain dysfunction · Cognitive impairment · Hypoperfusion · Cardioembolism

Introduction

Heart and brain have several connections between them and if it is well known that the functioning of the heart undergoes numerous influences from the brain and the central nervous system, it is equally well demonstrated that the heart functioning can affect the brain activity. In fact, the heart and the brain do not share only the same risk factors, but there are several types of heart disease that potentially affect the brain.

Atrial Fibrillation

Atrial fibrillation (AF) is one of the most common arrhythmias, with higher incidence and prevalence rates in developed countries [1]. It is estimated that in Europe AF is present in 3.7–4.2% of people aged 60–70 years and in 10–17% of those aged 80 years or older [2]. AF is one of the major causes of stroke, heart failure, sudden death, and cardiovascular morbidity in the world [3] and it is independently associated with a twofold increased risk of all-cause mortality in women and a 1.5-fold increase in men [4]. It is well demonstrated that the presence of AF can influence the brain activity in many ways. The risk of ischemic stroke is increased if AF is present due to the increased risk of thromboembolism, originating mainly from the left atrial appendage, caused by this arrhythmia [5], and the CHA2DS2-VASc score is the most effective and clinically used score to estimate the risk of stroke and thromboembolism in AF patients [6]. Oral anticoagulation (OAC) with vitamin K antagonists (VKAs) [7] or non-VKA oral anticoagulants (NOACs) [8–12] markedly reduces stroke and mortality in AF patients. Moreover, NOACs seem not only to have better long-term efficacy and safety compared with warfarin, but also to be associated with a lower risk of cerebral ischemic events and new-onset dementia [13]. AF is not only associated with an increased risk of symptomatic stroke, but also TIAs and silent cerebral infarctions [14]. It was indeed demonstrated that patient with paroxysmal and persistent AF had a higher prevalence and number of areas of silent cerebral ischemia than controls in sinus rhythm and this is associated with worse cognitive performance in immediate memory, visual-spatial abilities, language, attention, and delayed memory [15]. Furthermore, AF is associated with a higher risk of cognitive impairment and dementia, independent of ischemic stroke [16] both in elderly people and in younger one. Regarding younger people, a longer exposure period might lead to changes that produce greater neuronal injury and loss, possibly due to the interaction of degenerative and vascular changes [17], and they are likely to reach thresholds of cognitive impairment or dementia at earlier ages than people with no history of atrial fibrillation [18]. It was also demonstrated that people with atrial fibrillation treated with long-term warfarin anticoagulation have higher rates of all dementia types compared with patients receiving long-term warfarin for other indications [19]. The brain functions impaired by the presence of AF can vary, such as learning and memory, attention and executive functions, working memory, visuospatial skills [20], and different subtypes of dementia can be promoted, especially Alzheimer's disease and vascular dementia [21]. The underlying mechanisms that link AF and cognitive impairment are not well known and many factors seem to play a role. AF decreases blood flow to the brain as well as perfusion of brain tissue compared with sinus rhythm [22], and this reduction and variation beat-to-beat

of cerebral perfusion certainly plays an important role in the development of cognitive impairment [23]. Furthermore, if AF is associated with heart failure, the cognitive deficit is exacerbated possibly through their association in decreasing cerebral perfusion [22]. Other possible mechanisms that explain this fact seems to be cerebral microinfarcts, an important neuropathological predictor of clinical dementia [24], due to microemboli [23]. In fact, AF leads to a hypercoagulatory state [25] that could give rise to subclinical cerebral embolism, and transcranial Doppler ultrasonography has detected cerebral microemboli in up to 30% of patients with AF [26]. Also genetic polymorphisms, especially apoE genotype, are related with cognitive impairment in AF [27]. In addition, AF is demonstrated to be associated with increased hippocampal atrophy and smaller brain volume, evaluated with magnetic resonance imaging, and this association is stronger with increasing burden of the arrhythmia, suggesting a cumulative negative effect of AF on the brain independent of cerebral infarcts [28]. Consistently with all these evidences, especially with the ones which underlying the link between reduction in brain perfusion during AF and cognitive decline, the strategy of atrioventricular node ablation and pacing improve left ventricular systolic function, thereby increasing blood pressure and improving cerebral perfusion with an improvement in immediate and delayed verbal memory, abstract mentation, attention, psychomotor speed, as well as in learning [29]. On the other hand, postoperative neurocognitive dysfunction and neuropsychological decline, especially in memory, seem to be related to the procedure of transcatheter AF ablation, [30] but there are conflicting evidences on that [31].

Anxiety and depression are more frequent in patient with AF than in general population [32], especially in patient with persistent AF respect to patient with paroxysmal AF [33], increasing the perception of severity of symptoms related to AF [34] and driving to a reduction in health-related quality of life [35]. Catheter ablation is more effective for improving depression, anxiety, and quality of life in patients with AF compared with antiarrhythmic drug therapy [36].

Arterial Hypertension

Arterial hypertension is defined as values $\geq$140 mmHg of systolic blood pressure (SBP) and/or $\geq$ 90 mmHg of diastolic blood pressure (DBP). Overall, the prevalence of hypertension appears to be around 30–45% of the general population, with a steep increase with aging. The most common types of brain lesions favored by hypertension are white matter hyperintensities, silent infarcts, and microbleeds. White matter hyperintensities and silent infarcts are associated with an increased risk of stroke, cognitive decline, and dementia [37]. In particular, regarding the risk of stroke, it is well demonstrated since decades that it is increased by the presence of arterial hypertension through many mechanism: a high intraluminal pressure will lead to extensive alteration in endothelium and smooth muscle function in intracerebral arteries that can lead to local thrombi formation and ischemic lesions, to fibrinoid necrosis that can cause lacunar infarcts through focal stenosis and occlusions and to degenerative changes in smooth muscle cells and endothelium that predisposes for intracerebral hemorrhages. Furthermore, hypertension accelerates the arteriosclerotic process, thus increasing the likelihood for cerebral lesions related to stenosis and embolism originating from large extracranial vessels, the aortic arch, and from the heart. Moreover, adaptive structural changes in the resistance vessels, while having the positive effect of reducing the vessel wall tension, have the negative consequence of increasing peripheral vascular resistance that may compromise the collateral circulation and enhance the risk for ischemic events in connection with episodes of hypotension or distal to a stenosis [38]. An antihypertensive stepped-care drug treatment has the capability to dramatically reduce the incidence of total stroke and major cardiovascular events [39]. It is also known for years that hypertension-associated

pathogenic processes may cause mild cognitive impairment [40] and that arterial hypertension, especially the SBP, predict the onset of impaired cognitive performance affecting attention, learning and memory, executive functions, visuospatial skills, psychomotor abilities, and perceptual skills [41]. The underlying mechanisms are not fully known, but a role in cognitive dysfunction is played by the reductions in cerebral blood flow and metabolism driven by long-standing hypertension [42]. Moreover, as mentioned at the beginning of this chapter, cerebral white matter hyperintensities (WMHs), which are believed to be the consequence of small vessel disease, are one of the stronger predictors of dementia and cognitive decline [43]. WMHs are associated both with high SBP and high DBP [44], and there are evidences that adequate treatment of hypertension may reduce the course of WMHs progression [45]. However, the fact that antihypertensive treatment can reduce the risk of the onset of dementia is not fully proven as there are conflicting evidences [37]. Other factors have been related to the decline of cognitive function due to hypertension, in particular there are evidences on the fact that the role of neuroinflammation in the susceptibility of the brain for neurodegeneration and memory impairment is enhanced in hypertension, and that ACE inhibition can play a protective role [46]. Moreover, genetic probably play a significant role, as it was demonstrated that the interaction between hypertension and the presence of the APOE ε4 allele was associated with steeper cognitive decline over a long period [47]. Finally, recent evidence focuses on the importance of small vessel disease and in particular on the role of hypertension as a contributing factor to worse clinical outcomes, especially cognitive impairment, and neuroradiological presentation in patients with sporadic small vessel disease [48]. Concluding, blood pressure has complex relationships with cognitive functioning and poorly controlled hypertension increases the risk of cognitive dysfunction and perhaps vascular and possibly other types of dementia, affecting also the quality of life of the patients. Therefore, it is important to provide appropriate patient education regarding likely risks associated with hypertension [49].

Heart Failure

Heart Failure (HF) is a clinical syndrome characterized by typical symptoms (e.g., breathlessness, ankle swelling, and fatigue) that may be accompanied by signs (e.g., elevated jugular venous pressure, pulmonary crackles, and peripheral edema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output (HF with reduced ejection fraction) and/or elevated intracardiac pressures (HF with preserved ejection fraction) at rest or during stress and leading to the fact that the metabolic requirements are not met [50]. About 1–2% of the adult population in developed countries is affected by HF, and this percentage increase with the age up to 10% in patients aged over 70 years [51]. It is known for many years that the presence of HF is associated in many patients with brain failure [52, 53], and this correlation is present in all ages, also in pediatric population [54]. There are many evidences supporting that severity of cognitive impairment is associated with the severity of HF, quantified as reduction of ejection fraction (EF) or symptom burden, [55] and the association between HF and cognitive decline is also found in patient with reduced EF, but without symptoms [56]. Moreover, the brain failure seems to be present equally in patients with HF with reduced EF and in patient with HF with preserved EF [53]. It is possible to recognize two different types of cognitive problem in HF: an acute change in cognition during an acute presentation of HF (delirium) and a chronic decrease of the cognitive abilities in chronic HF. Regarding delirium, it is common in many acute medical conditions, so it is difficult to establish a direct correlation with HF, but it was demonstrated that its presence during hospitalization for HF increases the length of hospital stay, worsens the outcome, and increases the mortality [57]. As for the chronic decrease of the cognitive abilities, it affects many abilities and cognitive domains as deficits in attention, executive functioning, visuospatial functioning, memory, perceptual speed, and language [58], leading to an increased risk to develop different type of dementia, including vascular dementia [59] and

Alzheimer's disease [60]. Furthermore, HF is associated with poor level of self-care management, which can also affect the adherence to the therapy [61]. The potential pathophysiological explanations of cognitive impairment in heart failure vary and different factors can coexist in the same patient. The formation of tangle and plaque-like structures and fibrillar deposits (that is, the "hallmark" lesions of Alzheimer's disease (AD) dementia), which was demonstrated within the myocardium of patients with hypertrophic cardiomyopathy and idiopathic dilated cardiomyopathy, explains the possibility of a common myocardial and cerebral pathology in a subset of patients with HF [60, 62], whereas the systemic inflammatory state recognized in patients with HF may also contribute to cognitive impairment through different cytokine-mediated interactions between neurons and glial cells [63]. The reduction in cerebral blood flow caused by low cardiac output, low systolic blood pressure, and impaired autoregulatory mechanisms are probably also involved in brain changes affecting people with HF [64]. Moreover, as during AF, cardioembolism may play a role in the development of cognitive impairment in HF, as it was seen in HF patients with sinus rhythm. Reduced EF seems to be the most important determinant of thrombus formation and potential embolic cerebral infarction in these patients [65]. At a macroscopic level, it was demonstrated, via magnetic resonance images, that patients with HF have a gray matter loss in the left cingulate, in the right inferior frontal gyrus, in the left middle and superior frontal gyri, in the right middle temporal lobe, in the right and left anterior cingulate, in the right middle frontal gyrus, in the inferior and pre-central frontal gyri, in the right caudate, and in the occipital-parietal regions involving the left precuneus, which are relevant brain regions for cognitive function and that compromise performance on cognitive tasks that require mental effort [66]. The risk for cognitive decline in HF patients appeared to be modifiable with cardiac treatment, as clinical interventions that improve cardiac function can also improve cognitive function [67] and better treatment adherence predict improved cognition 1 year later [68]. These facts underlie the importance to screen for cognitive impairment in HF patients and, although Mini-Mental State Examination (MMSE) is one of the most widely used, the Montreal Cognitive Assessment (MoCA) seems to be more comprehensive and appears to be the most suitable screening tool for HF as it tests all of the domains most often affected in this disease [69].

Finally, it should not be forgotten that depression plays an important role in HF. Approximately, 20% of these patients have clinically significant depression and another 35% have minor depression [70] and is often underdiagnosed [71]. Depression was associated with poorer outcome in HF patients [72], so it is recommended to screen for it using tool as PHQ-2 and PHQ-9 [73] and treat it using, for example, SSRIs, which are considered to be both efficacious and safe [74].

Ischemic Heart Disease

Ischemic heart disease (IHD) is the leading cause of death all over the world [75] and consists of several different conditions, such as myocardial infarction (MI) and angina pectoris (AP), which are the most prevalent ones. IHD is mainly due to the development of atherosclerosis in the coronary arteries, with reduction of blood supply to heart muscle, so it is also known as coronary artery disease (CAD) [76]. The prevalence of IHD is about 20% in people over 65 years old, 7% in those 45–64, and 1.3% in those 18–45, with higher rates among men than women of a given age [77]. The literature on the presence of cognitive dysfunction in IHD patients is mixed in general, the majority of prospective and cross-sectional studies demonstrating a significant association with cognition or dementia, resulting in a 45% increased risk of cognitive impairment or dementia [78]. In fact, cognitive impairment is observed in about 35% of the patients with a previous history of IHD and most of the cognitive domains are affected even if a predominance of impairment in verbal memory learning and executive function was reported [79]. IHD patients had lower cognitive performance and greater degrees

of decline compared to people without IHD [80]. Moreover, atherosclerosis extent and severity of angina pectoris were demonstrated to be associated with the severity of cognitive decline [81]. The exact biological mechanism underlying the association between IHD and cognitive impairment or dementia is not still fully known, but many pathways seem to play a role [78]. First of all, the common risk factors for IHD and dementia are the same, like as obesity, type-2 diabetes, smoking, hypertension, physical inactivity, and hypercholesterolemia [82], but the association between IHD and dementia cannot lay only on this [78]. Moreover, IHD can be associated with other cardiac diseases, like atrial fibrillation and heart failure, which, as explained previously, increase the risk of cognitive impairment and dementia. Vascular insufficiency consequent to IHD could also be involved leading to cerebrovascular changes such as a reduced cerebral blood flow and cerebral hypoperfusion [83], brain infarctions, and white matter lesions [84], which are associated with reduced cognitive functioning and risk of dementia [85]. Furthermore, patients with IHD have a loss of gray matter in some specific brain regions that are relevant to cognitive function, and the greater is the extent of coronary stenosis, the greater is the loss [86]. It was also hypothesized, in a single study in adult rat, that the increased production of hydrogen peroxide in the hippocampus could play a role in the myocardial infarction induced cognitive dysfunction. More evidences are needed to support this mechanism [87]. An important aspect to be addressed is the cardiac surgery consequent to IHD: the cerebral dysfunction following cardiac surgery is an important complication and can occur in different ways, classified as stroke, encephalopathy (including delirium), or postoperative cognitive dysfunction (POCD). The etiologies involved are cerebral emboli, hypoperfusion, or inflammation that has largely been attributed to the use of cardiopulmonary bypass [88]. The most important predictors associated with cognitive decline in the postoperative period were demonstrated to be older age, female gender, higher bleeding episodes, and high postsurgery creatinine level [89]. Regarding cardiac treatment, it seems to be able not only to increase cardiac function, but also to have beneficial effects on brain function [90], though beta-1–selective beta-blocker use was associated with worse incidental learning [91]. As in atrial fibrillation and heart failure, also in IHD patients, the depression is an important aspect to be studied in deep. In fact, somatic symptoms of depression after a myocardial infarction predicted subsequent mortality, whilst depression, anxiety, and type D personality were associated with worse cognitive performance independent of clinical CAD severity and sociodemographic characteristics, especially in younger people [92, 93]. The effective treatment of depression reduces mortality in depressed postmyocardial infarction patients. In conclusion, considering the association of IHD and cognitive dysfunction, it is really important to screen for it and for depression before hospital discharge and during follow-up to improve its recognition and treatment [94].

Valvular Heart Disease

The risk of cognitive impairment in patients with valvular disease is present mainly when a valve correction is to be performed. In fact, clinically silent brain injury detected with cerebral magnetic resonance imaging (MRI) is well known after various cardiovascular interventions, including surgical valve correction, and they can favor cognitive decline [95]. However, from the 1990s, new techniques for percutaneous valve corrections have been developed, especially for high-risk patients, such as transcatheter aortic valve implantation (TAVI) and MitraClip [96, 97]. Regarding TAVI, it is known to be associated with silent cerebral injury as well as surgical aortic valve replacement (AVR), but the risk of cerebral emboli seems to be inferior respect AVR. However, both AVR and TAVI are associated with a significant improvement of quality of life without a detrimental effect on cognitive function, despite the high intrinsic risk for cognitive deterioration of this population [98]. Also MitraClip procedure causes acute cerebral lesions in the vast majority of patients, but these lesions resolve completely in the follow-up.

Nevertheless, the number of lesions may have an impact on cognitive function as patients with more lesions showed a significant decline in their test scores in a single study [99].

Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH) is a rare and debilitating chronic disease of the pulmonary vasculature, characterized by increased blood pressure within the arteries of the lungs, which ultimately leads to right heart failure and death. The most common symptoms are shortness of breath, tiredness, and syncope. PAH is classified in different subgroups depending on its etiology and different mechanisms can be involved, including left heart disease (group WHO II) and chronic arterial obstruction (group WHO IV), the latter which is represented mainly by chronic thromboembolic pulmonary hypertension (CTEPH) [100]. Patients with PAH may suffer from cognitive impairments, depression, and anxiety [101]. In particular, cognitive deficits seem to be related to reduced oxygen delivery and cerebral tissue oxygenation (CTO), which is the strongest predictor of cognitive dysfunction, and disease-targeted medications result in better cognitive function [102]. Moreover, mental disorders, exercise capacity, long-term oxygen therapy, right heart failure, and age play an important role in the quality of life of these patients and advanced practice nursing strategies (such as counseling, psychiatric referrals, psychotherapy, guided imagery, leading support groups, and low-grade resistance training) may help to increase their quality of life [103]. Considering these evidences, it is clear the importance of screening PAH patients to assess their outcomes, and a new questionnaire, called PAH-SYMPACT, was recently proposed for clinical use including also cognitive/emotional impact of PAH [104]. Regarding the subgroup of CTEPH, pulmonary endarterectomy with repeated short periods of circulatory arrest with moderate hypothermia results in a better quality of life and reduced symptoms of depression and anxiety without worsening cognitive function [105].

Sudden Cardiac Arrest

Sudden cardiac arrest (SCA) affects about 1 person per 1000 inhabitants every year and is one of the leading causes of death in the industrialized countries, with a mean survival to hospital discharge of 5–10% [106]. During a cardiac arrest, the brain can suffer from a temporary limitation in blood supply, which can lead to hypoxic brain injury. Postcardiac arrest brain injury manifests as coma, seizures, myoclonus, and brain death. Among patients surviving to ICU admission but subsequently dying in hospital, brain injury is the cause of death in approximately two thirds after out-of-hospital cardiac arrest and approximately in 25% after in-hospital cardiac arrest. Unlike cardiovascular failure, which cause death in the first three days after the event, brain injury accounts for most of the later deaths [107, 108]. Postcardiac arrest brain injury may be exacerbated by microcirculatory failure, impaired autoregulation, hypotension, hypercarbia, hypoxemia, hyperoxemia, pyrexia, hypoglycemia, hyperglycemia, and seizures [109]. In patients who survive at hospital discharge, one of the main clinical consequences of hypoxic brain injury is cognitive impairment [110]. Cognitive problems affect about half of the survivors of out-of-hospital cardiac arrest [111]. The cognitive domains that were affected most frequently are memory, attention, processing speed, and executive functioning, but also other domains can be affected. Moreover, memory problems were reported most frequently, especially regarding the episodic long-term memory functioning [112]. A possible explanation for this is that the hippocampus, a brain structure important for the storage of information, is very sensitive to decreased cerebral perfusion [113]. Furthermore, memory seems to be affected by global brain ischemia rather than focal brain lesions [112] and by the global cerebral atrophy seen after out-of-hospital cardiac arrest, which can also explain why so many cognitive domains can be impaired after cardiac arrest [114]. Mild induced hypothermia 32–36 °C is recommended as a neuroprotective strategy for patients who remain comatose after hospital admission [115] as it can improve outcome after a period of global cerebral hypoxia-ischemia [116].

Cooling suppresses many of the pathways leading to delayed cell death, including apoptosis, and also decreases the cerebral metabolic rate for oxygen by about 6% for each 1 °C reduction in core temperature, and this may reduce the release of excitatory amino acids and free radicals [117, 118]. Hypothermia also blocks the intracellular consequences of excitotoxin exposure (high calcium and glutamate concentrations) and reduces the inflammatory response associated with the postcardiac arrest syndrome [109, 119]. Cognitive function is similar in patients with cardiac arrest receiving targeted temperature management at 33 °C or 36 °C [120]. Cognitive impairment was significantly associated with lower participation, together with the closely related symptoms of fatigue, depression, and restricted mobility. All these predictive variables should be used during follow-up to identify SCA survivors at risk of a less successful recovery that may benefit from further support and rehabilitation [121]. Another important aspect that needs to be considered is the presence of anxiety and depression in SCA survivors, which are present in up to 50% of the patients independently of SCA characteristics [122, 123] and negatively affect the quality of life and the outcomes [124]. All these evidences support the need of comprehensive outcome measurements of SCA survivors: a recent advisory statement from the International Liaison Committee on Resuscitation (COSCA – Core Outcome Set for Cardiac Arrest) suggests that evaluation should include survival, neurological function, and health-related quality of life (HRQoL). In particular, the statement recommends reporting the survival status and modified Rankin Scale (mRS) at hospital discharge, 30 days, or both. mRS is preferred over cerebral performance category (CPC) or other scales because it is a brief, clinician-completed, ordinal hierarchical rating scale used to determine a summary score of global disability after a neurological event or condition; it captures impairment of physical and cognitive abilities; and it can discriminate between levels of mild and moderate disability. Moreover, HRQoL should be measured with $\geq$1 tools from the HUI3, SF-36v2, or EQ-5D-5L at 90 days and at periodic intervals up to 1 year after cardiac arrest, if it is possible [125].

Brain dysfunction is also fundamental in prognostication: bilateral absence of either pupillary and corneal reflexes or N20 wave of short-latency somatosensory-evoked potentials were identified as the most robust predictors of poor outcome in comatose patients with absent or extensor motor response at $\geq$72 h from SCA, either treated or not treated with controlled temperature. Early status myoclonus, elevated values of neuron specific enolase at 48–72 h from SCA, unreactive malignant EEG patterns after rewarming, and presence of diffuse signs of postanoxic injury on either computed tomography or magnetic resonance imaging were identified as useful but less robust predictors. If the initial assessment is inconclusive, prolonged observation and repeated assessments should be considered [124].

References

1. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, Gillum RF, Kim YH, McAnulty JH Jr, Zheng ZJ, Forouzanfar MH, Naghavi M, Mensah GA, Ezzati M, Murray CJ. Worldwide epidemiology of atrial fibrillation: a global burden of disease 2010 study. Circulation. 2014;129(8):837–47. https://doi.org/10.1161/CIRCULATIONAHA.113.005119.
2. Zoni-Berisso M, Lercari F, Carazza T, Domenicucci S. Epidemiology of atrial fibrillation: European perspective. Clin Epidemiol. 2014;6:213–20. https://doi.org/10.2147/CLEP.S47385.
3. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P, ESC Scientific Document Group. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2016;37(38):2893–962. https://doi.org/10.1093/eurheartj/ehw210.
4. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham heart study. Circulation. 1998;98(10):946–52.
5. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham study. Stroke. 1991;22(8):983–8.
6. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest. 2010;137(2):263–72. https://doi.org/10.1378/chest.09-1584.

7. Hylek EM, Go AS, Chang Y, Jensvold NG, Henault LE, Selby JV, Singer DE. Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. N Engl J Med. 2003;349(11):1019–26.
8. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L, RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361(12):1139–51. https://doi.org/10.1056/NEJMoa0905561.
9. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM, ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365(10):883–91. https://doi.org/10.1056/NEJMoa1009638.
10. Hankey GJ, Patel MR, Stevens SR, Becker RC, Breithardt G, Carolei A, Diener HC, Donnan GA, Halperin JL, Mahaffey KW, Mas JL, Massaro A, Norrving B, Nessel CC, Paolini JF, Roine RO, Singer DE, Wong L, Califf RM, Fox KA, Hacke W, ROCKET AF Steering Committee Investigators. Rivaroxaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a subgroup analysis of ROCKET AF. Lancet Neurol. 2012;11(4):315–22. https://doi.org/10.1016/S1474-4422(12)70042-X.
11. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Špinar J, Ruzyllo W, Ruda M, Koretsune Y, Betcher J, Shi M, Grip LT, Patel SP, Patel I, Hanyok JJ, Mercuri M, Antman EM, ENGAGE AF-TIMI 48 Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013;369(22):2093–104. https://doi.org/10.1056/NEJMoa1310907.
12. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FW, Zhu J, Wallentin L, ARISTOTLE cCommittees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365(11):981–92. https://doi.org/10.1056/NEJMoa1107039.
13. Jacobs V, May HT, Bair TL, Crandall BG, Cutler MJ, Day JD, Mallender C, Osborn JS, Stevens SM, Weiss JP, Woller SC, Bunch TJ. Long-term population-based cerebral ischemic event and cognitive outcomes of direct oral anticoagulants compared with warfarin among long-term anticoagulated patients for atrial fibrillation. Am J Cardiol. 2016;118(2):210–4. https://doi.org/10.1016/j.amjcard.2016.04.039.
14. Ezekowitz MD, James KE, Nazarian SM, Davenport J, Broderick JP, Gupta SR, Thadani V, Meyer ML, Bridgers SL. Silent cerebral infarction in patients with nonrheumatic atrial fibrillation. The veterans affairs stroke prevention in nonrheumatic atrial fibrillation Investigators. Circulation. 1995;92(8):2178–82.
15. Gaita F, Corsinovi L, Anselmino M, Raimondo C, Pianelli M, Toso E, Bergamasco L, Boffano C, Valentini MC, Cesarani F, Scaglione M. Prevalence of silent cerebral ischemia in paroxysmal and persistent atrial fibrillation and correlation with cognitive function. J Am Coll Cardiol. 2013;62(21):1990–7. https://doi.org/10.1016/j.jacc.2013.05.074.
16. Chen LY, Norby FL, Gottesman RF, Mosley TH, Soliman EZ, Agarwal SK, Loehr LR, Folsom AR, Coresh J, Alonso A. Association of atrial fibrillation with cognitive decline and dementia over 20 years: the ARIC-NCS (Atherosclerosis Risk in Communities Neurocognitive Study). J Am Heart Assoc. 2018;7(6):pii: e007301. https://doi.org/10.1161/JAHA.117.007301.
17. Singh-Manoux A, Fayosse A, Sabia S, Canonico M, Bobak M, Elbaz A, Kivimäki M, Dugravot A. Atrial fibrillation as a risk factor for cognitive decline and dementia. Eur Heart J. 2017;38(34):2612–8. https://doi.org/10.1093/eurheartj/ehx208.
18. Thacker EL, McKnight B, Psaty BM, Longstreth WT Jr, Sitlani CM, Dublin S, Arnold AM, Fitzpatrick AL, Gottesman RF, Heckbert SR. Atrial fibrillation and cognitive decline: a longitudinal cohort study. Neurology. 2013;81(2):119–25. https://doi.org/10.1212/WNL.0b013e31829a33d1.
19. Bunch TJ, May HT, Bair TL, Crandall BG, Cutler MJ, Day JD, Jacobs V, Mallender C, Osborn JS, Stevens SM, Weiss JP, Woller SC. Atrial fibrillation patients treated with long-term warfarin anticoagulation have higher rates of all dementia types compared with patients receiving long-term warfarin for other indications. J Am Heart Assoc. 2016;5(7):pii: e003932. https://doi.org/10.1161/JAHA.116.003932.
20. Knecht S, Oelschläger C, Duning T, Lohmann H, Albers J, Stehling C, Heindel W, Breithardt G, Berger K, Ringelstein EB, Kirchhof P, Wersching H. Atrial fibrillation in stroke-free patients is associated with memory impairment and hippocampal atrophy. Eur Heart J. 2008;29(17):2125–32. https://doi.org/10.1093/eurheartj/ehn341.
21. Ott A, Breteler MM, de Bruyne MC, van Harskamp F, Grobbee DE, Hofman A. Atrial fibrillation and dementia in a population-based study. The Rotterdam study. Stroke. 1997;28(2):316–21.
22. Gardarsdottir M, Sigurdsson S, Aspelund T, Rokita H, Launer LJ, Gudnason V, Arnar DO. Atrial fibrillation is associated with decreased total cerebral blood flow and brain perfusion. Europace. 2017; https://doi.org/10.1093/europace/eux220.
23. Dublin S, Anderson ML, Haneuse SJ, Heckbert SR, Crane PK, Breitner JC, McCormick W, Bowen JD, Teri L, McCurry SM, Larson EB. Atrial fibrillation

and risk of dementia: a prospective cohort study. J Am Geriatr Soc. 2011;59(8):1369–75. https://doi.org/10.1111/j.1532-5415.2011.03508.x.
24. Sonnen JA, Larson EB, Crane PK, Haneuse S, Li G, Schellenberg GD, Craft S, Leverenz JB, Montine TJ. Pathological correlates of dementia in a longitudinal, population-based sample of aging. Ann Neurol. 2007;62(4):406–13.
25. Barber M, Tait RC, Scott J, Rumley A, Lowe GD, Stott DJ. Dementia in subjects with atrial fibrillation: hemostatic function and the role of anticoagulation. J Thromb Haemost. 2004;2(11):1873–8.
26. Kumral E, Balkir K, Uzuner N, Evyapan D, Nalbantgil S. Microembolic signal detection in patients with symptomatic and asymptomatic lone atrial fibrillation. Cerebrovasc Dis. 2001;12(3):192–6.
27. Falsetti L, Viticchi G, Buratti L, Grigioni F, Capucci A, Silvestrini M. Interactions between atrial fibrillation, cardiovascular risk factors, and ApoE genotype in promoting cognitive decline in patients with Alzheimer's disease: a prospective cohort study. J Alzheimers Dis. 2018;62(2):713–25. https://doi.org/10.3233/JAD-170544.
28. Stefansdottir H, Arnar DO, Aspelund T, Sigurdsson S, Jonsdottir MK, Hjaltason H, Launer LJ, Gudnason V. Atrial fibrillation is associated with reduced brain volume and cognitive function independent of cerebral infarcts. Stroke. 2013;44(4):1020–5. https://doi.org/10.1161/STROKEAHA.12.679381.
29. Efimova I, Efimova N, Chernov V, Popov S, Lishmanov Y. Ablation and pacing: improving brain perfusion and cognitive function in patients with atrial fibrillation and uncontrolled ventricular rates. Pacing Clin Electrophysiol. 2012;35(3):320–6. https://doi.org/10.1111/j.1540-8159.2011.03277.x.
30. Medi C, Evered L, Silbert B, Teh A, Halloran K, Morton J, Kistler P, Kalman J. Subtle post-procedural cognitive dysfunction after atrial fibrillation ablation. J Am Coll Cardiol. 2013;62(6):531–9. https://doi.org/10.1016/j.jacc.2013.03.073.
31. Herm J, Fiebach JB, Koch L, Kopp UA, Kunze C, Wollboldt C, Brunecker P, Schultheiss HP, Schirdewan A, Endres M, Haeusler KG. Neuropsychological effects of MRI-detected brain lesions after left atrial catheter ablation for atrial fibrillation: long-term results of the MACPAF study. Circ Arrhythm Electrophysiol. 2013;6(5):843–50. https://doi.org/10.1161/CIRCEP.113.000174.
32. Schnabel RB, Michal M, Wilde S, Wiltink J, Wild PS, Sinning CR, Lubos E, Ojeda FM, Zeller T, Munzel T, Blankenberg S, Beutel ME. Depression in atrial fibrillation in the general population. PLoS One. 2013;8(12):e79109. https://doi.org/10.1371/journal.pone.0079109.
33. von Eisenhart Rothe AF, Goette A, Kirchhof P, Breithardt G, Limbourg T, Calvert M, Baumert J, Ladwig KH. Depression in paroxysmal and persistent atrial fibrillation patients: a cross-sectional comparison of patients enroled in two large clinical trials. Europace. 2014;16(6):812–9. https://doi.org/10.1093/europace/eut361.
34. Thompson TS, Barksdale DJ, Sears SF, Mounsey JP, Pursell I, Gehi AK. The effect of anxiety and depression on symptoms attributed to atrial fibrillation. Pacing Clin Electrophysiol. 2014;37(4):439–46. https://doi.org/10.1111/pace.12292.
35. Akintade BF, Chapa D, Friedmann E, Thomas SA. The influence of depression and anxiety symptoms on health-related quality of life in patients with atrial fibrillation and atrial flutter. J Cardiovasc Nurs. 2015;30(1):66–73. https://doi.org/10.1097/JCN.0000000000000107.
36. Efremidis M, Letsas KP, Lioni L, Giannopoulos G, Korantzopoulos P, Vlachos K, Dimopoulos NP, Karlis D, Bouras G, Sideris A, Deftereos S. Association of quality of life, anxiety, and depression with left atrial ablation outcomes. Pacing Clin Electrophysiol. 2014;37(6):703–11. https://doi.org/10.1111/pace.12420.
37. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Böhm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F, Redon J, Dominiczak A, Narkiewicz K, Nilsson PM, Burnier M, Viigimaa M, Ambrosioni E, Caufield M, Coca A, Olsen MH, Schmieder RE, Tsioufis C, van de Borne P, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S, Clement DL, Coca A, Gillebert TC, Tendera M, Rosei EA, Ambrosioni E, Anker SD, Bauersachs J, Hitij JB, Caulfield M, De Buyzere M, De Geest S, Derumeaux GA, Erdine S, Farsang C, Funck-Brentano C, Gerc V, Germano G, Gielen S, Haller H, Hoes AW, Jordan J, Kahan T, Komajda M, Lovic D, Mahrholdt H, Olsen MH, Ostergren J, Parati G, Perk J, Polonia J, Popescu BA, Reiner Z, Rydén L, Sirenko Y, Stanton A, Struijker-Boudier H, Tsioufis C, van de Borne P, Vlachopoulos C, Volpe M, Wood DA. 2013 ESH/ESC guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J. 2013;34(28):2159–219. https://doi.org/10.1093/eurheartj/eht151.
38. Johansson BB. Hypertension mechanisms causing stroke. Clin Exp Pharmacol Physiol. 1999;26(7):563–5.
39. Wolf-Maier K, Cooper RS, Banegas JR, Giampaoli S, Hense HW, Joffres M, Kastarinen M, Poulter N, Primatesta P, Rodríguez-Artalejo F, Stegmayr B, Thamm M, Tuomilehto J, Vanuzzo D, Vescio F. Hypertension prevalence and blood pressure levels

in 6 European countries, Canada, and the United States. JAMA. 2003;289(18):2363–9.
40. Elias MF, Wolf PA, D'Agostino RB, Cobb J, White LR. Untreated blood pressure level is inversely related to cognitive functioning: the Framingham study. Am J Epidemiol. 1993;138(6):353–64.
41. Waldstein SR. The relation of hypertension to cognitive function. Curr Dir Psychol Sci. 2003;12(1):9–12.
42. Fujishima M, Ibayashi S, Fujii K, Mori S. Cerebral blood flow and brain function in hypertension. Hypertens Res. 1995;18(2):111–7.
43. Dufouil C, Godin O, Chalmers J, Coskun O, MacMahon S, Tzourio-Mazoyer N, Bousser MG, Anderson C, Mazoyer B, Tzourio C, PROGRESS MRI Substudy Investigators. Severe cerebral white matter hyperintensities predict severe cognitive decline in patients with cerebrovascular disease history. Stroke. 2009;40(6):2219–21. https://doi.org/10.1161/STROKEAHA.108.540633.
44. Shokouhi M, Qiu D, Samman Tahhan A, Quyyumi AA, Hajjar I. Differential associations of diastolic and systolic pressures with cerebral measures in older individuals with mild cognitive impairment. Am J Hypertens. 2018; https://doi.org/10.1093/ajh/hpy104.
45. Godin O, Tzourio C, Maillard P, Mazoyer B, Dufouil C. Antihypertensive treatment and change in blood pressure are associated with the progression of white matter lesion volumes: the Three-City (3C)-Dijon magnetic resonance imaging study. Circulation. 2011;123(3):266–73. https://doi.org/10.1161/CIRCULATIONAHA.110.961052.
46. Goel R, Bhat SA, Rajasekar N, Hanif K, Nath C, Shukla R. Hypertension exacerbates predisposition to neurodegeneration and memory impairment in the presence of a neuroinflammatory stimulus: protection by angiotensin converting enzyme inhibition. Pharmacol Biochem Behav. 2015;133:132–45. https://doi.org/10.1016/j.pbb.2015.04.002.
47. de Frias CM, Schaie KW, Willis SL. Hypertension moderates the effect of APOE on 21-year cognitive trajectories. Psychol Aging. 2014;29(2):431–9. https://doi.org/10.1037/a0036828.
48. Pavlovic AM, Pekmezovic T, Trajkovic JZ, Tomic G, Cvitan E, Sternic N. Increased risk of cognitive impairment and more severe brain lesions in hypertensive compared to non-hypertensive patients with cerebral small vessel disease. J Clin Hypertens (Greenwich). 2018; https://doi.org/10.1111/jch.13357.
49. Perna R. Hypertension and its effects on brain functioning and cognition. Hypertens Curr Concepts Ther. 2016;1(1):1–2. https://doi.org/10.15761/HCCT.1000103.
50. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, ESC Scientific Document Group. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the heart failure association (HFA) of the ESC. Eur Heart J. 2016;37(27):2129–200. https://doi.org/10.1093/eurheartj/ehw128.
51. Jhund PS, Macintyre K, Simpson CR, Lewsey JD, Stewart S, Redpath A, Chalmers JW, Capewell S, McMurray JJ. Long-term trends in first hospitalization for heart failure and subsequent survival between 1986 and 2003: a population study of 5.1 million people. Circulation. 2009;119(4):515–23. https://doi.org/10.1161/CIRCULATIONAHA.108.812172.
52. Grubb NR, Simpson C, Fox KA. Memory function in patients with stable, moderate to severe cardiac failure. Am Heart J. 2000;140(1):E1–5.
53. Huijts M, van Oostenbrugge RJ, Duits A, Burkard T, Muzzarelli S, Maeder MT, Schindler R, Pfisterer ME, Brunner-La Rocca HP, Investigators TIME-CHF. Cognitive impairment in heart failure: results from the trial of intensified versus standard medical therapy in elderly patients with congestive heart failure (TIME-CHF) randomized trial. Eur J Heart Fail. 2013;15(6):699–707. https://doi.org/10.1093/eurjhf/hft020.
54. Hollander SA, Callus E. Cognitive and psycholologic considerations in pediatric heart failure. J Card Fail. 2014;20(10):782–5. https://doi.org/10.1016/j.cardfail.2014.07.001.
55. Sauvé MJ, Lewis WR, Blankenbiller M, Rickabaugh B, Pressler SJ. Cognitive impairments in chronic heart failure: a case controlled study. J Card Fail. 2009;15(1):1–10. https://doi.org/10.1016/j.cardfail.2008.08.007.
56. Callegari S, Majani G, Giardini A, Pierobon A, Opasich C, Cobelli F, Tavazzi L. Relationship between cognitive impairment and clinical status in chronic heart failure patients. Monaldi Arch Chest Dis. 2002;58(1):19–25.
57. Uthamalingam S, Gurm GS, Daley M, Flynn J, Capodilupo R. Usefulness of acute delirium as a predictor of adverse outcomes in patients >65 years of age with acute decompensated heart failure. Am J Cardiol. 2011;108(3):402–8. https://doi.org/10.1016/j.amjcard.2011.03.059.
58. Alosco ML, Spitznagel MB, Raz N, Cohen R, Sweet LH, Colbert LH, Josephson R, van Dulmen M, Hughes J, Rosneck J, Gunstad J. Obesity interacts with cerebral hypoperfusion to exacerbate cognitive impairment in older adults with heart failure. Cerebrovasc Dis Extra. 2012;2(1):88–98. https://doi.org/10.1159/000343222.
59. Hjelm C, Broström A, Dahl A, Johansson B, Fredrikson M, Strömberg A. Factors associated with increased risk for dementia in individuals age 80 years or older with congestive heart failure. J Cardiovasc Nurs. 2014;29(1):82–90. https://doi.org/10.1097/JCN.0b013e318275543d.

60. Alosco ML, Hayes SM. Structural brain alterations in heart failure: a review of the literature and implications for risk of Alzheimer's disease. Heart Fail Rev. 2015;20(5):561–71. https://doi.org/10.1007/s10741-015-9488-5.
61. Harkness K, Heckman GA, Akhtar-Danesh N, Demers C, Gunn E, McKelvie RS. Cognitive function and self-care management in older patients with heart failure. Eur J Cardiovasc Nurs. 2014;13(3):277–84. https://doi.org/10.1177/1474515113492603.
62. Willis MS, Patterson C. Proteotoxicity and cardiac dysfunction – Alzheimer's disease of the heart? N Engl J Med. 2013;368(5):455–64. https://doi.org/10.1056/NEJMra1106180.
63. Athilingam P, Moynihan J, Chen L, D'Aoust R, Groer M, Kip K. Elevated levels of interleukin 6 and C-reactive protein associated with cognitive impairment in heart failure. Congest Heart Fail. 2013;19(2):92–8. https://doi.org/10.1111/chf.12007.
64. Alves TC, Rays J, Fráguas R Jr, Wajngarten M, Meneghetti JC, Prando S, Busatto GF. Localized cerebral blood flow reductions in patients with heart failure: a study using 99mTc-HMPAO SPECT. J Neuroimaging. 2005;15(2):150–6.
65. Kalaria VG, Passannante MR, Shah T, Modi K, Weisse AB. Effect of mitral regurgitation on left ventricular thrombus formation in dilated cardiomyopathy. Am Heart J. 1998;135(2 Pt 1):215–20.
66. Almeida OP, Garrido GJ, Beer C, Lautenschlager NT, Arnolda L, Flicker L. Cognitive and brain changes associated with ischaemic heart disease and heart failure. Eur Heart J. 2012;33(14):1769–76. https://doi.org/10.1093/eurheartj/ehr467.
67. Hajduk AM, Kiefe CI, Person SD, Gore JG, Saczynski JS. Cognitive change in heart failure: a systematic review. Circ Cardiovasc Qual Outcomes. 2013;6(4):451–60. https://doi.org/10.1161/CIRCOUTCOMES.113.000121.
68. Alosco ML, Spitznagel MB, Cohen R, Sweet LH, Josephson R, Hughes J, Rosneck J, Gunstad J. Better adherence to treatment recommendations in heart failure predicts improved cognitive function at a one-year follow-up. J Clin Exp Neuropsychol. 2014;36(9):956–66. https://doi.org/10.1080/13803395.2014.957167.
69. Davis KK, Allen JK. Identifying cognitive impairment in heart failure: a review of screening measures. Heart Lung. 2013;42(2):92–7. https://doi.org/10.1016/j.hrtlng.2012.11.003.
70. Rutledge T, Reis VA, Linke SE, Greenberg BH, Mills PJ. Depression in heart failure a meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes. J Am Coll Cardiol. 2006;48(8):1527–37.
71. Moudgil R, Haddad H. Depression in heart failure. Curr Opin Cardiol. 2013;28(2):249–58. https://doi.org/10.1097/HCO.0b013e32835ced80.
72. Diez-Quevedo C, Lupón J, González B, Urrutia A, Cano L, Cabanes R, Altimir S, Coll R, Pascual T, de Antonio M, Bayes-Genis A. Depression, antidepressants, and long-term mortality in heart failure. Int J Cardiol. 2013;167(4):1217–25. https://doi.org/10.1016/j.ijcard.2012.03.143.
73. Newhouse A, Jiang W. Heart failure and depression. Heart Fail Clin. 2014;10(2):295–304. https://doi.org/10.1016/j.hfc.2013.10.004.
74. Tousoulis D, Antonopoulos AS, Antoniades C, Saldari C, Stefanadi E, Siasos G, Stougianos P, Plastiras A, Korompelis P, Stefanadis C. Role of depression in heart failure – choosing the right antidepressive treatment. Int J Cardiol. 2010;140(1):12–8. https://doi.org/10.1016/j.ijcard.2009.05.022.
75. GBD 2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of disease study 2015. Lancet. 2016;388(10053):1459–544. https://doi.org/10.1016/S0140-6736(16)31012-1.
76. Mendis S, Puska P, Norrving B. Global atlas on cardiovascular disease prevention and control. Geneva: World Health Organization; 2011.
77. Centers for Disease Control and Prevention (CDC). Prevalence of coronary heart disease – United States, 2006–2010. MMWR Morb Mortal Wkly Rep. 2011;60(40):1377–81.
78. Deckers K, Schievink SHJ, Rodriquez MMF, van Oostenbrugge RJ, van Boxtel MPJ, Verhey FRJ, Köhler S. Coronary heart disease and risk for cognitive impairment or dementia: systematic review and meta-analysis. PLoS One. 2017;12(9):e0184244. https://doi.org/10.1371/journal.pone.0184244.
79. Zheng L, Mack WJ, Chui HC, Heflin L, Mungas D, Reed B, DeCarli C, Weiner MW, Kramer JH. Coronary artery disease is associated with cognitive decline independent of changes on magnetic resonance imaging in cognitively normal elderly adults. J Am Geriatr Soc. 2012;60(3):499–504. https://doi.org/10.1111/j.1532-5415.2011.03839.x.
80. Selnes OA, Grega MA, Bailey MM, Pham LD, Zeger SL, Baumgartner WA, McKhann GM. Do management strategies for coronary artery disease influence 6-year cognitive outcomes? Ann Thorac Surg. 2009;88(2):445–54. https://doi.org/10.1016/j.athoracsur.2009.04.061.
81. Weinstein G, Goldbourt U, Tanne D. Angina pectoris severity among coronary heart disease patients is associated with subsequent cognitive impairment. Alzheimer Dis Assoc Disord. 2015;29(1):6–11. https://doi.org/10.1097/WAD.0000000000000038.
82. Justin BN, Turek M, Hakim AM. Heart disease as a risk factor for dementia. Clin Epidemiol. 2013;5:135–45. https://doi.org/10.2147/CLEP.S30621.
83. Gruhn N, Larsen FS, Boesgaard S, Knudsen GM, Mortensen SA, Thomsen G, Aldershvile J. Cerebral blood flow in patients with chronic heart failure before and after heart transplantation. Stroke. 2001;32(11):2530–3.

84. Ikram MA, van Oijen M, de Jong FJ, Kors JA, Koudstaal PJ, Hofman A, Witteman JC, Breteler MM. Unrecognized myocardial infarction in relation to risk of dementia and cerebral small vessel disease. Stroke. 2008;39(5):1421–6. https://doi.org/10.1161/STROKEAHA.107.501106.
85. Debette S, Markus HS. The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. BMJ. 2010;341:c3666. https://doi.org/10.1136/bmj.c3666.
86. Barekatain M, Askarpour H, Zahedian F, Walterfang M, Velakoulis D, Maracy MR, Jazi MH. The relationship between regional brain volumes and the extent of coronary artery disease in mild cognitive impairment. J Res Med Sci. 2014;19(8):739–45.
87. Liu C, Liu Y, Yang Z. Myocardial infarction induces cognitive impairment by increasing the production of hydrogen peroxide in adult rat hippocampus. Neurosci Lett. 2014;560:112–6. https://doi.org/10.1016/j.neulet.2013.12.027.
88. Goto T, Maekawa K. Cerebral dysfunction after coronary artery bypass surgery. J Anesth. 2014;28(2):242–8. https://doi.org/10.1007/s00540-013-1699-0.
89. Habib S, Au K, Afridi MI, Saeed A, Jan AF, Amjad N. Frequency and predictors of cognitive decline in patients undergoing coronary artery bypass graft surgery. J Coll Physicians Surg Pak. 2014;24(8):543–8. https://doi.org/08.2014/JCPSP.543548.
90. Hoth KF, Poppas A, Ellison KE, Paul RH, Sokobin A, Cho Y, Cohen RA. Link between change in cognition and left ventricular function following cardiac resynchronization therapy. J Cardiopulm Rehabil Prev. 2010;30(6):401–8. https://doi.org/10.1097/HCR.0b013e3181e1739a.
91. Burkauskas J, Noreikaite A, Bunevicius A, Brozaitiene J, Neverauskas J, Mickuviene N, Bunevicius R. Beta-1-selective Beta-blockers and cognitive functions in patients with coronary artery disease: a cross-sectional study. J Neuropsychiatry Clin Neurosci. 2016;28(2):143–6. https://doi.org/10.1176/appi.neuropsych.15040088.
92. Burkauskas J, Brozaitiene J, Bunevicius A, Neverauskas J, Zaliunaite V, Bunevicius R. Association of Depression, anxiety, and type D personality with cognitive function in patients with coronary artery disease. Cogn Behav Neurol. 2016;29(2):91–9. https://doi.org/10.1097/WNN.0000000000000093.
93. Denollet J, Freedland KE, Carney RM, de Jonge P, Roest AM. Cognitive-affective symptoms of depression after myocardial infarction: different prognostic importance across age groups. Psychosom Med. 2013;75(7):701–8. https://doi.org/10.1097/PSY.0b013e31829dbd36.
94. Levine DA, Davydow DS, Hough CL, Langa KM, Rogers MA, Iwashyna TJ. Functional disability and cognitive impairment after hospitalization for myocardial infarction and stroke. Circ Cardiovasc Qual Outcomes. 2014;7(6):863–71. https://doi.org/10.1161/HCQ.0000000000000008.
95. Patel N, Minhas JS, Chung EM. Risk factors associated with cognitive decline after cardiac surgery: a systematic review. Cardiovasc Psychiatry Neurol. 2015;2015:370612. https://doi.org/10.1155/2015/370612.
96. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Brown DL, Block PC, Guyton RA, Pichard AD, Bavaria JE, Herrmann HC, Douglas PS, Petersen JL, Akin JJ, Anderson WN, Wang D, Pocock S, PARTNER Trial Investigators. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med. 2010;363(17):1597–607. https://doi.org/10.1056/NEJMoa1008232.
97. Wan B, Rahnavardi M, Tian DH, Phan K, Munkholm-Larsen S, Bannon PG, Yan TD. A meta-analysis of MitraClip system versus surgery for treatment of severe mitral regurgitation. Ann Cardiothorac Surg. 2013;2(6):683–92. https://doi.org/10.3978/j.issn.2225-319X.2013.11.02.
98. Ghanem A, Kocurek J, Sinning JM, Wagner M, Becker BV, Vogel M, Schröder T, Wolfsgruber S, Vasa-Nicotera M, Hammerstingl C, Schwab JO, Thomas D, Werner N, Grube E, Nickenig G, Müller A. Cognitive trajectory after transcatheter aortic valve implantation. Circ Cardiovasc Interv. 2013;6(6):615–24. https://doi.org/10.1161/CIRCINTERVENTIONS.112.000429.
99. Barth S, Hamm K, Fodor S, Reents W, Kerber S, Halbfass P, Hautmann MB, Schieffer B, Soda H. Incidence and clinical impact of cerebral lesions after the MitraClipÂ® procedure. J Heart Valve Dis. 2017;26(2):175–84.
100. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M, ESC Scientific Document Group. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J. 2016;37(1):67–119. https://doi.org/10.1093/eurheartj/ehv317.
101. White J, Hopkins RO, Glissmeyer EW, Kitterman N, Elliott CG. Cognitive, emotional, and quality of life outcomes in patients with pulmonary arterial hypertension. Respir Res. 2006;7:55.
102. Somaini G. Disease-targeted treatment improves cognitive function in patients with precapillary pulmonary hypertension. Respiration. 2015;90:376–83.

103. Halank M, Einsle F, Lehman S, Bremer H, Ewert R, Wilkens H, Meyer FJ, Grünig E, Seyfarth HJ, Kolditz M, Wieder G, Höffken G, Köllner V. Exercise capacity affects quality of life in patients with pulmonary hypertension. Lung. 2013;191(4):337–43. https://doi.org/10.1007/s00408-013-9472-6.
104. Chin KM, Gomberg-Maitland M, Channick RN, Cuttica MJ, Fischer A, Frantz RP, Hunsche E, Kleinman L, McConnell JW, McLaughlin VV, Miller CE, Zamanian RT, Zastrow MS, Badesch DB. Psychometric validation of the pulmonary arterial hypertension-symptoms and impact (PAH-SYMPACT) questionnaire: results of the SYMPHONY trial. Chest. 2018;154:pii: S0012-3692(18)30649-4. https://doi.org/10.1016/j.chest.2018.04.027.
105. Vanini B, Grazioli V, Sciortino A, Pin M, Merli VN, Celentano A, Parisi I, Klersy C, Petrucci L, Salati M, Politi P, D'Armini AM. Neuropsychological outcomes after pulmonary endarterectomy using moderate hypothermia and periodic circulatory arrest. J Heart Lung Transplant. 2018;37(7):860–4. https://doi.org/10.1016/j.healun.2018.02.007.
106. Gräsner JT, Lefering R, Koster RW, Masterson S, Böttiger BW, Herlitz J, Wnent J, Tjelmeland IB, Ortiz FR, Maurer H, Baubin M, Mols P, Hadžibegović I, Ioannides M, Škulec R, Wissenberg M, Salo A, Hubert H, Nikolaou NI, Lóczi G, Svavarsdóttir H, Semeraro F, Wright PJ, Clarens C, Pijls R, Cebula G, Correia VG, Cimpoesu D, Raffay V, Trenkler S, Markota A, Strömsöe A, Burkart R, Perkins GD, Bossaert LL, Collaborators ERCONE. EuReCa ONE-27 nations, ONE Europe, ONE registry: a prospective one month analysis of out-of-hospital cardiac arrest outcomes in 27 countries in Europe. Resuscitation. 2016;105:188–95. https://doi.org/10.1016/j.resuscitation.2016.06.004.
107. Lemiale V, Dumas F, Mongardon N, Giovanetti O, Charpentier J, Chiche JD, Carli P, Mira JP, Nolan J, Cariou A. Intensive care unit mortality after cardiac arrest: the relative contribution of shock and brain injury in a large cohort. Intensive Care Med. 2013;39(11):1972–80. https://doi.org/10.1007/s00134-013-3043-4.
108. Dragancea I, Rundgren M, Englund E, Friberg H, Cronberg T. The influence of induced hypothermia and delayed prognostication on the mode of death after cardiac arrest. Resuscitation. 2013;84(3):337–42. https://doi.org/10.1016/j.resuscitation.2012.09.015.
109. Nolan JP, Soar J, Cariou A, Cronberg T, Moulaert VR, Deakin CD, Bottiger BW, Friberg H, Sunde K, Sandroni C. European Resuscitation Council and European Society of Intensive Care Medicine guidelines for post-resuscitation care 2015: section 5 of the European Resuscitation Council guidelines for resuscitation 2015. Resuscitation. 2015;95:202–22. https://doi.org/10.1016/j.resuscitation.2015.07.018.
110. Moulaert VR, Verbunt JA, van Heugten CM, Wade DT. Cognitive impairments in survivors of out-of-hospital cardiac arrest: a systematic review. Resuscitation. 2009;80(3):297–305. https://doi.org/10.1016/j.resuscitation.2008.10.034.
111. Lilja G, Nielsen N, Friberg H, Horn J, Kjaergaard J, Nilsson F, Pellis T, Wetterslev J, Wise MP, Bosch F, Bro-Jeppesen J, Brunetti I, Buratti AF, Hassager C, Hofgren C, Insorsi A, Kuiper M, Martini A, Palmer N, Rundgren M, Rylander C, van der Veen A, Wanscher M, Watkins H, Cronberg T. Cognitive function in survivors of out-of-hospital cardiac arrest after target temperature management at 33°C versus 36°C. Circulation. 2015;131(15):1340–9. https://doi.org/10.1161/CIRCULATIONAHA.114.014414.
112. Sulzgruber P, Kliegel A, Wandaller C, Uray T, Losert H, Laggner AN, Sterz F, Kliegel M. Survivors of cardiac arrest with good neurological outcome show considerable impairments of memory functioning. Resuscitation. 2015;88:120–5. https://doi.org/10.1016/j.resuscitation.2014.11.009.
113. Harukuni I, Bhardwaj A. Mechanisms of brain injury after global cerebral ischemia. Neurol Clin. 2006;24(1):1–21.
114. Grubb NR, Fox KA, Smith K, Best J, Blane A, Ebmeier KP, Glabus MF, O'Carroll RE. Memory impairment in out-of-hospital cardiac arrest survivors is associated with global reduction in brain volume, not focal hippocampal injury. Stroke. 2000;31(7):1509–14.
115. Nielsen N, Wetterslev J, Cronberg T, Erlinge D, Gasche Y, Hassager C, Horn J, Hovdenes J, Kjaergaard J, Kuiper M, Pellis T, Stammet P, Wanscher M, Wise MP, Åneman A, Al-Subaie N, Boesgaard S, Bro-Jeppesen J, Brunetti I, Bugge JF, Hingston CD, Juffermans NP, Koopmans M, Køber L, Langørgen J, Lilja G, Møller JE, Rundgren M, Rylander C, Smid O, Werer C, Winkel P, Friberg H, Trial Investigators TTM. Targeted temperature management at 33°C versus 36°C after cardiac arrest. N Engl J Med. 2013;369(23):2197–206. https://doi.org/10.1056/NEJMoa1310519.
116. Froehler MT, Geocadin RG. Hypothermia for neuroprotection after cardiac arrest: mechanisms, clinical trials and patient care. J Neurol Sci. 2007;261(1–2):118–26.
117. McCullough JN, Zhang N, Reich DL, Juvonen TS, Klein JJ, Spielvogel D, Ergin MA, Griepp RB. Cerebral metabolic suppression during hypothermic circulatory arrest in humans. Ann Thorac Surg. 1999;67(6):1895–9; discussion 1919–21
118. Bro-Jeppesen J, Kjaergaard J, Wanscher M, Nielsen N, Friberg H, Bjerre M, Hassager C. The inflammatory response after out-of-hospital cardiac arrest is not modified by targeted temperature management at 33 °C or 36 °C. Resuscitation. 2014;85(11):1480–7. https://doi.org/10.1016/j.resuscitation.2014.08.007.
119. Cronberg T, Lilja G, Horn J, Kjaergaard J, Wise MP, Pellis T, Hovdenes J, Gasche Y, Åneman A, Stammet P, Erlinge D, Friberg H, Hassager C, Kuiper M, Wanscher M, Bosch F, Cranshaw J, Kleger GR, Persson S, Undén J, Walden A, Winkel P, Wetterslev J, Nielsen N, Trial Investigators TTM. Neurologic function and health-

related quality of life in patients following targeted temperature management at 33°C vs 36°C after out-of-hospital cardiac arrest: a randomized clinical trial. JAMA Neurol. 2015;72(6):634–41. https://doi.org/10.1001/jamaneurol.2015.0169.

120. Lilja G, Nielsen N, Bro-Jeppesen J, Dunford H, Friberg H, Hofgren C, Horn J, Insorsi A, Kjaergaard J, Nilsson F, Pelosi P, Winters T, Wise MP, Cronberg T. Return to work and participation in society after out-of-hospital cardiac arrest. Circ Cardiovasc Qual Outcomes. 2018;11(1):e003566. https://doi.org/10.1161/CIRCOUTCOMES.117.003566.
121. Wachelder EM, Moulaert VR, van Heugten C, Verbunt JA, Bekkers SC, Wade DT. Life after survival: long-term daily functioning and quality of life after an out-of-hospital cardiac arrest. Resuscitation. 2009;80(5):517–22. https://doi.org/10.1016/j.resuscitation.2009.01.020.
122. Baldi E, Vanini B, Savastano S, Danza AI, Martinelli V, Politi P. Depression after a cardiac arrest: an unpredictable issue to always investigate for. Resuscitation. 2018;127:e10–1. https://doi.org/10.1016/j.resuscitation.2018.03.027.
123. Lilja G, Nilsson G, Nielsen N, Friberg H, Hassager C, Koopmans M, Kuiper M, Martini A, Mellinghoff J, Pelosi P, Wanscher M, Wise MP, Östman I, Cronberg T. Anxiety and depression among out-of-hospital cardiac arrest survivors. Resuscitation. 2015;97:68–75. https://doi.org/10.1016/j.resuscitation.2015.09.389.
124. Haywood K, Whitehead L, Nadkarni VM, Achana F, Beesems S, Böttiger BW, Brooks A, Castrén M, Ong MEH, Hazinski MF, Koster RW, Lilja G, Long J, Monsieurs KG, Morley PT, Morrison L, Nichol G, Oriolo V, Saposnik G, Smyth M, Spearpoint K, Williams B, Perkins GD, Collaborators COSCA. COSCA (Core outcome set for cardiac arrest) in adults: an advisory statement from the international liaison committee on resuscitation. Resuscitation. 2018;127:147–63. https://doi.org/10.1016/j.resuscitation.2018.03.022.
125. Sandroni C, Cariou A, Cavallaro F, Cronberg T, Friberg H, Hoedemaekers C, Horn J, Nolan JP, Rossetti AO, Soar J. Prognostication in comatose survivors of cardiac arrest: an advisory statement from the European Resuscitation Council and the European Society of Intensive Care Medicine. Resuscitation. 2014;85(12):1779–89.

Emotional Processing and Heart Activity

12

Umberto Provenzani

Contents

Abstract

In many cultures throughout history, the heart always gathered several qualities to be pronounced as "the seat of life," where emotions increased its activity, and even to this day, heart imagery is often used to refer to emotional experience. Where does this association come from, and what relevance does it have for clinical research today? An increasing knowledge about afferent circuits to the nervous system (and efferent circuits to the body organs) resulted in new theories integrating the interplay of the heart and brain into emotional processes. Since the normal variability in heart rate is influenced by sympathetic or parasympathetic dominance, depending on environmental changes, the variation and the degree of its variability (heart rate variability (HRV)) have been found to provide information about emotional processing and the heart's ability to respond to it. The two main models linking autonomic regulation to physiological and emotional processes are the polyvagal theory and the neurovisceral integration model, both presented here. Another important side of the connection between emotional processing and heart activity is represented by the concept of emotions as a risk factor for cardiovascular disease. The hypothesized link

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*,
https://doi.org/10.1007/978-3-030-28008-6_15

between negative emotional triggers and clinical events is mediated through neurophysiological responses such as autonomic dysfunction, hemodynamic responses, neuroendocrine activation, and inflammatory and prothrombotic responses. A wide array of negative and positive emotions, briefly summarized in this chapter, has been shown to independently increase or decrease the risk of a CVD-related event and mortality in different populations.

Keywords

Emotion · Processing · Heart · Activity · Variability · HRV · CVD

Introduction

In many cultures throughout history, the heart always gathered several qualities to be pronounced as the seat of life, where emotions and passions of the body increased its frequency, and the same occurred with fear or a sudden external menace [1]. Ancient Hindus, Samoyeds, and certain West African populations saw the heart as the location of the soul [2], whereas ancient Egyptians were convinced that the heart generated emotions, thought, and will. Also, they believed that the weight of the heart, measured in the afterlife, would be used to judge the deceased persons' life and to determine their ultimate fate [3]. Ancient Greek mythology, as well, considered the heart as the seat of the vital, emotional, and spiritual life, grouping all the components of the soul [4]. Aristotle saw the heart as the main keeper of body heat, carried by the blood, linking the idea of body heat as the source of "the sensory soul," referring to physical sensations, temperament, and emotions [5]. While most early Stoics adopted a unitary view of the soul, Galen rather favored Plato's tripartite model, in which he assigned various functions to different parts of the body: reason was located in the brain, emotion (particularly anger) in the heart, and desire in the liver [6]. Of note, Galen's theory assumed that the ventricles of the brain were the seat of thoughts, called "spirits," while emotions resided in the vascular system, with four "humors" or secretions influencing the temperament ("sanguine," "choleric," "phlegmatic," and "melancholic"). Through modern biomedical research and the progress of neuroscience, the "spirits" circulating in the ventricles have turned out to be neural electrical activity while the "humors" flowing in the vascular system, endocrine secretions [7].

Even to this day, heart imagery is often used to refer to emotional experience (i.e., "I mean it with all my heart," "lighthearted," "heartless," "my heart skipped a beat"), and, when describing extreme feelings, it is a common gesture to clasp our hands to our hearts, indicating both the symbolic associations of the heart with emotions and the stress-related physical changes we feel in the body [8]. Where does this association come from, and what relevance does it have for clinical research today? The purpose of this chapter is, along these lines, to summarize historical upgrades in the exploration of the intimate connection between the heart and the emotional processes of the nervous system, illustrate the modern conception of the heart-brain interplay with its theoretical models, and review how pathological states of both systems can affect the other in a dynamical perspective. We will use the term "emotion" referring to the array of neurophysiological reactions that occur, more or less unconsciously, when the brain detects certain challenging situations, while we use the term "feeling" to refer to the conscious experience of these somatic and cognitive changes.

The Emotional Brain and the Heart

Even if body and soul, in human history, have often been considered the battlefield for a perpetual fight between intellect and emotion (or the brain versus the heart), modern research now agrees that cognition and emotion are two distinct functions but organized through bidirectional neural connections (i.e., between the frontal cortex and amygdala) to modulate cognitive input and emotional information processing [9]. Patients

with a damage in the brain frontal lobes, a presumed key site of integration between cognitive and emotional systems, struggle to function effectively in daily activities, even though their intellectual abilities are conserved. This evidence supports the seemingly counterintuitive position (especially if compared to historical thinking) that input from the emotional system not only facilitates but is actually indispensable to the process of rational decision-making [10]. Emotions can also direct attention on stimuli that are congruent to our current emotional state (mood-congruity effect [11]) and influence memory and learning [12].

It was William James, in 1884, who formally began the scientific quest for the source of emotional experience with its article "What is an emotion?". James proposed that emotions actually arise from organic changes in the body, in response to an arousing stimulus. Rather than an emotion causing the physiological response, it's the perception of the external stimulus that will cause early visceral changes, and their interpretation will then create the experience of the emotion itself ("we feel sorry because we cry") [13]. However, in the 1920s, Walter Cannon argued that this supposed signaling from the body was too slow and did not have a sufficient differentiation to explain the dynamic range and variety of emotional expression. Working on animal models, Cannon observed that a transection of the brain below the level of the hypothalamus eliminated a coordinated emotional reaction of rage, while it was still present if the section was conducted above the same level. This reaction was called "sham rage" as it was disconnected from cortical areas, which were assumed to be critical for the emotional experience. In Cannon's view, sensory information from the thalamus was sent to the brain cortex to produce conscious feelings and through the hypothalamus to the body (through the brain stem and spinal cord) to produce physiological responses, implying that the hypothalamus was critical for the assessment of emotional significance of external stimuli. His main research focused on the autonomic nervous system and particularly the sympathetic division, with its responses to fear and threat, resulting in the "fight-or-flight" model of response [14] described later in the chapter for its influences on cardiac function.

Later contributions on the genesis of emotional responses came with the "limbic theory" of Papez in 1937, later elaborated by Paul McLean in the 1950s, that expanded Cannon's framework. The model proposed that the hypothalamus sends signals to the anterior thalamus and then to the cingulate cortex, which integrates signals from the sensory cortex and from the hypothalamus directly, thus generating the conscious experience of feeling. Projections from the sensory cortex back to both the cingulate cortex and the hippocampus, and from the hippocampus back to the mammillary bodies of the hypothalamus, complete the loop (called "the Papez circuit"). Papez's theory was modified by MacLean, who reintroduced the term "limbic system" referring to the emotional components of the brain, moving the spotlight from the cingulate cortex to the hippocampus as the main brain area of feelings, where the external world (represented in sensory regions on the lateral cortex) converged with the internal world (represented in the medial cortex and hypothalamus) [15].

Furthermore, studies in nonhuman primates suggested the earliest clues that the amygdala had a key role in emotional reactions to environmental stimuli. Following the studies of Weiskrantz [16], who lesioned the amygdala in monkeys demonstrating an impairment in acquiring behavioral responses to shock-predictive cues, subsequent studies in both rodents [17] and humans [18] indicated the amygdala as an important seat of recognition of environmental stimuli, also connected to a type of emotional learning called fear conditioning [19]. Additionally, the breakthrough of emotional stimuli into consciousness within emotional tasks is now known to be gated by the amygdala, which appears to be involved in translating stimuli into bodily arousal (i.e., increasing blood pressure) [20], but this relationship could be bidirectional. Afferent signals of physiological arousal, in fact, are processed in the amygdala and integrated with threat stimuli [21], and it has been demonstrated that sensitivity to fear stimuli is also modulated by the cardiac

cycle [22]. Additionally, fear states elicit a marked sympathetic nervous activation, and anxious individuals show increased sensitivity to psychological threat that translates into enhanced autonomic reactivity [23] and superior detection of internal bodily sensations, notably heartbeats [24]. Even if a complete overview about evolving theoretical models integrating the amygdala with other brain areas exceeds the purpose of this chapter, it has to be underlined that the amygdala is now known to be part of a larger circuit involved in emotional processing, including the hypothalamus, the periaqueductal gray region of the brain stem, and also cortical areas (like the ventral region of the anterior cingulate cortex, the insular cortex, and the ventromedial prefrontal cortex) which are related to complex emotional states [15].

Focusing on the brain-heart interplay in emotional processing, throughout the years an advanced knowledge of the importance of afferent circuits to the nervous system resulted in new theories, integrating the input from the heart and other organs into the emotional processes in the brain. In fact, the heart is particularly sensitive to changes in a number of other psychophysiological systems and is also an endocrine organ that, with each beat, transmits dynamic patterns of hormonal, neurological, and electromagnetical information to the brain and the body [25]. An important progress toward the discovery of the bidirectional influence between the cardiovascular system and the emotional system was achieved with the work of John and Beatrice Lacey throughout the 1960s and the 1970s, with their behavioral and neurophysiological research on sensory-motor integration. Challenging Cannon's theory that physiological indicators of emotion and autonomic responses, like heart rate and blood pressure, increased in concert when the body is aroused under the control of the brain, Lacey and Lacey observed that the heart seemed to produce, at times, a response that did not match with other physiological indexes [26]. For example, an increase in skin conductance and respiration rate was associated with a decrease in heart rate. This "directional fractionation" was specific to the peculiar type of stimulation provided and the mental process involved: attention toward an internal task (i.e., calculations) produced an increase in heart rate, while attention to the environment (i.e., watching a theatrical performance) decreased the heart rate, but skin conductance increased in both cases [27]. Also, the autonomical response changed according to the context of a specific task but also with its emotional content: for example, heart rate decreased when subjects were confronted with distressing emotional stimuli in the external environment, but it increased when they had to remember the same situation [28].

Additionally, Lacey and Lacey observed that in subjects performing tasks which required environmental intake and emotional arousal, repeated studies proved an anticipatory cardiac deceleration. Their theory implied cardio-cortical interaction and proposed that, following each heartbeat, the stimulation of baroceptors located in the arterial system (and particularly in the carotid sinus) brought information through Hering's nerve and the glossopharyngeal nerve to the medulla and subsequently to higher centers. This feedback loop served to reduce daily variation in arterial blood pressure [29] and suggested that cortical activity is briefly inhibited as a result of baroceptor activity. Another point of this model underlined that faster reaction times in response to an environmental stimuli (such as a task) were preceded by a greater decrease in heart rate, proposing that sensory intake is enhanced if information occurs when the baroceptor discharge is reduced [30]. Subsequent studies confirmed that, on the other hand, an increase in heart rate and consequent increased afferent discharge of baroceptors inhibited cortical activity during a reaction time task [31].

Heart Rate Variability

Although there are many factors creating the interplay between cardiac activity and the environment, an element with special importance is the well-described model of psychophysiological arousal modulated by the autonomic nervous

system (ANS), divided into the excitatory sympathetic nervous system (SNS) and the inhibitory parasympathetic nervous system (PNS). SNS and PNS work in opposite directions to generate different physiological responses of arousal. SNS becomes dominant in case of exercise and some heart diseases or when the body needs to avoid or challenge threats of psychological or physiological stress, producing a peculiar set of responses (originally named "fight or flight" in Cannon's historical model proposed in 1932) which include an increase in heart rate, through a stimulation of pacemaker cells in the sinoatrial node. PNS activity, on the other hand, is more active during phases of relative safety and stability, maintaining a lower degree of arousal and decreasing heart rate, keeping it below the intrinsic firing rate of the sinoatrial node.

A key point in this two-way model is flexibility: emotions and their psychophysiological correlates (in everyday life and even more in stressful situations) can have a wide spectrum in quantity and quality; therefore, an excessive rigidity of the autonomic system would impair our ability to produce an appropriate emotional response to external and internal stimulations. Since the normal variability in heart rate is influenced by sympathetic and parasympathetic dominance, according to this model, the variation and the degree of variability in the heart rate (heart rate variability; HRV) can provide information about the autonomic neural regulation and the heart's ability to respond to it.

HRV Measurement

HRV has been an object of study for the past 50 years, but its clinical interpretations and integrative theories have only emerged at the end of the last century. The investigation of HRV, in fact, was strictly related to the precision of the measurement of beat-to-beat changes. The early psychophysiologists relied on the polygraph to obtain measurements of psychological processes, and the cardiotocograph discovered by Boas defined a remarkable improvement, but before the invention of computers, R-R intervals were still measured with a ruler, and HRV was viewed as error variance due to poor experimental control [32]. From a conceptual point of view, also, HRV was related to individual differences in physiological reactivity or behavioral impulsivity [33]. Spectral analysis of HRV was introduced by Saykrs in 1973, and it was followed by cross-spectral analysis in 1976 by Porges, who applied it to define a theory of cardiac vagal tone.Since HRV measurements became easier to perform and noninvasive with good reproducibility (if used under standardized conditions), HRV became an increasingly used marker of emotion regulatory ability. It can be analyzed simply with an ECG lead II configuration (one electrode on the right arm, one on the left leg, plus a ground): HRV measures are then calculated assessing the variation of interbeat intervals, defined as the distance between two R spikes on the ECG. The set of interbeat intervals can be consequently analyzed with different types of variance-based models. In particular, power spectral analysis can be used to separate the variance of the intervals into spectrums of frequencies, and, afterward, statistical analysis can be performed to obtain overall HRV or HRV at different frequencies [34]. This technique is used to obtain a power spectrum that reveals variance in heart rate in specific ranges of frequencies: high-frequency components (15–40 Hz) will primary reflect parasympathetic modulation and sinus arrhythmia, and low-frequency components (0.04–0.15 Hz) will reflect a shift toward sympathetic modulation [35].

Therefore, **heart rate variability (HRV)** can be used as:

- **A sign of sympathetic-parasympathetic autonomic balance**. SNS and PNS produce different modulations of the interval of QRS complexes in the ECG. As already mentioned, sympathetic activity is associated with the low-frequency range (0.04–0.15 Hz), while parasympathetic activity is associated with the higher-frequency range (0.15–0.4 Hz) of modulation frequencies of heart rate: this difference in frequency ranges allows to

separate, during HRV analysis, the distinctive sympathetic and parasympathetic contributions [36]. These notions also reflect how the two branches work with different signaling mechanisms and temporal effects: sympathetic influence on heart rate is mediated by the release of norepinephrine, with a slow action on cardiac function (peak effect after 4 s), while parasympathetic regulation has a shorter latency response (about 0.5 s) and is mediated by acetylcholine [35].

- **A mirror of the cardiorespiratory control system**. A rhythmic and cyclic variation in heart rate is produced by the different phases of inspiration and expiration, and it has been called respiratory sinus arrhythmia [37]. Specifically, inspiration temporarily inhibits parasympathetic influence on heart rate (resulting in a heart rate increase), while expiration restores it (resulting in a heart rate decrease). Since the PNS is the only system with a sufficient latency of action to be synchronized with respiration, sinus arrhythmia is mostly mediated by PNS and thus represents a parasympathetically mediated HRV [38].
- **An indicator of the heart's possibility to adapt to the environment**, including its emotional content, by identifying and responding quickly to stimulation [39]. The rest of this paragraph will focus on this feature.

The interpretation of HRV is thus dependent on appropriate technologies and methodologies, in parallel with the knowledge of the underlying neural mechanisms. Progress in these fields has led to the articulation of two major neurophysiological models related to HRV, linking autonomic regulation to physiological, psychological, and behavioral processes.

The Polyvagal Theory

Formulated by Porges in 1995 [40], the polyvagal theory is based within an evolutionary framework, articulating three phylogenetic stages of development of the human autonomic nervous system, each stage associated with a distinct autonomic subsystem and function:

1. *Unmyelinated vagus* (*dorsal vagal complex*) supports simple immobilization (i.e., freezing) in response to threat and has its lower motor neurons in the dorsal motor nucleus of the vagus. The dorsal vagal complex slows heart rate through tonic inhibition of sinoatrial node activity.
2. *Sympathetic-adrenal system* is involved in active mobilization responses (i.e., "fight or flight") and has its lower motor neurons in the spinal cord. The activation of this system increases heart rate, with the purpose of mobilizing useful resources.
3. *Myelinated vagus* (*ventral vagal complex*) is related to social communication, self-soothing, and calming, and its lower motor neurons are in the nucleus ambiguus. It can rapidly withdraw or restore an inhibitory influence on the sinoatrial node. It also has afferent fibers terminating in the nuclei of the facial and trigeminal nerves and includes portions of cranial nerves that mediate facial expression, head turning, vocalization, listening, and other socially relevant behaviors. The connection of the ventral vagal complex and these cranial nerves provides a mechanism by which cardiac states can be coordinated with social behaviors.

The most phylogenetically primitive subset, the unmyelinated vagus (also responsible of the vasovagal syncope), is shared with most vertebrates, together with the more recent sympathetic-adrenal system connected to the HPA axis. The three circuits can be conceptualized as a dynamic, adaptive response to external events and contexts. Their hierarchy follows the Jacksonian "principle of dissolution" (proposed by Jackson in 1958 to explain changes in the functions of the brain due to damage): higher neural circuits (i.e., phylogenetically newer) inhibit the lower circuits (i.e., phylogenetically older).

With the perception of a safe environment, the body is regulated toward visceral homeostasis

through the ventral vagal complex, inhibiting the stress response system of the HPA axis and decreasing heart rate. Also, brain stem nuclei regulating this complex are linked to facial and head muscles: this connection is responsible of associations between social engagement and bodily states. When confronted to a threat, the defensive strategy is organized by the two more primitive neural circuits, which become responsible of influencing heart rate. The modulation of cardiac activity is also linked to the availability of metabolic resources required for mobilization: cardiac output must be regulated for the body to remain calm in safe environments, to mobilize for fight-or-flight behaviors, or to immobilize for avoidance behaviors.

The human heart is thus mainly regulated by the strong tonic vagal influence, through myelinated fibers, which keeps the heart rate lower than the intrinsic rate of the sinoatrial node. This is unique to mammals, where the ventral vagal complex operates as an active "vagal brake" [41], maintaining a low level of arousal and promoting social communication. The modulation of the vagal brake on the heart's output generates a fast and flexible balance decreasing the inhibitory control to increase heart rate (and increasing the inhibitory control to slow heart rate): this rapid downregulation of vagal break thus provides an effective way of influencing the heart rate, without activating the sympathetic system and mobilizing metabolic resources in a faster and more powerful way. Deficits in the regulation of the vagal break will result in the recruitment of older autonomic systems, also associated with health-related (i.e., hypertension, gastric ulcers) and behavioral (i.e., irritability) costs. The older systems, in fact, although functional in the short term, may result in damage when expressed for longer periods (probably, the stress and coping neurophysiological strategies that are adaptive for reptiles, such as apnea and bradycardia, may be lethal for mammals) [42].

The assessment of risk is performed by the brain through the integration of sensory information from the environment. This evaluation may involve subcortical limbic structures and can be operated on an unconscious level: this is considered as the foundation of "neuroception," a neural process different from perception, involved in environmental risk assessment. From a clinical point of view, anxiety disorders would thus represent a maladaptive behavior characterized by the inability to inhibit defense systems (i.e., the dorsal vagal complex and the sympathetic system) in safe environments, resulting in an inappropriate increase of arousal, heart rate, and impairment of social communication [43].

Additionally, even if the modulation of heart rate is associated to different mechanisms, the ventral vagal complex is thus considered the main efferent pathway that can provide the immediate changes characterizing the respiratory sinus arrhythmia (RSA) and, consequently, HRV. This is why the measurement of RSA can also provide an assessment of the vagal brake and an index of emotional control. Many studies, in fact, support the theory that an effective and high-level suppression of RSA is a sign of an appropriate social and emotional regulation, strictly linked to pertinent differences in facial movements [44]. Children with problems in behavioral regulation have lower baseline RSA and RSA responses [45], while stable RSA suppression is linked to fewer behavioral problems, better social skills, and greater emotional expressivity [46]. Adolescent brothers of crime offenders with higher RSA have a reduced risk of externalizing psychopathology [47]. In adults, higher RSA predicts greater self-reported emotional control and decreased arousal in response to stressors, while a lower modulation of RSA is associated with social anxiety [48].

The Neurovisceral Integration Model

The neurovisceral integration model, proposed by Thayer et al. in 2000 [49], attempts to integrate the complex interactions of cognitive, affective, behavioral, and physiological components of normal and pathological affective states, into a network aimed at regulation of emotions. The anatomical structures included in this model are represented by areas of the central nervous system (particularly the cingulate cortex) and peripheral

organs, with a focus on the cardiovascular system. This network is related to important functions such as attentional regulation, classical conditioning, affective information processing, and physiological flexibility.

In this model, emotions are considered self-regulatory responses that coordinate the body in a goal-directed behavior, aimed at the response to an environmental event, through the activation of multiple sub-systems. This integration is an index of the body's ability to adjust to external changes and demands. Specific emotions imply peculiar eliciting signals, followed by specific action tendencies such as selective attention to relevant stimuli [50]. A flexible emotional control will choose an appropriate response from an adequate behavioral repertoire, inhibiting other less appropriate responses. In this view the whole organism is seen as a complex set of sub-systems working together in a coordinated fashion, through feedback and feed-forward circuits: the emotional response will be then organized through this interaction, as a distributed system. The arrays of processes involved in emotional response are thus considered to be subsets of a larger, self-organizing system, and specific emotion states emerge from interactions among these lower-level elements.

Within this model, a disorder of emotional control, such as an anxiety disorder, may be viewed as the inability to shift into an emotional state that is appropriate to an external demand, resulting in an incorrect behavioral pattern characterized by inflexibility [51]. Essential to this complex task is the ability of reading the emotional environment (with the aid of self-monitoring) disregarding nonessential information through selective attention. HRV thus appears here to be strictly related to attentional control and emotional regulation [52], and cardiac vagal tone, as already mentioned, can be used as an index of the efficiency of central-peripheral neural feedback mechanisms (specifically high vagal tone is associated with a greater ability to self-regulate and behavioral flexibility).

The functional unit within the CNS that appears to control goal-directed behaviors and adaptability is the central autonomic network (CAN), which anatomical structures include the anterior cingulate, insular and ventromedial prefrontal cortices, the central nucleus of the amygdala, the paraventricular and related nuclei of the hypothalamus, the periaqueductal gray matter, the parabrachial nucleus, the nucleus of the solitary tract (NTS), the nucleus ambiguus, the ventrolateral medulla, the ventromedial medulla, and the medullary tegmental field [53]. The primary output of the CAN is mediated through parasympathetic neurons, connected to the heart via the stellate ganglia and the vagus nerve, linking the CAN directly to HRV. Sensory information from the heart is also fed back to the CAN (i.e., baroceptor reflex). Since the singular components of the CAN are interconnected, their reciprocal feedback constitutes a nonlinear dynamical system which allows multiple strategies to a given response. For example, increasing the heart rate can be obtained with CAN direct and indirect pathways, which can modulate the output through various combinations of sympathetic and parasympathetic influence to the sinoatrial node. Of note, the CAN is under tonic inhibitory control obtained through GABA interneurons in the nucleus of the solitary tract: an alteration of this pathway can lead to hypertension and sinus tachycardia. This model thus identifies in the CAN the neurophysiological command center, organizing cognitive, behavioral, and physiological processes into regulated emotion states. This coordination is obtained by inhibiting other potential responses, synaptically in the brain and vagally in the periphery [54]. From this perspective, HRV can be considered a mirror of the CAN's function to regulate the timing and magnitude of an emotional response through inhibition, according to environmental stimuli.

Since neurovisceral integration of emotions and self-regulatory ability are reflected by the autonomically mediated cardiovascular variability, and vagal influences dominate cardiovascular control with a tonic vagal inhibition, the reductions of HRV in certain pathological conditions are consistent to this model. Studies on depression [52] and generalized anxiety [55] have shown a relative reduction in vagally mediated HRV associated to cardiac symptoms of panic anxiety,

within a psychological framework of poor attentional control, behavioral inflexibility, and ineffective emotional regulation. A decrease in cardiac control through the vagal nerve, and a consequent reduction of HRV, will result in a disinhibition of the slower sympathetic influence, reflecting the body's inability of tracking rapid changes in environmental demands and organizing an appropriate response. Vagal inhibition has also been related to behavioral hostility and risk for cardiovascular disease [56], while other studies have suggested that it might represent the link between psychological factors and myocardial ischemia [57].

Comment on Both Theories

The polyvagal theory and the neurovisceral integration model present similarities in two assumptions. First, they both indicate a key role for the vagally mediated inhibition of autonomic responses in the expression and regulation of emotions. Second, they propose that HRV measures are a mirror of the body's ability to regulate properly this emotional responding. Nonetheless, the two models show also some major differences.

Whereas the neurovisceral integration model underlines the importance of neuroanatomical connections between the autonomic system and brain regions associated with emotional processing (i.e., cortical and limbic areas of the CAN), the polyvagal theory's core relies on the links between the vagus and other cranial nerves involved in behavioral expression of emotions (i.e., facial muscles). The focus on different neural circuits generated diverging extensions of both theories: the model of neurovisceral integration was used to analyze emotional dysregulation in affective dysfunctions while the polyvagal theory to explain deficits in social and developmental processes. Further research and combination of the elements from both theories could help to create a more complex and detailed model integrating autonomic, cognitive, and behavioral aspects of emotional expression and regulation. Additionally, a synthesis between these perspectives might provide a more complete understanding of the role of HRV in emotional responding [39].

Emotional Triggering of Cardiovascular Disease (CVD)

Over the past decade, emotion dysregulation has become a very popular term in psychiatric and clinical psychology literature, and it has been described as a key component in a wide range of mental disorders. For this reason, it has been recently called the "hallmark of psychopathology" [58]. Results from a recent meta-analysis, including 92 studies with a worldwide distribution, established that people with severe mental illness (schizophrenia spectrum disorders, bipolar spectrum disorders, major depressive disorders) have a 53% higher risk for having CVD, a 78% risk for developing CVD, and an 85% risk of death from CVD compared to the regionally matched general population [59]. Evidence is constantly accumulating also for chronic psychosocial stress, anxiety disorders, and depression.

The role of emotional triggers in cardiac pathology was acknowledged since the beginning of the last century, but the first large-scale study evaluating emotional triggers and their influence on cardiovascular events was the Multicenter Investigation of Limitation of Infarct Size (MILIS) published in 1990. Eighteen percent of the subjects reported emotional upset in the period preceding cardiovascular symptom onset [60]. In the TRIMM study, published in 1991, 35% of the patients reported either emotional upset or stress within hours before acute myocardial infarction [61]. The growing body of research on the role of mental stressors on CVD made possible to define coronary heart disease as a (now well-recognized) psychosomatic illness [62].

A well-studied example of emotionally triggered CVD is Takotsubo cardiomyopathy (also known as "broken heart syndrome"), which can occur after acute mental or physical stress and takes its name from a Japanese octopus fishing pot, built with an apical ballooning with a narrow neck [63]. The first observations of this phenomenon occurred in Japan more than 20 years ago.

In 85% of cases, Takotsubo cardiomyopathy is preceded by an emotionally or physically stressful event, usually within an interval that varies from minutes to hours. Emotional stressors can include grief (death of a loved one), fear (armed robbery, public speaking), anger (argument with spouse), relationship conflicts (dissolution of marriage), and financial problems (gambling loss, job loss) [64]. Clinically, it is characterized by transient systolic dysfunction of the apical and mid-ventricular segments in patients without coronary artery disease. It starts abruptly, with symptoms of chest pain and shortness of breath, mimicking acute myocardial infarction (the differential diagnosis can be challenging without imaging). The pathophysiology of the disorder remains to be elucidated but may involve catecholamine excess and vasospasm [65].

Pathophysiology of Emotionally Triggered CVD

The hypothesized link between negative emotional triggers and clinical cardiovascular events is mediated through neurophysiological responses such as:

- *Autonomic dysfunction*: both sympathetic overstimulation and parasympathetic withdrawal are responsible of increased pressor responses, stimulation of malignant arrhythmias, and lowering the threshold for ventricular fibrillation. Reduced parasympathetic activity, indexed by decreased HRV, is a predictor of coronary heart disease, death in patients following acute myocardial infarction, and sudden cardiac death [66]
- *Hemodynamic responses*: anger-provoking tasks induce coronary vasoconstriction in patients with coronary heart disease. Also, harmful hemodynamic responses to stress are stimulated in part through autonomic dysfunction as described earlier.
- *Neuroendocrine activation*: also associated with autonomic dysfunction, it is well known that stress and negative emotions induce increases in hypothalamic-pituitary-adrenocortical activity and in catecholamine levels.
- *Inflammatory response*: inflammatory markers such as interleukin-6 and TNFα are increased after emotional stress.
- *Prothrombotic response*: inflammatory cytokines are strictly involved in advance atherosclerosis and in thrombus formation: release of cytokines by activated T lymphocytes produces a decrease in production of collagen in smooth muscles, destabilizing plaques. Also, they stimulate monocytes to produce tissue factor, which increases blood coagulation, and influence production of fibrinogen, an acute-phase protein that increases blood viscosity and coagulation [67]. The activation of platelets and production of fibrinogen are also stimulated directly by emotional stress, with more prolonged responses in patients who already suffer with coronary heart disease [68].

These responses could lead to pathological events evolving in thrombus formation, plaque disruption, cardiac electrical instability, and myocardial ischemia: the resulting clinical events are myocardial infarction, unstable angina, and ventricular tachycardia or fibrillation [69].

Emotional Risk Factors of CVD

The idea of an association between emotions and cardiovascular disease has a very long history, but evidence-based studies of the association are comparatively recent. Throughout the years, the understanding of the mechanisms involved in CVD has been extremely increasing, and consistent with this knowledge is the view that emotional processes could be risk factors for heart disease. A wide array of negative emotions has been shown to independently increase the risk of a CVD-related event and/or mortality in different cardiac populations, briefly summarized here:

Acute negative emotions: Intense emotions like outbursts of anger and acute life "stressors" (which are usually linked to intense emotions) can

trigger cardiovascular events and increase mortality within a few hours to several months, i.e., following the death of a loved one [70], natural disasters [71], military/terrorist attacks [72], or even major football tournaments [73]. The incidence of acute coronary syndromes, fatal arrhythmias, and sudden cardiac death was also observed with noteworthy incidence in patients with pre-existent CVD [74]. A recent meta-analysis including different cardiovascular events (i.e., ischemic stroke, ventricular arrhythmia, and ruptured intercranial aneurysm) proved an increased risk for all those events in the hours after an anger outburst [75]. Another meta-analysis of 44 studies, investigating CVD outcomes, found that anger was associated with increased CVD events both in healthy population studies and in samples with existing CVD [76]

- *Anxiety*: Anxiety has been implicated in arterial hypertension, coronary heart disease (CHD), and open-heart surgery outcomes for more than 100 years [77]. Of note, the clinical presentation of CVDs and anxiety have frequently common features such as atypical chest pain, dyspnea, palpitations, and arrhythmias [78]; therefore, the differential diagnosis is not always straightforward [79]. Healthy individuals with high anxiety were found at increased risk for incident CHD and cardiac death, independent of demographic variables, biological risk factors, and health behaviors [80], and conversely the prevalence of anxiety disorders is significantly higher in subjects with CVD compared to the general population [81].
- *Chronic psychological distress*: There is an enormous amount of literature about the connection between psychological stress and cardiovascular disease, exploring the differences of the effects of acute versus long-term stressors on cardiac functioning. The largest body of evidence on chronic stress still comes from the study of work-related stressors [82]. The INTERHEART study investigated the association of chronic stressors and incidence of myocardial infarction in a sample of 25,000 people from 52 countries: after adjusting for confounders (age, gender, geographic region, and smoking), those who reported "permanent stress" at work or at home had >2.1 times the risk for developing myocardial infarction [83]. Several other reviews summarizing the evidence from studies on chronic stress and coronary heart disease have been published [84, 85], but a meta-analysis published in 2006 [86] also provided quantitative estimates, showing that employees exposed to stress in the workplace have an average 50% excess risk of CHD compared with those who do not experience this type of stress.
- *Depressive symptoms*: the association between depression and cardiovascular disease can be considered a "downward spiral" in which depressive symptoms and CVD reinforce each other [87]. Incidence rates of depression in patients with CVD reach up to 20–40% [88], and conversely depression has been proved to increase the risk of cardiac death [89]. A meta-analysis integrating results from 21 studies (involving over 120,000 subjects) stated that depression can increase the risk of CVD onset up to 80–90% [90].

Conversely, there is still little evidence about a protective effect of positive emotions on the cardiovascular system [91], and the mechanisms underlying the association between positive emotions and many aspects of physical health are still unclear [92]. The experience of positive emotions has been associated with a lower likelihood of cardiovascular disease [93], but conflicting evidence showing no association has also been published [94]. Positive emotions and well-being could influence susceptibility to CVD inhibiting the sympathetic nervous system and increasing vagal activation, thus increasing HRV and lowering blood pressure [95]. Positive emotions and vagal tone, additionally, show the reciprocal influence indicative of an upward spiral dynamic [96]. The role of positive affects is also linked to a decreased production of inflammatory and coagulation factors such as fibrinogen and interleukin-6 [97] (which are stress-induced and

markedly involved in cardiovascular disease) and reduced vulnerability to infections [98]. Positive emotions, to conclude, have also been associated with reduced cardiovascular mortality not only in healthy population studies but also in patients with established cardiovascular disease [99].

References

1. Lykouras E, Poulakou-Rebelakou E, Ploumpidis DN. Searching the seat of the soul in Ancient Greek and Byzantine medical literature. Acta Cardiol. 2010;65(6):619–26.
2. Arnett LD. The soul: a study of past and present beliefs. Am J Psychol. 1904;15(3):347–82.
3. el-Sayed e-A. Archaic Egyptian Cosmology. Anthropos. 1997;92(1/3):69–81.
4. Smith W. Dictionary of Greek and Roman biography and mythology (Vol. 1, 2 and 3). CC Little and J. Brown. 1849.
5. Fortenbaugh WW. Aristotle: animals, emotion and moral virtue. Arethusa. 1971;4(2):137–65.
6. Schmitter AM. 17th and 18th century theories of emotions. In: Zalta EN, editor. 17th and 18th century theories of emotions: metaphysics research lab. Stanford: Stanford University; 2016.
7. McCraty R. Heart-brain neurodynamics: The making of emotions. In Media Models to Foster Collective Human Coherence in the PSYCHecology (pp. 191–219). IGI Global. 2019.
8. Goodhart A. The relationship between heart and 'inner self' from Aristotle to current clinical practice. Med Humanit. 2014;40(1):61–6.
9. LeDoux J. The emotional brain: the mysterious underpinnings of emotional life. New York: Simon and Schuster; 1998.
10. Damasio AR. Descartes' error: emotion, rationality and the human brain. London: Vintage Books; 1994.
11. Forgas JP. The role of emotion in social judgments: an introductory review and an Affect Infusion Model (AIM). Eur J Soc Psychol. 1994;24(1):1–24.
12. Bower GH. How might emotions affect learning? The handbook of emotion and memory: research and theory. Hillsdale: Lawrence Erlbaum Associates, Inc; 1992. p. 3–31.
13. James W. What is an emotion? Mind. 1884;9(34):188–205.
14. Cannon WB. Bodily changes in pain, hunger, fear and rage. Oxford: Appleton; 1929. p. 404.
15. Damasio AR, LeDoux J. Emotions and feelings. In: Kandel E, editor. Principles of neural science. 5th ed. New York: McGraw-Hill; 2012.
16. Weiskrantz L. Behavioral changes associated with ablation of the amygdaloid complex in monkeys. J Comp Physiol Psychol. 1956;49(4):381–91.
17. Blanchard DC, Blanchard RJ. Innate and conditioned reactions to threat in rats with amygdaloid lesions. J Comp Physiol Psychol. 1972;81(2):281–90.
18. Adolphs R, Tranel D, Damasio H, Damasio A. Impaired recognition of emotion in facial expressions following bilateral damage to the human amygdala. Nature. 1994;372(6507):669–72.
19. Janak PH, Tye KM. From circuits to behaviour in the amygdala. Nature. 2015;517(7534):284–92.
20. Gianaros PJ, Sheu LK, Matthews KA, Jennings JR, Manuck SB, Hariri AR. Individual differences in stressor-evoked blood pressure reactivity vary with activation, volume, and functional connectivity of the amygdala. J Neurosci Off J Soc Neurosci. 2008;28(4):990–9.
21. Critchley HD, Melmed RN, Featherstone E, Mathias CJ, Dolan RJ. Volitional control of autonomic arousal: a functional magnetic resonance study. NeuroImage. 2002;16(4):909–19.
22. Garfinkel SN, Minati L, Gray MA, Seth AK, Dolan RJ, Critchley HD. Fear from the heart: sensitivity to fear stimuli depends on individual heartbeats. J Neurosci. 2014;34(19):6573–82.
23. Tsunoda T, Yoshino A, Furusawa T, Miyazaki M, Takahashi Y, Nomura S. Social anxiety predicts unconsciously provoked emotional responses to facial expression. Physiol Behav. 2008;93(1–2):172–6.
24. Domschke K, Stevens S, Pfleiderer B, Gerlach AL. Interoceptive sensitivity in anxiety and anxiety disorders: an overview and integration of neurobiological findings. Clin Psychol Rev. 2010;30(1):1–11.
25. Ogawa T, de Bold AJ. The heart as an endocrine organ. Endocrine Connections. 2014;3(2):R31–44.
26. Lacey JI. Somatic response patterning and stress: some revisions of activation theory. In: Psychological stress: issues in research. New York: Appleton-Century-Crofts; 1967. p. 14–37.
27. Lacey JI. Psychophysiological approaches to the evaluation of psychotherapeutic process and outcome. In: Research in psychotherapy. Washington, DC: American Psychological Association; 1959. p. 160–208.
28. Lacey JI, Kagan J, Lacey BC, Moss HA. The visceral level: situational determinants and behavioral correlates of autonomic response patterns. In: Knapp PH, editor. Expression of the emotions in man. New York: International Universities Press; 1963.
29. Guyton AC, Hall JE. Human physiology and mechanisms of disease. Philadelphia: W.B. Saunders; 1992.
30. Lacey U, Lacey BC. Some autonomic-central nervous system interrelationships. In: Physiological correlates of emotion. New York: Academic; 1970. p. 205–27.
31. Koriath JJ, Lindholm E. Cardiac-related cortical inhibition during a fixed foreperiod reaction time task. Int J Psychophysiol. 1986;4(3):183–95.
32. Porges SW. The polyvagal perspective. Biol Psychol. 2007;74(2):116–43.
33. Lacey JI, Lacey BC. Verification and extension of the principle of autonomic response-stereotypy. Am J Psychol. 1958;71(1):50–73.

34. Kleiger R, Stein P, Bosner M, Rottman J. Time domain measurements of heart rate variability. Cardiol Clin. 1992;10(3):487–98.
35. Pumprla J, Howorka K, Groves D, Chester M, Nolan J. Functional assessment of heart rate variability: physiological basis and practical applications. Int J Cardiol. 2002;84(1):1–14.
36. Rajendra Acharya U, Paul Joseph K, Kannathal N, Lim CM, Suri JS. Heart rate variability: a review. Med Biol Eng Comput. 2006;44(12):1031–51.
37. Bernardi L, Porta C, Gabutti A, Spicuzza L, Sleight P. Modulatory effects of respiration. Auton Neurosci. 2001;90(1-2):47–56.
38. Pyetan E, Akselrod S. Do the high-frequency indexes of HRV provide a faithful assessment of cardiac vagal tone? A critical theoretical evaluation. IEEE Trans Biomed Eng. 2003;50(6):777–83.
39. Appelhans B, Luecken L. Heart rate variability as an index of regulated emotional responding. Rev Gen Psychol. 2006;10:229–40.
40. Porges SW. Orienting in a defensive world: Mammalian modifications of our evolutionary heritage. A polyvagal theory. Psychophysiology. 1995;32(4):301–18.
41. Porges SW. Emotion: an evolutionary by-product of the neural regulation of the autonomic nervous system. Annals of the New York Academy of Sciences. 1997;807(1):62–77.
42. Porges SW. The polyvagal theory: phylogenetic substrates of a social nervous system. Int J Psychophysiol. 2001;42(2):123–46.
43. Porges SW. Neuroception: a subconscious system for detecting threats and safety. Zero to Three (J). 2004;24(5):19–24.
44. Sulik MJ, Eisenberg N, Spinrad TL, Silva KM. Associations between respiratory sinus arrhythmia (RSA) reactivity and effortful control in preschool-age children. Dev Psychobiol. 2015;57(5):596–606.
45. Blair C, Peters R. Physiological and neurocognitive correlates of adaptive behavior in preschool among children in Head Start. Dev Neuropsychol. 2003;24(1):479–97.
46. Calkins SD, Keane SP. Cardiac vagal regulation across the preschool period: stability, continuity, and implications for childhood adjustment. Dev Psychobiol. 2004;45(3):101–12.
47. Pine DS, Wasserman GA, Miller L, Coplan JD, Bagiella E, Kovelenku P, et al. Heart period variability and psychopathology in urban boys at risk for delinquency. Psychophysiology. 1998;35(5):521–9.
48. Movius HL, Allen JJ. Cardiac vagal tone, defensiveness, and motivational style. Biol Psychol. 2005;68(2):147–62.
49. Thayer JF, Lane RD. A model of neurovisceral integration in emotion regulation and dysregulation. J Affect Disord. 2000;61(3):201–16.
50. Frijda NH. The laws of emotion. Am Psychol. 1988;43(5):349–58.
51. Stormark KM, Laberg JC, Nordby H, Hugdahl K. Heart rate responses indicate locked-in attention in alcoholics immediately prior to drinking. Addict Behav. 1998;23(2):251–5.
52. Thayer JF, Friedman BH, Borkovec TD, Johnsen BH, Molina S. Phasic heart period reactions to cued threat and nonthreat stimuli in generalized anxiety disorder. Psychophysiology. 2000;37(3):361–8.
53. Benarroch EE. Central autonomic network: functional organization and clinical correlations. Armonk: Futura Publishing Company; 1997.
54. Thayer JF, Siegle GJ. Neurovisceral integration in cardiac and emotional regulation. IEEE Eng Med Biol Mag. 2002;21(4):24–9.
55. Thayer JF, Friedman BH, Borkovec TD. Autonomic characteristics of generalized anxiety disorder and worry. Biol Psychiatry. 1996;39(4):255–66.
56. Brosschot JF, Thayer JF. Anger inhibition, cardiovascular recovery, and vagal function: a model of the link between hostility and cardiovascular disease. Ann Behav Med. 1998;20(4):326–32.
57. Sroka K, Peimann C-J, Seevers H. Heart rate variability in myocardial ischemia during daily life. J Electrocardiol. 1997;30(1):45–56.
58. Beauchaine TP, Gatzke-Kopp L, Mead HK. Polyvagal theory and developmental psychopathology: Emotion dysregulation and conduct problems from preschool to adolescence. Biol Psychol. 2007;74(2):174–84.
59. Correll CU, Solmi M, Veronese N, Bortolato B, Rosson S, Santonastaso P, et al. Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: a large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls. World Psychiatry. 2017;16(2):163–80.
60. Tofler GH, Stone PH, Maclure M, Edelman E, Davis VG, Robertson T, et al. Analysis of possible triggers of acute myocardial infarction (the MILIS study). Am J Cardiol. 1990;66(1):22–7.
61. Willich SN, Löwel H, Lewis M, Arntz R, Baur R, Winther K, et al. Association of wake time and the onset of myocardial infarction. Triggers and mechanisms of myocardial infarction (TRIMM) pilot study. TRIMM Study Group. Circulation. 1991;84(6 Suppl):VI62–7.
62. Tennant C, McLean L. The impact of emotions on coronary heart disease risk. J Cardiovasc Risk. 2001;8(3):175–83.
63. Veillet-Chowdhury M, Hassan SF, Stergiopoulos K. Takotsubo cardiomyopathy: a review. Acute Card Care. 2014;16(1):15–22.
64. Sharkey SW, Lesser JR, Maron BJ. Cardiology patient page. Takotsubo (stress) cardiomyopathy. Circulation. 2011;124(18):e460–2.
65. Lacey C, Mulder R, Bridgman P, Kimber B, Zarifeh J, Kennedy M, et al. Broken heart syndrome – is it a psychosomatic disorder? J Psychosom Res. 2014;77(2):158–60.
66. Thayer JF, Lane RD. The role of vagal function in the risk for cardiovascular disease and mortality. Biol Psychol. 2007;74(2):224–42.

67. Steptoe A, Brydon L. Emotional triggering of cardiac events. Neurosci Biobehav Rev. 2009;33(2):63–70.
68. Strike PC, Magid K, Brydon L, Edwards S, McEwan JR, Steptoe A. Exaggerated platelet and hemodynamic reactivity to mental stress in men with coronary artery disease. Psychosom Med. 2004;66(4):492–500.
69. Bhattacharyya MR, Steptoe A. Emotional triggers of acute coronary syndromes: strength of evidence, biological processes, and clinical implications. Prog Cardiovasc Dis. 2007;49(5):353–65.
70. Li J, Hansen D, Mortensen PB, Olsen J. Myocardial infarction in parents who lost a child: a nationwide prospective cohort study in Denmark. Circulation. 2002;106(13):1634–9.
71. Leor J, Poole WK, Kloner RA. Sudden cardiac death triggered by an earthquake. N Engl J Med. 1996;334(7):413–9.
72. Meisel SR, Kutz I, Dayan KI, Pauzner H, Chetboun I, Arbel Y, et al. Effect of Iraqi missile war on incidence of acute myocardial infarction and sudden death in Israeli civilians. The Lancet. 1991;338:660.
73. Carroll D, Ebrahim S, Tilling K, Macleod J, Smith GD. Admissions for myocardial infarction and World Cup football: database survey. BMJ. 2002;325(7378):1439–42.
74. Pogosova N, Saner H, Pedersen SS, Cupples ME, McGee H, Hofer S, et al. Psychosocial aspects in cardiac rehabilitation: from theory to practice. A position paper from the Cardiac Rehabilitation Section of the European Association of Cardiovascular Prevention and Rehabilitation of the European Society of Cardiology. Eur J Prev Cardiol. 2015;22(10):1290–306.
75. Mostofsky E, Penner EA, Mittleman MA. Outbursts of anger as a trigger of acute cardiovascular events: a systematic review and meta-analysis. Eur Heart J. 2014;35(21):1404–10.
76. Chida Y, Steptoe A. The association of anger and hostility with future coronary heart disease: a meta-analytic review of prospective evidence. J Am Coll Cardiol. 2009;53(11):936–46.
77. Fish F. The psychiatric aspects of paroxysmal tachycardia. Br J Psychiatry. 2018;110(465):205–10.
78. Tully PJ, Cosh SM, Baumeister H. The anxious heart in whose mind? A systematic review and meta-regression of factors associated with anxiety disorder diagnosis, treatment and morbidity risk in coronary heart disease. J Psychosom Res. 2014;77(6):439–48.
79. Katon W, Lin EH, Kroenke K. The association of depression and anxiety with medical symptom burden in patients with chronic medical illness. Gen Hosp Psychiatry. 2007;29(2):147–55.
80. Roest AM, Martens EJ, de Jonge P, Denollet J. Anxiety and risk of incident coronary heart disease: a meta-analysis. J Am Coll Cardiol. 2010;56(1):38–46.
81. Tully PJ, Harrison NJ, Cheung P, Cosh S. Anxiety and cardiovascular disease risk: a review. Curr Cardiol Rep. 2016;18(12):120.
82. Dimsdale JE. Psychological stress and cardiovascular disease. J Am Coll Cardiol. 2008;51(13):1237–46.
83. Rosengren A, Hawken S, Ôunpuu S, Sliwa K, Zubaid M, Almahmeed WA, et al. Association of psychosocial risk factors with risk of acute myocardial infarction in 11 119 cases and 13 648 controls from 52 countries (the INTERHEART study): case-control study. Lancet. 2004;364(9438):953–62.
84. Steptoe A, Kivimäki M. Stress and cardiovascular disease. Nat Rev Cardiol. 2012;9:360.
85. Backe EM, Seidler A, Latza U, Rossnagel K, Schumann B. The role of psychosocial stress at work for the development of cardiovascular diseases: a systematic review. Int Arch Occup Environ Health. 2012;85(1):67–79.
86. Kivimäki M, Virtanen M, Elovainio M, Kouvonen A, Väänänen A, Vahtera J. Work stress in the etiology of coronary heart disease – a meta-analysis. Scand J Work Environ Health. 2006;32:431–42.
87. Penninx BW. Depression and cardiovascular disease: epidemiological evidence on their linking mechanisms. Neurosci Biobehav Rev. 2017;74(Pt B):277–86.
88. Whooley MA. Depression and cardiovascular disease: healing the broken-hearted. JAMA. 2006;295(24):2874–81.
89. Bradley SM, Rumsfeld JS. Depression and cardiovascular disease. Trends Cardiovasc Med. 2015;25(7):614–22.
90. Nicholson A, Kuper H, Hemingway H. Depression as an aetiologic and prognostic factor in coronary heart disease: a meta-analysis of 6362 events among 146 538 participants in 54 observational studies. Eur Heart J. 2006;27(23):2763–74.
91. Meyer FA, von Kanel R, Saner H, Schmid JP, Stauber S. Positive affect moderates the effect of negative affect on cardiovascular disease-related hospitalizations and all-cause mortality after cardiac rehabilitation. Eur J Prev Cardiol. 2015;22(10):1247–53.
92. Kok BE, Coffey KA, Cohn MA, Catalino LI, Vacharkulksemsuk T, Algoe SB, et al. How positive emotions build physical health: perceived positive social connections account for the upward spiral between positive emotions and vagal tone. Psychol Sci. 2013;24(7):1123–32.
93. Boehm JK, Kubzansky LD. The heart's content: the association between positive psychological well-being and cardiovascular health. Psychol Bull. 2012;138(4):655.
94. Freak-Poli R, Mirza SS, Franco OH, Ikram MA, Hofman A, Tiemeier H. Positive affect is not associated with incidence of cardiovascular disease: a population-based study of older persons. Prev Med. 2015;74:14–20.
95. Steptoe A. Psychophysiological contributions to behavioral medicine and psychosomatics. In: Handbook of psychophysiology. New York: Cambridge University Press; 2007.
96. Kok BE, Fredrickson BL. Upward spirals of the heart: autonomic flexibility, as indexed by vagal

tone, reciprocally and prospectively predicts positive emotions and social connectedness. Biol Psychol. 2010;85(3):432–6.
97. Steptoe A, O'donnell K, Badrick E, Kumari M, Marmot M. Neuroendocrine and inflammatory factors associated with positive affect in healthy men and women: the Whitehall II study. Am J Epidemiol. 2007;167(1):96–102.
98. Cohen S, Alper CM, Doyle WJ, Treanor JJ, Turner RB. Positive emotional style predicts resistance to illness after experimental exposure to rhinovirus or influenza A virus. Psychosom Med. 2006;68(6):809–15.
99. Chida Y, Steptoe A. Positive psychological well-being and mortality: a quantitative review of prospective observational studies. Psychosom Med. 2008;70(7):741–56.

13 The Relationship Between Psychological Distress and Bio-behavioral Processes in Cardiovascular Disease

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Contents

Abstract

Cardiovascular disease (CVD) has been proven to be the largest contributor to morbidity and mortality in the developed world. By considering the psychosocial factors that have been linked to CVD, this chapter will focus on the role of psychological *distress*. Existing empirical evidence shows that stress can be considered as a risk factor starting from the early years, while in adulthood the risk associated with distress derives mainly from either social isolation or workplace-related chronic stressors. Both behavioral and neurobiological mechanisms have been proposed to underlie this association, including sustained activation of the sympathetic nervous system and reduced heart rate variability. Finally, we report research emphasizing the potential protective

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*,
https://doi.org/10.1007/978-3-030-28008-6_14

role of positive psychological constructs such as well-being, optimism, and positive affect.

Keywords

Stress · Distress · Cardiovascular disease · Well-being · Risk factors

Introduction

Cardiovascular disease (CVD) has been proven to be the largest contributor to morbidity and mortality in the developed world [1]. Extensive literature has so far targeted the identification of risk factors for CVD as well as the assessment of their predictive ability, as these factors are critical for disease prevention and treatment. Risk factors can be defined as the measurable characteristics that have been shown to increase a person's probability of heart disease based on epidemiological evidence [2]. Risk for heart disease is determined based on the "total risk," that is, a summation of all possible risk factors, because one single high-level risk variable may contribute to a lower overall risk than a number of low-level risk variables [3, 4].

A great deal of research has been conducted on the impact of the so-called traditional risk factors on CVD [1], which include physical inactivity, diabetes, cigarette smoking, hypertension, dyslipidemia, and family history of premature coronary disease [5]. By contrast, the body of research on nontraditional risk factors – comprising biomarkers such as oxidative stress, inflammation, and insulin resistance [6] – is smaller [7]. Among nontraditional risk factors, several authors have emphasized the role of the *psychosocial* factors [8], which include stress/distress [9], emotional disorders such as anxiety and depression [10], and personality traits [11].

By considering the psychosocial factors that have been linked to CVD, this chapter will focus on the role of psychological *distress*. First, we will examine the definitions of distress, and of *stress* more broadly, provided by psychological literature in the attempt to disentangle related constructs. We will then address existing empirical evidence linking psychological stress and distress to CVD. Third, the main behavioral and neurobiological mechanisms that have been proposed to underlie this association will be briefly considered. Finally, we will conclude by highlighting the potential protective role of psychological variables such as well-being, optimism, and positive emotions. Although the chapter is meant to provide an overview of the link between CVD and distress, it is important to bear in mind that psychosocial factors are likely to occur and cluster together, raising in this way the risk ratios for cardiac events [12].

Stress and Distress: Definitions

Stress: A Challenging Definition

Stress can be defined as a perturbation to the organism, which can derive from changes to the physiological homeostasis or psychological well-being.

The first definition of stress was suggested in the 1950s by Selye [13] who, starting from his medical training, measured stress in terms of physiological responses, focusing mainly on the sympathetic adrenal-medullary activity and the pituitary-adrenal-cortical activity. Selye also discussed what he called the general adaptation syndrome (GAS), suggesting that being overexposed to stressful situation would lead the individual's body to overproduce chemicals that would lead to ulcers and high blood pressure. In his view, though, stress was mainly conceived as a non-specific response of the body to any noxious stimulus. For this reason, this initial definition has long proven to be only partially correct. Yet, it is important because it was the first attempt to explain how disease can be caused not by a purely physiological cause but how stress can affect the immune system as well as the adrenal glands.

The second step was introducing some more specific elements, by distinguishing between stressors and stress responses. Internal or external changes that can trigger a stress response are defined as stressors. A stressor has been commonly intended as a stimulus that threatens

homeostasis, and the stress response is the reaction of the organism aimed to regain homeostasis [14]. When the body perceives the change triggered by the stressor, it activates different coping mechanisms or adaptive changes, including behavioral reactions, activation of the sympathetic nervous system and adrenal medulla, secretion of stress hormones (e.g., glucocorticoids and prolactin), and mobilization of the immune system.

There at least two problematic aspects about these definitions. The first one is linked to the term homeostasis, which was originally introduced by Cannon [15], and is commonly used when referring both to stress and to stressors. Since homeostasis is a virtual baseline, it is easy to understand how almost any activity of the organism itself concerns, more or less directly, a form of defense of the homeostasis. For these reasons, several authors [16, 17] pointed out how defining of stress as a threat to homeostasis is not exhaustive and how more critical consideration to get to a better understanding of stress and stressors is needed.

The second problematic aspect is linked to the fact that many times authors do not consider if a stimulus is indeed perceived as a stressor in the sense that it is considered as an actual threat to homeostasis and thus to physical and psychological health, but they either only focus on detecting the presence of a stress response, which is read as an indicator of stress exposure [18], or focus on a stimulus that they classify as aversive and consequently interpret the response to that stimulus as a stress response [19].

Stress and Distress

The individual's perception and evaluation of a stressor have been accounted by Lazarus' theory of stress [20], which focused on the wide range of cognitive and behavioral responses people commonly use to cope with stress and face everyday problems. Lazarus' theory stressed the role of cognitive appraisal in the individual's response to a stressful situation and focused attention to the ways in which the individual copes with such a situation. According to Lazarus' model, three different kinds of evaluation take place: (a) the primary appraisal, which consists of how the situation is evaluated; (b) the secondary appraisal, which deals with how the organism views its own capabilities and resources to respond; (c) and finally the coping process, which is how the organisms attempt to manage the relation with the environment that caused stress [21]. In this perspective, it is not stress itself that constitutes a threat to a person's overall well-being but how the individual copes with it: "stress is a natural and expectable feature of living, but it also makes the coping process necessary" [22]. If coping is effective, stress is likely to remain under control, whereas if coping is ineffective, stress may have damaging consequences for physical and psychological health. Although extensive research has examined the strategies through which people cope with stressors and their impact on psychological health outcomes (under the hypothesis that coping strategies moderate the harmful effects of stress on health), far less research has addressed the association between coping and biological health indicators, including indicators of CVD [23].

Along with this line of reasoning, *distress* is thought to occur when the individual cannot cope against the assault of one or more stressors. Distress has been defined as an aversive, negative state in which coping and adaptation processes fail; it can include a variety of negative affective responses such as anxiety and sadness, together with a sense of helplessness [24]. The transition of stress to distress may depend on several factors. Existing research suggests that unpredictability and uncontrollability (the absence of an anticipatory response and loss of control) are central features of stressful experiences that can qualify as distress and end up having negative consequences on the organism [19]. For this reason, negative stress, or distress, should be used as a construct when predictability and controllability are at stake [19]. Especially when focusing on clinical or preclinical samples, it is also important to highlight how evidence from the human literature on stress and distress supports the fact that it is not the actual control that counts but the perceived control [25], with data supporting increased stress and

perceived pain in response to unpredictable stimuli [26, 27].

Both acute (deriving from demands and pressures of the recent past or the near future) and chronic stress (ongoing environmental condition or as a stressor with enduring impact) can be linked to distress [28], but chronic stress appears to have a strong link to distress, as we just defined it, because of the fact that the longer a stressor lasts, the more likely it is to be perceived as out of control from the individual experiencing it. This line of reasoning is confirmed by the fact that chronic stress, both at early life and adulthood, has been associated with increased risk of CVD (up to 60%) [29] and individuals who report "permanent stress" at work or at home are more than two times more likely to suffer from a myocardial infarction [30].

Finally, a relevant distinction concerns the concept of stress/distress (i.e., the response to a current stressor) and an individual's general, stable propensity to experience distress, which has been captured by different personality traits and mood dispositions. In other terms, people may differ in their tendency to chronically experience distress. For instance, Costa and McCrae [31] have defined *neuroticism* as the tendency to experience and report negative emotional states. Similarly, Watson and Clark [32] have proposed *negative affectivity* to correspond to a general dimension of subjective distress, reflecting stable individual differences in negative mood. Other research has examined the so-called Type D (Distressed) personality defined as the tendency toward negative affectivity and social inhibition, finding that it is linked to adverse cardiovascular outcomes (for a review, see [11]).

In the next paragraph, we will discuss more specifically the role of stress as a risk factor for cardiovascular diseases.

Stress as a Risk Factor for Cardiovascular Disease

The different levels of risks for CVD that are associated with distress have been widely explored in literature [29], supporting the hypothesis of stress as a predictor of CVD. A recent review [29] reports how stress can be considered as a risk factor starting from the early years: childhood abuse and early socioeconomic adversity are positively correlated with higher risk of CVD in adulthood. A meta-analysis [4] also highlights the risk associated with distress derived either from social isolation or workplace-related chronic stressors.

Early Life Experiences

Recent literature reporting clinical studies on different population has been increasingly stressing how being exposed to early life stress can be seen as an independent risk factor for the development of chronic diseases. Among the most frequently reported, we can find several CVD like ischemic heart disease, cardiovascular disease, and stroke [33–36].

Childhood abuse has been proved [37] to be a predictor of specific CVD, such as heart attack and stroke. Self-report data support the notion that even less traumatic childhood adversities can double the risk of CVD, when individuals reported three or more [38]. Focusing specifically on a sample of women, a 45-year follow-up study allowed to add the role of early experienced chronic stress (linked to low childhood socioeconomic status) as a risk factor, which appeared to increase the chances of mortality by CVD by 1.4 times [39].

Evidence from meta-analysis and reviews highlights how it is not always the distress experienced early in life the source of the problem per se: Traumatic events can not only be harmful but also have some partially positive effects on the development of successful coping mechanism, depending on their duration, intensity, and timing [40]. This line of reasoning is supported by the evidence that can be found in literature, supporting the fact that the intensity, length, and number of adverse factors seem to have an additive effect in the physiological outcomes analyzed and certainly predict an enhanced risk to develop cardiovascular disease during the adult life [41].

Work-Related Distress

Work-related stress is the most widely studied form of chronic stress, and in line with what we have been discussing, at a general level, low job control predicts future cardiac problems [42]. Being more specific, both chronic and subacute work-related distress (i.e., the accumulation of stressful life events over several months) have been widely investigated as a possible risk factor for CVD, and several interesting correlations have been reported in literature. For example, higher level of distress appears to be positively correlated with elevation of arterial blood pressure [43] and neurohumoral arousal [44]. This symptom has also been frequently reported in association with subacute distress [45]. The level of subacute stress has been proved to be positively correlated with sudden cardiac death in different samples, like healthy middle-aged men [46] as well as patients presenting with acute myocardial infarction [47]. A more specific example relates to the number of hours per week an individual tends to work: long hours (>55 h on the average week) increase the risk of CVD of 40% [48].

The relevance of stress as a risk factor for CVD appears to be also linked to whether stress is the only risk factor or if it happens to be associated with other potential risks. For example, when studying the risk ratios for myocardial infarction, both distress and social isolation appear to be valid predictors [49]. Yet, when these two factors happen together, the risk of a myocardial infarction to happen doubled [49]. The same trend has also been reported when studying risks factors in healthy individuals [46].

Social Isolation

Chronic stress derived from social isolation and loneliness experienced by adults [50], especially when older, is another significant risk factor for CVD. To be more precise, according to meta-analytic evidence, social isolation does not appear to trigger CVD but is significantly linked to a worse prognosis [51].

Many studies report a strong positive correlation between perceived lack of social/emotional support and subsequent incidence of CVD [51]. Other studies assessing directly the magnitude of actual social support experienced by different samples reported a negative correlation between the level of social support and future incidence of CVD [51–53]. Interestingly enough, those adults who report the need for seeking social support in response to distress, because they feel like they are lacking a supportive social network in their life [54], tended to be readmitted more often for coronary heart disease [55].

Mechanisms Underlying the Link Between Psychological Stress and CVD

Several researchers have focused their attention on the bio-behavioral processes that mediate the relationship between psychological stress and CVD (for reviews, see, for instance, [8, 56]). The understanding of these underlying processes may in fact contribute to the prevention and treatment of stress-related cardiovascular pathologies. A first type of processes concerns behavioral mechanisms, in which stress is thought to lead to higher risk of CVD by means of its association with adverse health and lifestyle behavior [12]. In other words, stressful experiences increase the likelihood that individuals engage in unhealthy behaviors such as smoking and substance abuse [57–60], which in turn have been shown to represent risk factors for CVD.

A second class of mediators includes pathophysiological mechanisms, which are thought to act at many points along the pathophysiological steps leading to cardiac events (for a discussion, see, for instance, [56]). Within this class, research has examined the role of the autonomic nervous system (ANS) – which comprises the sympathetic (SNS) and parasympathetic nervous system (PNS) – and of the hypothalamic-pituitary-adrenocortical (HPA) axis, as they represent major components of the physiological response to stress [61].

The HPA Axis

The HPA axis is one of the primary biological systems activated during a stress response [29, 61]. A recent review [62] has examined the effects of the hormones produced by the HPA axis on the cardiovascular systems showing that the prolonged dysregulation of the HPA axis and glucocorticoid production may lead to various types of pathologies, including hypertension and vascular damage. It is still unclear, however, whether risk for CVD is directly linked to the activation of the HPA due to stress or heart disease may develop as a consequence of the metabolic strain generated by extreme levels of glucocorticoids.

Autonomic Imbalance

Autonomic imbalance between the sympathetic and parasympathetic regulation of the heart – characterized by heightened activity of the SNS and suppressed activity of the PNS – has been proposed as a key component in stress-related cardiovascular disease [63, 64].

Autonomic responses prepare the body to cope with stressors: The general response to stress involves the activation of the SNS, which is in charge of defensive behavior (e.g., the so-called "fight or flight" response), together with the inhibition of the PNS [65]. Sympathetic activation increases myocardial oxygen demand by increasing heart rate, blood pressure, and cardiac contractility. Although this acute mobilization most often represents an adaptive bodily response to stressors and threats, persistent activation of SNS (e.g., due to prolonged or repeated stress exposure) can have adverse health effects, including cardiovascular problems [24]. Sustained stimulation of cardiac sympathetic outflow has been identified as a contributor to cardiac events such as myocardial infarction, ventricular arrhythmias, and sudden death [8]. It is thought that sympathetic activation triggered by acute physical or mental stressors may contribute to the development of CVD through various pathways, such as increased platelet aggregation, potential atherosclerotic plaque rupture, reduced blood flow to the myocardium, and electrical instability of the heart [8]. Likewise, excessive activation of the SNS has been proposed as a mediator between chronic distress (e.g., work stress) and adverse cardiovascular consequences, such as the development of hypertension and atherosclerosis [12].

A second (smaller) group of studies has considered the mediating role of impaired cardiac vagal control in the association of CVD with stress (for a review, see [63, 66, 67]) – notably, several risk factors for CVD such as hypertension, diabetes, and cholesterol have been related to decreased vagal function [67, 68]. For instance, it has been shown that work stress predicts coronary heart disease and that this association may be partly mediated by lowered heart rate variability [57, 64]. Other studies have found impaired control of parasympathetic regulation of the heart to be associated with cardiovascular mortality in patients with coronary artery disease and in elderly people [69, 70]. Finally, cardiac vagal control was found to mediate cardiovascular responses (e.g., diastolic blood pressure, peripheral resistance, myocardial oxygen demand) to a mental stress task in patients with coronary artery disease [71].

Cardiovascular Reactivity

Cardiovascular reactivity (CR) has been defined as a dispositional, stable tendency to exhibit SNS hyper-reactivity (i.e., pronounced heart rate and blood pressure responses) in front of stressors [72, 73]. Researchers have advanced the hypothesis (called the *reactivity hypothesis*) that people with the largest physiological response to stressors are at a higher risk for CVD [74, 75]. So far, studies have found some empirical evidence of an association of CR with hypertension [76] and atherosclerosis [77, 78].

To explain how cardiac reactivity may lead to CVD, Lovallo and Gerin [73] have proposed a three-level bio-behavioral model linking the brain and the heart under the hypothesis that

both the central and the peripheral nervous systems may contribute to heightened CR. More in detail, this model assumes that individual differences in CR may be accounted for by considering (1) cognitive-emotional responses to stressors, (2) heightened hypothalamic and brainstem responsivity, and (3) peripherally altered tissue function.

At the top level, cognitive (e.g., threat appraisals) and emotional responses to stressors can shape autonomic and endocrine activation patterns [79]. These responses depend on the activity of the frontal cortex and the limbic system, which have been shown to underlie the organism's ability to detect external challenges/threats and to coordinate both behavioral and physiological reactions to them [80]. Notably, individuals differ with respect to their habitual emotional response styles in terms of temperament and personality traits (e.g., neuroticism, hostility) [81], so that biases at this level may result in altered reactivity to stress and contribute to CVD [82].

The next level includes the hypothalamus and brainstem activity, as these brain structures regulate autonomic and endocrine pathways by means of which emotional responses are translated into physiological outputs. At this level, CR is thought to result from altered hypothalamic and brainstem functions: For instance, some studies have found that greater physiological activation in response to anticipation of physical stress was related to negative cardiovascular consequences [83], while other studies have shown that individuals with borderline hypertension tended to exhibit higher activation to mental stress tasks than control healthy individuals, even though no difference emerged in self-reported emotional evaluations [84].

Finally, peripherally altered tissue functions (e.g., vascular wall thickening, coronary artery plaque) may cause excessive responses to stimuli even when emotional and brainstem outputs are normal [85]. A person may thus show exaggerated reactions to stressors without any malfunction in cognitive appraisals or emotions or alteration in endocrine or autonomic outflow.

Psychological Protective Factors: Positive Psychological Functioning

While risk factors are associated with increased likelihood to develop CVD, protective factors can be defined as those characteristics or variables associated with lower probability of adverse cardiac outcomes, or able to reduce the impact of a risk factor.

In recent years, positive psychology has complemented the traditional focus of psychological literature on pathology with the scientific study of the individual's well-being and positive or "optimal" functioning [86]. Well-being and ill-being have been shown to represent independent dimensions of mental health, so that well-being is not simply an absence of pathology but implies that the individual feels good about his/her life and functions well [87].

Notably, positive psychological functioning has been shown to have a beneficial impact on cardiovascular health and a protective role against CVD [for a review see [88]]. For instance, some studies have found higher optimism (defined as the cognitive disposition to expect positive, favorable outcomes in one's life [89]) to be associated with lower risk of CVD [90], stroke [91], hospitalization after bypass surgery [92], and heart failure [93] in middle-aged and elderly adults. Also, highly optimistic individuals are more likely to engage in healthy behaviors such as physical activity and refrain from smoking [94]. Likewise, other studies have found significant associations between reduced risk of coronary heart disease and positive constructs such as emotional vitality [95, 96] and displays of positive affect [97].

Finally, a recent meta-analytic review [98] has focused on the effects of positive psychological constructs such as optimism, positive affect, and well-being on health-related outcomes (i.e., self-reported health status, mortality, and re-hospitalization) in patients with established heart disease (e.g., coronary artery disease, ventricular arrhythmia). The results showed that most of the studies considered in the review (though not all) found prospective significant associations between positive psychological constructs and

health outcomes within multiple forms of heart disease: Positive psychological characteristics predicted reduced rates of re-hospitalization and mortality.

Conclusions

This chapter aimed to provide an overview of the specific role that psychological distress plays as a risk factor for CVD.

We have seen how different categories of distress might predict the chances for individuals to develop CVD at various stages of their life.

Distress might start playing a role if experienced early in life [33–36], and it can mainly trigger chronic CVD. Yet experiencing distress per se does not automatically lead to a higher chance of developing CVD. The evidence discussed in the chapter highlights how the intensity, length, and number of adverse factors seem to predict better the level of risk to develop cardiovascular disease during adult life [41]. The same can be said for the other main categories of distress that are linked to CVD: work-related distress and social isolation.

If it is true that low job control predicts future cardiac problems [42] and lack of social support is related to the incidence of CVD [52, 53] and to the positive vs. negative prognosis of the disease [99], it is also true that the way people perceive the stressors and the coping mechanism that they adopt can moderate if not resolve the adverse effects of the distress per se.

This means that the reported effects on the HPA axis (one of the primary biological systems activated during a stress response [29, 61]), the autonomic imbalance between the sympathetic and parasympathetic regulation of the heart, and cardiovascular reactivity are moderated by the psychological responses of the individuals to the different life-related stressors.

This line of reasoning leads us to focus on what can constitute protective factors against developing CVD as a response to specific factors. Literature reports how positive psychological constructs such as optimism, positive affect, and well-being can influence health-related outcomes in patients with established heart disease [98] – possibly because they lead to a different evaluation and consequently bio-behavioral responses to different sources of distress.

References

1. Kelly BB, Fuster V. Promoting cardiovascular health in the developing world: a critical challenge to achieve global health. Washington, DC: National Academies Press; 2010.
2. Rosmond R, Bjorntorp P. The hypothalamic-pituitary-adrenal axis activity as a predictor of cardiovascular disease, type 2 diabetes and stroke. J Intern Med. 2000;247(2):188–97.
3. Ofori SN, Odia OJ. Risk assessment in the prevention of cardiovascular disease in low-resource settings. Indian Heart J. 2016;68(3):391–8.
4. Steptoe A, Kivimäki M. Stress and cardiovascular disease. Nat Rev Cardiol. 2012;9(6):360–70.
5. de Goma EM, Knowles JW, Angeli F, Budoff MJ, Rader DJ. The evolution and refinement of traditional risk factors for cardiovascular disease. Cardiol Rev. 2012;20(3):118–29.
6. Balagopal P, de Ferranti SD, Cook S, Daniels SR, Gidding SS, Hayman LL, et al. Nontraditional risk factors and biomarkers for cardiovascular disease: mechanistic, research, and clinical considerations for youth: a scientific statement from the American Heart Association. Circulation. 2011;123(23):2749–69.
7. Shaima C, Moorthi P, Shaheen N. Cardiovascular diseases: traditional and non-traditional risk factors. J Med Allied Sci. 2016;6(2):46.
8. Hering D, Lachowska K, Schlaich M. Role of the sympathetic nervous system in stress-mediated cardiovascular disease. Curr Hypertens Rep. 2015;17(10):80.
9. Ferketich AK, Binkley PF. Psychological distress and cardiovascular disease: results from the 2002 National Health Interview Survey. Eur Heart J. 2005;26(18):1923–9.
10. Chauvet-Gelinier J-C, Bonin B. Stress, anxiety and depression in heart disease patients: a major challenge for cardiac rehabilitation. Ann Phys Rehabil Med. 2017;60(1):6–12.
11. Denollet J, Schiffer AA, Spek V. A general propensity to psychological distress affects cardiovascular outcomes: evidence from research on the type D (distressed) personality profile. Circ Cardiovasc Qual Outcomes. 2010;3(5):546–57.
12. Rozanski A, Blumenthal JA, Kaplan J. Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. Circulation. 1999;99(16):2192–217.
13. Selye H. Endocrine reactions during stress.∗. Anesth Analg. 1956;35(3):182–93.
14. Chrousos GP. Stress and disorders of the stress system. Nat Rev Endocrinol. 2009;5(7):374–81.

15. Cannon WB. The wisdom of the body. New York: WW Norton and Company; 1939.
16. Day TA. Defining stress as a prelude to mapping its neurocircuitry: no help from allostasis. Prog Neuro-Psychopharmacol Biol Psychiatry. 2005;29(8): 1195–200.
17. Levine S. Developmental determinants of sensitivity and resistance to stress. Psychoneuroendocrinology. 2005;30(10):939–46.
18. Armario A. The hypothalamic-pituitary-adrenal axis: what can it tell us about stressors? CNS Neurol Disord Drug Targets. 2006;5(5):485–501.
19. Koolhaas JM, Bartolomucci A, Buwalda B, de Boer SF, Flügge G, Korte SM, et al. Stress revisited: a critical evaluation of the stress concept. Neurosci Biobehav Rev. 2011;35(5):1291–301.
20. Lazarus RS. Psychological stress and the coping process. New York: McGraw-Hill; 1966.
21. Somerfield MR, McCrae RR. Stress and coping research: methodological challenges, theoretical advances, and clinical applications. Am Psychol. 2000;55(6):620–5.
22. Lazarus RS. Emotions and interpersonal relationships: toward a person-centered conceptualization of emotions and coping. J Pers. 2006;74(1):9–46.
23. von Känel R, Mausbach BT, Dimsdale JE, Mills PJ, Patterson TL, Ancoli-Israel S, et al. Ways of coping and biomarkers of an increased Atherothrombotic cardiovascular disease risk in elderly individuals. Cardiovasc Psychiatry Neurol. 2012;2012:1–9.
24. Kemeny ME. The psychobiology of stress. Curr Dir Psychol Sci. 2003;12(4):124–9.
25. Salvador A. Coping with competitive situations in humans. Neurosci Biobehav Rev. 2005;29(1): 195–205.
26. Seidel E-M, Pfabigan DM, Hahn A, Sladky R, Grahl A, Paul K, et al. Uncertainty during pain anticipation: the adaptive value of preparatory processes: uncertainty during pain anticipation. Hum Brain Mapp. 2015; 36(2):744–55.
27. Yoshida W, Seymour B, Koltzenburg M, Dolan RJ. Uncertainty increases pain: evidence for a novel mechanism of pain modulation involving the periaqueductal gray. J Neurosci. 2013;33(13):5638–46.
28. Rojo-Moreno L, Livianos-Aldana L, Cervera-Martínez G, Dominguez-Carabantes JA, Reig-Cebrian MJ. The role of stress in the onset of depressive disorders. Soc Psychiatry Psychiatr Epidemiol. 2002; 37(12):592–8.
29. Steptoe A, Kivimäki M. Stress and cardiovascular disease: an update on current knowledge. Annu Rev Public Health. 2013;34(1):337–54.
30. Rosengren A, Hawken S, Ôunpuu S, Sliwa K, Zubaid M, Almahmeed WA, et al. Association of psychosocial risk factors with risk of acute myocardial infarction in 11 119 cases and 13 648 controls from 52 countries (the INTERHEART study): case-control study. Lancet. 2004;364(9438):953–62.
31. Costa PT, McCrae RR. The revised neo personality inventory (neo-pi-r). The SAGE handbook of personality theory and assessment. 2008;2(2):179–198.
32. Watson D, Clark LA. Negative affectivity: the disposition to experience aversive emotional states. Psychol Bull. 1984;96(3):465–90.
33. Alastalo H, Räikkönen K, Pesonen A-K, Osmond C, Barker DJP, Heinonen K, et al. Early life stress and blood pressure levels in late adulthood. J Hum Hypertens. 2013;27(2):90–4.
34. Low CA, Salomon K, Matthews KA. Chronic life stress, cardiovascular reactivity, and subclinical cardiovascular disease in adolescents. Psychosom Med. 2009;71(9):927–31.
35. Parrish C, Surkan PJ, Martins SS, Gattaz WF, Andrade LH, Viana MC. Childhood adversity and adult onset of hypertension and heart disease in São Paulo, Brazil. Prev Chronic Dis. 2013;10:130193.
36. Su S, Wang X, Pollock JS, Treiber FA, Xu X, Snieder H, et al. Adverse childhood experiences and blood pressure trajectories from childhood to young adulthood: the Georgia stress and heart study. Circulation. 2015;131(19):1674–81.
37. Wegman HL, Stetler C. A meta-analytic review of the effects of childhood abuse on medical outcomes in adulthood. Psychosom Med. 2009;71(8):805–12.
38. Scott KM. Association of childhood adversities and early-onset mental disorders with adult-onset chronic physical conditions. Arch Gen Psychiatry. 2011;68(8):838.
39. Power C, Hyppönen E, Davey Smith G. Socioeconomic position in childhood and early adult life and risk of mortality: a prospective study of the mothers of the 1958 British birth cohort. Am J Public Health. 2005;95(8):1396–402.
40. Garner AS, Shonkoff JP, Siegel BS, Dobbins MI, Earls MF, McGuinn L, et al. Early childhood adversity, toxic stress, and the role of the pediatrician: translating developmental science into lifelong health. Pediatrics. 2012;129(1):e224–e31.
41. Dong M, Giles WH, Felitti VJ, Dube SR, Williams JE, Chapman DP, et al. Insights into causal pathways for ischemic heart disease: adverse childhood experiences study. Circulation. 2004;110(13):1761–6.
42. Kivimäki M, Virtanen M, Elovainio M, Kouvonen A, Väänänen A, Vahtera J. Work stress in the etiology of coronary heart disease—a meta-analysis. Scand J Work Environ Health. 2006;32(6):431–42.
43. Schnall PL, Schwartz JE, Landsbergis PA, Warren K, Pickering TG. A longitudinal study of job strain and ambulatory blood pressure: results from a three-year follow-up. Psychosom Med. 1998;60(6):697–706.
44. Theorell T, Perski A, Akerstedt T, Sigala F, Ahlberg-Hulten G, Svensson J, et al. Changes in job strain in relation to changes in physiological state. A longitudinal study. Scand J Work Environ Health. 1988;14(3): 189–96.
45. Freeman LJ, Nixon PGF, Sallabank P, Reaveley D. Psychological stress and silent myocardial ischemia. Am Heart J. 1987;114(3):477–82.
46. Rosengren A, Orth-Gomer K, Wedel H, Wilhelmsen L. Stressful life events, social support, and mortality in men born in 1933. BMJ. 1993;307(6912):1102–5.

47. Pignalberi C, Patti G, Chimenti C, Pasceri V, Maseri A. Role of different determinants of psychological distress in acute coronary syndromes. J Am Coll Cardiol. 1998;32(3):613–9.
48. Virtanen M, Heikkila K, Jokela M, Ferrie JE, Batty GD, Vahtera J, et al. Long working hours and coronary heart disease: a systematic review and meta-analysis. Am J Epidemiol. 2012;176(7):586–96.
49. Ruberman W, Weinblatt E, Goldberg JD, Chaudhary BS. Psychosocial influences on mortality after myocardial infarction. N Engl J Med. 1984;311(9):552–9.
50. McPherson M, Smith-Lovin L, Brashears ME. Social isolation in America: changes in core discussion networks over two decades. Am Sociol Rev. 2006;71(3): 353–75.
51. Berkman LF. Emotional support and survival after myocardial infarction: a prospective, population-based study of the elderly. Ann Intern Med. 1992; 117(12):1003.
52. House JS, Robbins C, Metzner HL. The association of social relationships and activities with mortality: prospective evidence from the Tecumseh Community health study. Am J Epidemiol. 1982;116(1):123–40.
53. Welin L, Larsson B, Svardsudd K, Tibblin B, Tibblin G. Social network and activities in relation to mortality from cardiovascular diseases, cancer and other causes: a 12 year follow up of the study of men born in 1913 and 1923. J Epidemiol Community Health. 1992; 46(2):127–32.
54. Penley JA, Tomaka J, Wiebe JS. The association of coping to physical and psychological health outcomes: a meta-analytic review. J Behav Med. 2002;25(6): 551–603.
55. Stewart MJ, Hirth AM, Klassen G, Makrides L, Wolf H. Stress, coping, and social support as psychosocial factors in readmissions for ischaemic heart disease. Int J Nurs Stud. 1997;34(2):151–63.
56. Merz CNB, Dwyer J, Nordstrom CK, Walton KG, Salerno JW, Schneider RH. Psychosocial stress and cardiovascular disease: pathophysiological links. Behav Med. 2002;27(4):141–7.
57. Chandola T, Britton A, Brunner E, Hemingway H, Malik M, Kumari M, et al. Work stress and coronary heart disease: what are the mechanisms? Eur Heart J. 2008;29(5):640–8.
58. Kassel JD, Stroud LR, Paronis CA. Smoking, stress, and negative affect: correlation, causation, and context across stages of smoking. Psychol Bull. 2003;129(2): 270–304.
59. Sinha R. Chronic stress, drug use, and vulnerability to addiction. Ann N Y Acad Sci. 2008;1141(1):105–30.
60. Torres SJ, Nowson CA. Relationship between stress, eating behavior, and obesity. Nutrition. 2007;23 (11–12):887–94.
61. Ulrich-Lai YM, Herman JP. Neural regulation of endocrine and autonomic stress responses. Nat Rev Neurosci. 2009;10(6):397–409.
62. Burford N, Webster N, Cruz-Topete D. Hypothalamic-pituitary-adrenal Axis modulation of glucocorticoids in the cardiovascular system. Int J Mol Sci. 2017;18(10): 2150.
63. Thayer JF, Lane RD. The role of vagal function in the risk for cardiovascular disease and mortality. Biol Psychol. 2007;74(2):224–42.
64. Vrijkotte TGM, van Doornen LJP, de Geus EJC. Effects of work stress on ambulatory blood pressure, heart rate, and heart rate variability. Hypertension. 2000;35(4):880–6.
65. Porges SW. The polyvagal perspective. Biol Psychol. 2007;74(2):116–43.
66. Sharpley CF. Heart rate reactivity and variability as psychophysiological links between stress, anxiety, depression, and cardiovascular disease: implications for health psychology interventions. Aust Psychol. 2002;37(1):56–62.
67. Thayer JF, Yamamoto SS, Brosschot JF. The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. Int J Cardiol. 2010;141(2):122–31.
68. Masi CM, Hawkley LC, Rickett EM, Cacioppo JT. Respiratory sinus arrhythmia and diseases of aging: obesity, diabetes mellitus, and hypertension. Biol Psychol. 2007;74(2):212–23.
69. Bigger JT, Fleiss JL, Rolnitzky LM, Steinman RC. The ability of several short-term measures of RR variability to predict mortality after myocardial infarction. Circulation. 1993;88(3):927–34.
70. Tsuji H, Venditti FJ, Manders ES, Evans JC, Larson MG, Feldman CL, et al. Reduced heart rate variability and mortality risk in an elderly cohort. The Framingham heart study. Circulation. 1994;90(2):878–83.
71. Grossman P, Watkins LL, Wilhelm FH, Manolakis D, Lown B. Cardiac vagal control and dynamic responses to psychological stress among patients with coronary artery disease. Am J Cardiol. 1996;78(12):1424–7.
72. Lovallo WR. Cardiovascular reactivity: mechanisms and pathways to cardiovascular disease. Int J Psychophysiol. 2005;58(2–3):119–32.
73. Lovallo WR, Gerin W. Psychophysiological reactivity: mechanisms and pathways to cardiovascular disease. Psychosom Med. 2003;65(1):36–45.
74. Schwartz AR, Gerin W, Davidson KW, Pickering TG, Brosschot JF, Thayer JF, et al. Toward a causal model of cardiovascular responses to stress and the development of cardiovascular disease. Psychosom Med. 2003;65(1):22–35.
75. Treiber FA, Kamarck T, Schneiderman N, Sheffield D, Kapuku G, Taylor T. Cardiovascular reactivity and development of preclinical and clinical disease states. Psychosom Med. 2003;65(1):46–62.
76. Menkes MS, Matthews KA, Krantz DS, Lundberg U, Mead LA, Qaqish B, et al. Cardiovascular reactivity to the cold pressor test as a predictor of hypertension. Hypertension. 1989;14(5):524–30.
77. Kamarck TW, Everson SA, Kaplan GA, Manuck SB, Jennings JR, Salonen R, et al. Exaggerated blood pressure responses during mental stress are associated with enhanced carotid atherosclerosis in middle-aged

Finnish men: findings from the Kuopio ischemic heart disease study. Circulation. 1997;96(11):3842–8.
78. Lynch JW, Everson SA, Kaplan GA, Salonen R, Salonen JT. Does low socioeconomic status potentiate the effects of heightened cardiovascular responses to stress on the progression of carotid atherosclerosis? Am J Public Health. 1998;88(3):389–94.
79. Scherer KR, Schorr A, Johnstone T. Appraisal processes in emotion: theory, methods, research. New York: Oxford University Press; 2001.
80. Phillips ML, Drevets WC, Rauch SL, Lane R. Neurobiology of emotion perception I: the neural basis of normal emotion perception. Biol Psychiatry. 2003;54(5):504–14.
81. Bates JE. Temperament as an emotion construct: theoretical and practical issues. In: Handbook of emotions, vol. 2. New York: Guilford Press; 2000. p. 382–96.
82. Eysenck HJ. Prediction of Cancer and coronary heart disease mortality by means of a personality inventory: results of a 15-year follow-up study. Psychol Rep. 1993;72(2):499–516.
83. Everson SA, Kaplan GA, Goldberg DE, Salonen JT. Anticipatory blood pressure response to exercise predicts future high blood pressure in middle-aged men. Hypertension. 1996;27(5):1059–64.
84. al'Absi M, Lovallo WR, McKey BS, Pincomb GA. Borderline hypertensives produce exaggerated adrenocortical responses to mental stress. Psychosom Med. 1994;56(3):245–50.
85. Mills PJ, Dimsdale JE, Ziegler MG, Berry CC, Bain RD. Beta-adrenergic receptors predict heart rate reactivity to a psychosocial stressor. Psychosom Med. 1990;52(6):621–3.
86. Seligman MEP, Csikszentmihalyi M. Positive psychology: an introduction. Am Psychol. 2000;55(1):5–14.
87. Ryff CD, Dienberg Love G, Urry HL, Muller D, Rosenkranz MA, Friedman EM, et al. Psychological well-being and ill-being: do they have distinct or mirrored biological correlates? Psychother Psychosom. 2006;75(2):85–95.
88. Boehm JK, Kubzansky LD. The heart's content: the association between positive psychological well-being and cardiovascular health. Psychol Bull. 2012;138(4):655–91.
89. Scheier MF, Carver CS. Optimism, coping, and health: assessment and implications of generalized outcome expectancies. Health Psychol. 1985;4(3):219–47.
90. Giltay EJ, Geleijnse JM, Zitman FG, Hoekstra T, Schouten EG. Dispositional optimism and all-cause and cardiovascular mortality in a prospective cohort of elderly Dutch men and women. Arch Gen Psychiatry. 2004;61(11):1126.
91. Kim ES, Park N, Peterson C. Dispositional optimism protects older adults from stroke: the health and retirement study. Stroke. 2011;42(10):2855–9.
92. Scheier MF, Matthews KA, Owens JF, Magovern GJ, Lefebvre RC, Abbott RA, et al. Dispositional optimism and recovery from coronary artery bypass surgery: the beneficial effects on physical and psychological well-being. J Pers Soc Psychol. 1989;57(6):1024–40.
93. Kim ES, Smith J, Kubzansky LD. Prospective study of the association between dispositional optimism and incident heart failure. Circ Heart Fail. 2014;7(3):394–400.
94. Boehm JK, Williams DR, Rimm EB, Ryff C, Kubzansky LD. Association between optimism and serum antioxidants in the midlife in the United States study. Psychosom Med. 2013;75(1):2–10.
95. Boehm JK, Peterson C, Kivimaki M, Kubzansky L. A prospective study of positive psychological well-being and coronary heart disease. Health Psychol. 2011;30(3):259–67.
96. Kubzansky LD, Thurston RC. Emotional vitality and incident coronary heart disease: benefits of healthy psychological functioning. Arch Gen Psychiatry. 2007;64(12):1393.
97. Davidson KW, Mostofsky E, Whang W. Don't worry, be happy: positive affect and reduced 10-year incident coronary heart disease: the Canadian Nova Scotia health survey. Eur Heart J. 2010;31(9):1065–70.
98. DuBois CM, Lopez OV, Beale EE, Healy BC, Boehm JK, Huffman JC. Relationships between positive psychological constructs and health outcomes in patients with cardiovascular disease: a systematic review. Int J Cardiol. 2015;195:265–80.
99. Holt-Lunstad J, Smith TB, Layton JB. Social relationships and mortality risk: a meta-analytic review. PLoS Med. 2010;7(7):e1000316.

Part IV

Bidirectional Influences of Common Psychiatric Conditions and Cardiovascular Activity

Anxiety, Anger, Personality, and Heart Disease

14

Laura Fusar-Poli and Davide Arillotta

Contents

Abstract

For several centuries the connection between mind and heart has been debated among scholars. Particularly, it has been noticed that several psychopathological conditions might predispose to the onset and progression of cardiovascular diseases. The present chapter moves through the different aspects of this association. First, the role of anxiety in the etiopathogenesis of heart diseases has been discussed. Second, the prevalence and therapeutic options of anxiety disorders in individuals already suffering from a cardiovascular disease, as well as their role in the progression of these health conditions, have been explored. Finally, we described the interaction between some personality traits and cardiovascular health. Our chapter underlines the importance of investigating the presence of anxiety and personality disorders in people suffering from heart disease. Clinicians should accurately recognize mental health conditions and promptly treat them in cardiac patients who manifest psychological distress. Additionally, the

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*,
https://doi.org/10.1007/978-3-030-28008-6_19

prevention and the timely identification of cardiovascular issues in psychiatric patients appear to be of primary importance for limiting their progression and improving the short- and long-term outcome.

Keywords

Cardiovascular disease · Heart disease · Hypertension · Anxiety · Panic disorder · Takotsubo · Type A personality · Type D personality

Introduction

Since Hippocrates and Galen, it is acknowledged that individuals who chronically experience negative emotions are more likely to suffer from physical illnesses [1]. Descartes initially proposed dualism as an explanation for how mental and physical processes were independent of one another [2]. Later on, William James argued that our emotions, particularly anxiety, were little more than self-reports of our subjective perceptions of the somatic changes occurring during the flight/fight response [3]. During the American Civil War, Jacob Mendes Da Costa investigated and described what was then colloquially known as "soldier's heart" or "irritable heart," a condition in which the individual described the symptoms of heart disease, accompanied by feelings of fear, but in which physical examination failed to detect medical abnormalities [4]. Today, the International Classification of Diseases – 10th Revision (ICD-10) still classifies this condition as "Da Costa's syndrome," a type of health anxiety disorder focused on the heart [5]. This focus on emotion and disease was a precursor for the classic psychosomatic hypothesis that stress and negative emotions such as anger and anxiety, contributed to the development of physical diseases [6]. Since its dawn, the psychosomatic hypothesis has focused its interest on cardiovascular diseases, such as coronary heart disease, currently considered the main causes of morbidity and mortality worldwide. In the last half of the twentieth century, several studies have tried the first attempts to link both anxiety and personality to this old dispute [7]. Over the years, several larger and smaller studies have been conducted, and many biological and psychological mechanisms have been proposed as the link between anxiety, anger, personality, and heart disease.

Anxiety and Heart Disease

Anxiety and Anxiety Disorders

Anxiety is a feeling of uneasiness and worry, usually generalized and unfocused as an overreaction to a situation that is only subjectively seen as menacing. It is often accompanied by muscular tension, restlessness, fatigue, and problems in concentration. Anxiety is different from fear, which is a response to a real or perceived immediate threat [8]. In the study of anxiety, we can consider two complementary concepts: a psychophysiological state (state anxiety) and a personality trait (trait anxiety). State anxiety reflects the psychological and physiological transient reactions directly related to adverse situations in a specific moment. In contrast, trait anxiety refers to a trait of personality, describing individual differences related to a tendency to present state anxiety. Trait anxiety is, therefore, relatively stable over time and considered an important characteristic of patients with anxiety disorders, as they present higher trait anxiety in comparison to healthy individuals [9].

In fact, while anxiety can be appropriate in some occasions, it may turn into an anxiety disorder when experienced regularly by the individual. Anxiety disorders are among the most common psychiatric conditions worldwide, with estimated prevalences which can reach almost 70% among people with chronic diseases [10]. They can be defined as excess worry, hyperarousal, and fear that is counterproductive and debilitating [10]. Anxiety disorders are an expression of the pathological activation of an individual's defense system. When an anxious psychopathological phenomenon appears (e.g., unexpected panic attack) as an expression of the abnormal function of mental defenses, the defense system itself

reacts by activating other protective modules (e.g., anticipatory anxiety or avoidance of the situation/object invoking the perceived fear) that promote the human organism's ability to overcome or adapt to the anxious psychopathological phenomenon [11]. Over the years, the classification of anxiety disorders has not changed dramatically. A major change introduced with the 5th Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5 [8]) is that disturbances previously considered as "anxiety disorders" (i.e., obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), or acute stress disorder) are now classified in separate chapters.

The interest of researchers toward anxiety disorders has been constantly increasing, in large part because of a greater recognition of their burden and the implications associated with untreated illness [10]. Several authors have reported that the presence of an anxiety disorder represents a risk factor for the development of other psychiatric conditions and substance abuse. In clinical and population-based studies, the development of comorbidities makes the treatment of primary and secondary disorders difficult and contributes to low remission rates, poor prognosis, and risk of suicide [12]. Additionally, untreated anxiety has been associated with significant personal and societal costs, decreased work productivity, unemployment, and impaired social relationships [12].

A number of primary studies on the prevalence of anxiety have been undertaken, but the variability in findings has made generalizability to the wider population difficult. This variability mainly results from differences in study setting (i.e., culture; clinical vs. population-based), age and sex composition of samples, length of follow-up, methods of anxiety assessment, and caseness criteria (i.e., types and number of disorders examined) [10]. For this reason, readers should take into account these limitations while reading the findings reported in the present chapters. Moreover, some studies erroneously describe anxiety disorders in reference to self-report tools of anxiety [13], which may be related to "physiological" anxiety rather than a real psychiatric diagnosis. Also, it has to be noted that research has mainly focused on men, while anxiety disorders are more prevalent among women [10].

Do Anxiety and Anxiety Disorders Cause Cardiovascular Disease?

The recommendations of the American Heart Association (AHA) highlighted the potential role of some groups of psychiatric diseases, such as depressive disorders, in the onset and progression of cardiac diseases [14]. Conversely, the role of anxiety disorders as potential risk factors for heart disease remains still understudied. This is possibly connected with the contrasting report deriving from observational studies. On one hand, some findings surprisingly highlighted possible cardioprotective effects of trait and state anxiety [15] or linked generalized anxiety disorder (GAD) to a reduction in prognostic risk for major cardiac events [16]. On the other hand, recent reviews provide evidences according to which, in coronary heart disease, anxiety can increase the risk of major cardiac events and mortality along the years [17–19]. Part of the heterogeneity found in literature could derive from low methodological designs, as mentioned above.

Pathophysiological Mechanisms Linking Anxiety to Cardiovascular Disease

Anxiety has been associated with arterial hypertension, coronary artery disease (CAD), and open-heart surgery outcomes since half of last century [20–22]. Some models linking anxiety and cardiovascular diseases have been proposed.

According to the neurohormonal model, the disposition to experience strong and frequent negative emotions in response to stress was found to be associated with an abnormal activation of sympathetic nervous system, as manifested by impaired vagal control, reduction in heart rate variability, elevated levels of proinflammatory cytokines, and hypercortisolemia resulting in increased hypothalamic-adrenal-cortical responses [17]. A chronic experience of these emotions and sympathetic hyperresponsivity can in turn predispose to disturbances of cardiac rhythm, risk of coronary artery spasm, atherosclerosis, and other types of damage

[23] which can eventually lead to morbidity and mortality from cardiovascular events. Patients with a history of cardiovascular disease, diabetes, and hypertension who are found to have a decreased ability to maintain autonomic stability are at increased risk of all-cause mortality [24]. Therefore, dysfunction in the body's ability to regulate autonomic function in patients with anxiety disorders could be a mechanism linking anxiety disorders to cardiac health. As a matter of fact, acute episodes of negative affect (such as anger and fear) may potentiate sudden cardiac events, although perhaps only in persons who have pre-existing cardiac damage [25].

Both anxiety and anxiety disorders have been associated with increased inflammatory markers, which in turn may contribute to the development and progression of cardiac diseases [19]. Individuals with anxiety traits or disorders were found to have increased levels of C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), interleukine-6 (IL-6), homocysteine, and fibrinogen [26–28]. Such inflammatory pathways have all been implicated in the development of atherosclerosis and heart disease [29, 30] and also associated with poor outcomes in individuals already suffering from cardiovascular diseases [31, 32].

The vascular endothelium plays a key role in the health and maintenance of the circulatory system via regulation of platelet activity, thrombosis, vascular tone, and leukocyte adhesion [33]. Anxiety and anxiety disorders have been linked to endothelial dysfunctions [34, 35], which lead to the development of atherosclerosis [36]. Interestingly, also the serotonin system might be involved in the pathogenesis of cardiovascular disease in people with anxiety. In fact, serotonin has been shown to increase platelet aggregation, thus being associated with increased cardiac events [37]. Moreover, it is worth mentioning that patients with anxiety and acute stress generally showed a greater platelet aggregation [38, 39], and larger mean platelet volume [40].

Parallel to the biological construct, the behavioral model hypothesizes that individuals with anxiety disorders may be prone to follow unhealthy lifestyles [19]. Indeed, anxiety may impair energy, cognition, and motivation to engage in self-care behaviors [41]. Unhealthy diets, physical inactivity, and smoking may promote the development and clinical manifestations of heart disease [42]. Negative emotions may also exacerbate the progression of disease and reduce survival, both by means of direct physiological effects and through reduced compliance with recommended medical regimens. Evidence suggested that anxiety is a predictor of poor adherence to lifestyle change recommendations, adherence to medical therapy, and completion of cardiac rehabilitation programs [43]. These behavioral factors in patients with anxiety disorders could increase the likelihood of cardiovascular morbidity and mortality [13].

Association Between Anxiety Disorders and Heart Disease

The Normative Aging Study, a longitudinal study which have studied the effects of aging on various health issues, explored the relationship between anxiety and cardiac death, finding that psychogenic mortality (i.e., death consequent to a generalized human extreme psychosomatic reaction) was not associated with increased risk of myocardial infarction, but with sudden cardiac death [44]. A meta-analysis published in 2010 [45] focused on the association between anxiety and the incidence of CHD in initially healthy individuals. Anxious persons were found to be at risk of CHD and cardiac death, independently of demographic variables, biological risk factors, and health behaviors [45].

In another review, Tully et al. [46] reported that worry and generalized anxiety disorder (GAD) were associated with diminished heart rate variability (HRV) and elevated heart rate. Additionally, generalized anxiety was associated with blood pressure and diagnosed hypertension or medication use in both disease-free and established CHD populations. According to the authors, no evidence was found to support worry being beneficial to cardiovascular function or conducive to health promoting behaviors. The literature indicated that measures of worry were associated with fatal and nonfatal CHD in seven etiological studies of initially disease-free individuals. However, as mentioned above, a significant

limitation was that females were underrepresented. Some studies reported that GAD was associated with poorer prognosis in established CHD, independently from depression. It has been shown that GAD patients displayed lower inter-beat heart rate and lower heart rate variability, indicating that the worry type of anxiety disorders appears to substantially increase risk of cardiovascular disease possibly through decreased parasympathetic activity and increased sympathetic response [47, 48].

The linkage between phobic disorders and cardiovascular disease is more controversial. According to some authors [49], phobic disorders were not associated with heart disease. This is in contrast with other studies, reporting an increased risk of cardiovascular diseases among phobic patients [50, 51]. Moreover, Brennan et al. [52] found an association between phobic anxiety and higher serum concentrations of leptin and inflammatory markers in women with diabetes which indicates that there might be marked gender differences in the way anxiety impacts cardiovascular disease.

Finally, in patients with panic-type anxiety, there is evidence of an association with cardiovascular disease [53], cardiomyopathies [54], arrhythmias, and reductions in heart rate variability [47]. Coryell et al. [55] had earlier conducted a longitudinal study over 12 years and found that men with panic disorder were twice as likely to die from cardiovascular disease and suicide. In general, panic disorder sufferers are exposed to a range of cardiac complications which can occur, including triggered cardiac arrhythmias, recurrent emergency room attendances with angina and electrocardiographic changes of ischemia, and coronary artery spasm, in some cases complicated by coronary thrombosis [56]. Indeed, panic anxiety has been proposed as a better predictor of coronary artery disease than depression [57].

Psychogenic Hypertension

Hypertension is a condition in which the blood pressure is consistently higher than 130 over 80 millimeters of mercury (mmHg) [58]. Hypertension may arise from several factors: from social demands to metabolic syndrome and from sedentary life to chronic mental stress [59]. Since the first decades of the twentieth century, many researchers have argued a potential role of psychogenic stimuli on hypertension [60–62].

A recent meta-analysis reported that chronic psychosocial stress may be a risk factor for hypertension [63]. Another analysis of prospective studies found that anxiety symptoms were an independent risk factor for incident hypertension [64]. However, review authors stated that many studies were limited by the lack of control for confounding factors, such as risk behaviors and related psychological factors (e.g., anger), which may attenuate observed relationships between these emotional states and hypertension [64].

Notably, workplace hypertension has been documented in several studies and is often thought to be related to job stress [65]. Literature reports that there are two main patterns of adverse work environment which may cause high levels of blood pressure: First, the "high job strain" workplace that is characterized by lack of control over the pace of work, its goals, and deadlines [66] and, second, the "effort-reward imbalanced" workplace that is characterized by demanding work which causes little personal gratification because of lack of appreciation and unjustified criticism by workplace superiors [67].

Interestingly, the role of psychosocial stress on the pathogenesis of hypertension has been demonstrated by a 30-year follow-up study, finding that blood pressure remained remarkably stable in a group of nuns in Italy; conversely, the control group of laywomen showed the expected increase in blood pressure with age. Comparisons between survival curves were statistically significant between the two groups [68].

Additional key observations have been made on human populations who demonstrate blood pressure elevation after migration processes; this rise in pressure might be attributed primarily to mental stress, although changes in physical activity and diet may represent other potential risk factors for this specific population [69].

From a therapeutic perspective, it is worth mentioning that benzodiazepines (BZD), a traditional class of anxiolytic drugs, possess also myorelaxant and vasodilatory effects, thus being

hypothesized to have antihypertensive properties. Notably, BZD potentiate the inhibitory effect of γ-aminobutyric acid (GABA) in the central nervous system and bind the 18 kDa translocator protein (TPSO), also known as peripheral-type BDZ receptor [70]. TPSO is abundantly distributed in cardiovascular tissues and is involved in the myocardial response to ischemia [71], possibly explaining the endothelium-independent vasodilatory effect of BDZ [72]. BDZ have been shown to acutely decrease the sympathetic tone and blood pressure values in healthy volunteers [73] and in patients undergoing surgery [74]. Moreover, BZD were demonstrated to be effective as angiotensin-converting enzyme inhibitors in the treatment of hypertensive urgencies in the emergency department [75, 76]. These findings suggest potential benefits of BDZ in the setting of acute treatment of hypertension. Also, in their retrospective study, Mendelson et al. [77] found that treatment with BZD in the last 3 months was independently associated with lower systolic and diastolic blood pressure in subjects older than 60 years. Nevertheless, the chronic use of BZD should be considered very cautiously, especially in the elderly, since it is not free from side effects [70].

Takotsubo Cardiomyopathy

Takotsubo cardiomyopathy was firstly described in Japan in 1990 [78], and its name derives from the Japanese word *takotsubo* ("octopus pot") that resembles the shape of the affected heart. This CVD is characterized by a transient systolic and diastolic left ventricular dysfunction with a variety of wall-motion abnormalities [79]. It predominantly affects elderly women and is often preceded by an emotional or physical trigger. However, the condition has also been reported with no evident trigger.

Although the cause of takotsubo cardiomyopathy remains unknown, the role of the brain-heart axis in the pathogenesis of the disease has been described [80]. In particular, the potential role of catecholamine excess in the pathogenesis of takotsubo cardiomyopathy has been long debated [81]. In the acute phase, the clinical presentation, electrocardiographic findings, and biomarker profiles are often like those of an acute coronary syndrome. Since no randomized controlled trials have been conducted, therapeutic strategies based exclusively on clinical experience and expert consensus [82].

Recently, the International Takotsubo Registry investigated the clinical features, prognostic predictors, and outcome of takotsubo cardiomyopathy, comparing a large sample of patients with age- and sex-matched patients who had an acute coronary syndrome. The authors found that patients who suffered from takotsubo cardiomyopathy had long-term outcomes comparable to those of age- and sex-matched patients who suffered from acute coronary syndrome. Also, they demonstrated that takotsubo cardiomyopathy can either be benign or a life-threating condition depending on the inciting stress factor [83].

Anxiety Disorders in Patients Who Suffer from Cardiovascular Diseases

Anxiety not only represents a prominent psychosocial risk factor for the onset and progression of CVD but is also a psychological issue that frequently co-occurs with CVD, potentially influencing their progression and outcome [19]. For this reason, it is important to promptly recognize and treat anxiety disorders in people who suffer from CVD, for impeding a potential progression of the disease itself. However, diagnosis is challenging given the overlapping symptomatology between anxiety and heart disease. Medication, psychotherapy, and alternative treatments appear safe and generally efficacious in this population. With careful diagnosis and appropriate treatment, anxious patients could benefit of substantial improvements in quality of life, functioning, and cardiac health.

Epidemiology of Anxiety Disorders in CVD

The prevalence of anxiety disorders is substantially greater in CVD populations than in the general population. A meta-analysis indicated that the point prevalence rate of any anxiety disorders in CVD populations was approximately

16% [13]. However, in this type of population, we should consider relevant not only anxiety disorders per se but also "subthreshold" anxiety symptoms (i.e., levels of anxiety which do not reach the threshold for formulating a psychiatric diagnosis).

Following an acute coronary syndrome (ACS), 20–30% of patients experience elevated levels of anxiety [84]. While post-ACS anxiety may be transient for some patients, in half of cases anxiety persists several months after the event, suggesting that for many patients with heart disease, anxiety is a chronic condition [85]. Research has revealed similar prevalence rates in patients with coronary artery disease (CAD) awaiting coronary artery bypass graft surgery. In this population, 25% of patients experience elevated levels of anxiety pre-procedure, with many having a reduction in symptoms in the months following surgery [86].

Anxiety is common in patients with other forms of heart disease as well. In a recent meta-analysis of 38 studies, Easton and colleagues estimated that 32% of patients with heart failure (HF) experience elevated levels of anxiety and 13% meet criteria for an anxiety disorder [87]. Anxiety also affects approximately 20% of patients with more advanced HF who require implantation of a left ventricular assist device to support their cardiac function [88, 89]. Finally, among patients who have undergone implantation of an implantable cardioverter defibrillator to prevent the development of lethal arrhythmias, elevated anxiety is present in approximately 20–40% [90].

Among anxiety disorders, GAD and PD are the highly prevalent in patients with CVD. Recent meta-analyses found prevalence of GAD that ranged from 14% in patients with HF [87] to 26% lifetime prevalence of GAD in patients with coronary artery disease (CAD) [91]. GAD is independently associated with poor outcomes in patients with established cardiac disease, especially CAD, at all stages [92, 93]. PD is also common in patients with heart disease. Among patients with CAD, studies have estimated prevalence rates which vary between 5–8% [94, 95] and 10–50% [96]. However, a study of post-ACS patients found PD to be significantly less prevalent than GAD or depression [97]. While less common than GAD, PD significantly increases the risk of the development and progression of cardiac disease. In a cohort study of nearly 80,000 individuals without pre-established CAD (half of them diagnosed with PD), PD was associated with a nearly twofold increased risk of incident CAD [98]. In another cohort study of more than 50,000 patients with PD and nearly 350,000 age- and sex-matched controls, patients with PD had a significantly higher risk of the development of CAD but a lower risk of CAD-related mortality [99]. Finally, a systematic review and meta-regression analysis of over one million patients found that PD was significantly associated with incident CAD, major adverse cardiac events, and acute coronary events [53].

Diagnosis of Anxiety Disorders in Patients with CVD

Diagnosing anxiety disorders in patients with CVD is difficult given the overlapping symptoms between the two groups of conditions. Indeed, many symptoms of anxiety, such as restlessness, fatigue, poor concentration, and sleep disturbances, are very common also in patients with cardiac disease. Analogously, many symptoms of a panic attack (e.g., palpitations, diaphoresis, dyspnea, nausea, chest pain) could potentially be experienced during an arrhythmia, acute coronary syndrome, or paroxysmal nocturnal dyspnea [19].

Since anxiety disorders are often chronic, their identification may allow to establish a proper treatment, thus reducing their impact on mental and physical health. For an accurate diagnosis, it is important to focus on the cardinal psychological symptoms of the disorders and to closely follow the DSM-5 criteria [8], including the requirements regarding duration of symptoms and the effects on socio-occupational functioning. If there is a significant question about the duration of symptoms and whether they exist only in the context of an acute exacerbation of cardiac symptoms, it can be helpful to re-evaluate the patient during a period of medical stability to see if those symptoms persist. Information from family members, relatives, or friends can also be helpful for the clarification of the evolution of symptoms over time. Moreover, the consultation of a mental health professional may facilitate an accurate differential

diagnosis, to ensure the establishment of a proper therapy for those who need it and to avoid unnecessary treatments for those without a formal disorder [19].

Pharmacological Therapies

A recent systematic review found that even though the large amount of studies about treatment-related changes in anxiety in patients with CVD were reported, only a minority of the studies specifically targeted patients with anxiety disorders or elevated anxiety symptoms. Most studies, in fact, measured anxiety as a secondary outcome, with other outcomes (e.g., depression, quality of life, number of acute events) typically serving as the primary outcome [100]. Interventions for anxiety in CVD include pharmacological therapies, psychotherapies and counselling, educational, and complementary or alternative therapies,

Antidepressant medications are the most commonly used pharmacologic treatments for a variety of anxiety disorder, as suggested by guidelines. A recent meta-analysis evaluating the efficacy and tolerability of antidepressants in patients with ischemic heart disease and depression found no differences between antidepressants and placebo in terms of acceptability and tolerability, quality of life, mortality, and cardiovascular events [101]. However, no randomized controlled trials specifically evaluated antidepressants in patients suffering from cardiovascular disease and anxiety. Among antidepressant medications, selective serotonin reuptake inhibitors (SSRI) are the best studied and most frequently used agents in cardiac patients, given the minimum effect of blood pressure and intraventricular conduction [102]. Sertraline should be preferred [19, 101]. However, few molecules, i.e., citalopram and escitalopram, have been associated with a modest effect on the QT interval, with increased risk of torsades de pointes [103]. Other SSRI, such as fluvoxamine, fluoxetine, and paroxetine, can interact with cardiovascular medications [104]. Finally, SSRI may increase the risk of bleeding, especially in patients who use other anticoagulant medications, because of the inhibition of platelet aggregation/activation [105]. Of note, it has been recently shown that platelet inhibition of citalopram is independent of its ability to block serotonin uptake by the serotonin transporter and might be mediated by different mechanisms [106]. Nevertheless, given the effect of mood, there has been indirect evidence that SSRI be associated with lower cardiac mortality and lower rates of first MI [107].

Selective noradrenaline reuptake inhibitors (SNRI), such as venlafaxine and duloxetine, are sometimes used for the management of anxiety disorders, though data on their use in heart disorders are still sparse and somewhat contrasting. A meta-analysis showed no differences in terms of cardiovascular adverse events between duloxetine and placebo [108]. Other authors reported venlafaxine as causing mild increases in heart rate and blood pressure, also being associated with the development of acute HF in overdose [109]. Finally, while tricyclic antidepressants (TCA) can be used for the management of anxiety disorders, they are not recommended in patients with cardiovascular disease, given the potential side effects, such as tachycardia, orthostatic hypotension, and conduction abnormalities [102]. TCA also appear to prolong the QT interval to a greater degree than SSRI [103]. Due to their lack of superiority in terms of treatment efficacy and their significantly worse cardiac side effect profile, these medications are considered second- or third-line in patients with heart disease [19].

Benzodiazepines are frequently prescribed to people who suffer from anxiety disorders, especially for short-term acute anxiety or very specific indications. Although these agents may have beneficial cardiovascular effects, especially in the management of acute hypertensive crisis [75, 76], their use can cause respiratory depression, and they have been linked to falls in the elderly and confusion, so they should be used cautiously in patients with CVD [110].

Psychotherapy, Counselling, and Educational Treatments

Psychotherapy, such as cognitive behavioral therapy (CBT), is a reasonable alternative to pharmacotherapy, without relevant side effects or medication interactions. Therefore, it can be used in patients regardless of illness severity and

in some cases may be preferable to pharmacologic treatment [19]. A recent paper systematically reviewed studies about psychotherapy and counselling interventions in people with cardiovascular disease who were also suffering from anxiety. However, the authors reported that the efficacy of counselling and educational interventions for anxiety disorders seems still inconsistent; this could be due to the heterogeneity of the interventions and the outcomes measured [100].

Complementary and Alternative Therapies

Among complementary or alternative treatments, several papers specifically investigated relaxation therapies, such as deep breathing interventions, autogenic training, biofeedback, muscle relaxation therapy, guided imagery, mindfulness-based interventions, and music exercise. Other studies evaluated physical exercise and nutraceuticals or herbal therapies [100]. Of note, physical exercise has shown promising results in treating anxiety [111, 112]. Moreover, it has been extensively demonstrated that it may help in the prevention and management of cardiovascular diseases, given its multiple beneficial effects on the human organism [113]. Conversely, the efficacy of nutraceuticals (i.e., food or part of a food with medical or health benefits, including the prevention and/or treatment of a disease) for anxiety disorders in general is still controversial. Recently, Camfield [114] reported that preliminary research regarding the efficacy of myoinositol and N-acetylcysteine is promising, showing that these substances may have efficacy in the treatment of anxiety disorders. Conversely, B vitamins, magnesium, arginine, and lysine need to be further tested in clinical samples [114]. Moreover, some authors have suggested that the supplementation with some types of nutraceuticals (e.g., hawthorn, coenzyme Q10, L-carnitine, D-ribose, carnosine, vitamin D, some probiotics, omega-3 fatty acids, beet nitrates) may be a useful option for effective management of HF, being also well tolerated by patients [115]. Other authors also reported that the application of nutraceuticals may have the potential to increase the effectiveness of therapy for the prevention of CVD. However, there is often insufficient data available with respect to long-term safety and effectiveness against clinical outcomes such as myocardial infarction and mortality [116].

Personality and Heart Disease

Anger and Cardiovascular Disease

Anger can be defined as a multidimensional construct with distinct affective, behavioral, and cognitive dimensions that include specific physiological elements, which contribute to both the experience and expression of the emotion [9]. In anger, we could distinguish three dimensions: the affective dimension, the cognitive dimension, and the behavioral dimension. The affective dimension of anger refers to the emotional state, which occurs in response to an immediate stressor and may vary in both intensity and duration [117]. The cognitive dimension of anger, also denominated "hostility" in the literature, has been defined as a cognitive phenomenon of an attitudinal nature that contributes to the emotional process, but it would not represent an emotion per se [118]. The behavioral dimension of anger is simply the behavioral response to the subjective experience of anger and may be expressed outwardly or inwardly [117].

Numerous investigations regarding the effects of anger on physiological functions have been conducted [119]. They have primarily conceptualized anger as an emotion-induced physiological stressor. According to Selye's stress model, anger would increase and mantain the body's autonomic arousal [120]. Such rise in autonomic arousal may result in increased cardiovascular activity, glucose metabolism, and changes in patterns of cerebral cortical arousal. Therefore, it is reasonable to suggest that chronic feelings of anger or the subjective experience of anger are associated with increased autonomic arousal, as reported also for anxiety. In 1982, Diamond [121] critically discussed how anger and hostility may affect blood pressure and heart disease with a psychodynamic, personality, and psychophysiological approach. Anger has long been considered a

potential trigger of acute coronary syndromes and a significant risk factor for CHD [122, 123]. In 2009, a meta-analytic review of 44 prospective studies found that anger and hostility were associated with increased CHD events both in the healthy population studies (19% increase) and in the pre-existing CHD population studies (24% increase) [124]. These data suggest that anger could play a role in the development of acute myocardial ischemia. In 2015, Pimple and colleagues found that anger, both as an emotional state and as a personality trait, was significantly associated with propensity to develop myocardial ischemia during mental stress. Patients with this psychological profile may be at increased risk for silent ischemia induced by emotional stress, and this may translate into worse prognosis [125]. Conversely, a meta-analysis published in 2019 did not find any association of a higher level of anger and hostility with an increased risk of stroke [126]. Finally, anger and hostility appeared also associated with an increased risk of developing hypertension [127, 128].

Type A Personality

Type A personality behavior was firstly described as a potential risk factor for CVD in the 1950s by Rosenman and Friedman, two cardiologists who discovered that only the front part of the chairs in their waiting room was worn down. Type A personality can be defined as "an action-emotion complex that can be observed in any person who is aggressively involved in a chronic, incessant struggle to achieve more and more in less and less time and, if required to do so, against the opposing efforts of other things or persons" [129]. The hypothesis describes Type A individuals as rigidly organized, anxious, ambitious, impatient, hostile, proactive, and incredibly concerned with time management. Type A construct can be divided into two main factors: achievement striving (AS), characterized by being hardworkers, active, and taking work seriously, and impatience irritability (II), which is characterized by impatience, irritability, and anger [130]. People with Type A personalities are often high-achieving "workaholics," experiencing more job-related stress and less job satisfaction [131].

In their research, after long-term study of healthy men, Rosenman and Friedman estimated that Type A behavior may double the risk of coronary heart disease in otherwise healthy individuals [129]. However, subsequent analysis indicated that although Type A personality is associated with the incidence of coronary heart disease, it does not seem to be a risk factor for mortality [132]. Mechanisms proposed for the link between Type A personality and the higher risk for CVD are hostility, which can be triggered even by irrelevant incidents; time urgency and impatience, causing irritation and exasperation; and competition proneness, which causes stress and an achievement driven mentality [133].

After the first description of Type A personality construct, for a couple of decades, findings mainly indicated a positive association with coronary and cardiovascular events and negative outcomes. In particular, the long-term follow-ups promoted by the Western Collaborative Group Study (WCGS) and the Framingham Heart Study (FHS) contributed to raise Type A to the levels of independent conventional cardiovascular risk factors in 1981 [134]. However, later reports started to show weak or no association between Type A personality and health-related outcomes. Interestingly, a meta-analysis conducted by Myrtek [135] concluded that Type A was related with a negligible for negative cardiovascular events. However, some studies published in more recent years still showed a negative effect of Type A personality on cardiovascular health [136]. In 2015, the review by Šmigelskas and colleagues [137] concluded that Type A measures were inconsistently associated with cardiovascular mortality and most associations were nonsignificant. Some scales even suggested slightly decreased, rather than increased, risk of CVD death during the follow-up associations with non-cardiovascular deaths was even weaker. Potential explanations for the contrasting results could be related to the specific sample or environment, to the follow-up time, and to the heterogeneous methodology adopted in early studies [138].

Type D Personality

A different psychological construct has been referred as the Type D or "distressed" personality construct. It is characterized by a high score on two stable personality traits, negative affectivity and social inhibition [139, 140]. Negative affectivity (NA) refers to the tendency to experience negative emotions such as anger or anxiety across time and situations [141]. Social inhibition (SI) is the tendency to inhibit the expression of emotions and behaviors in social interactions, because of fear of rejection or disapproval [142].

The Type D personality construct was originally developed by Johan Denollet to study the role of personality traits in coronary heart disease outcomes [139]. Literature estimated the prevalence of Type D personality between 13% and 24% in the general population [143] while reported a higher prevalence among (between 24% and 37%) among cardiovascular patients [144].

Type D personality has been proposed as an independent predictor of negative outcomes such as poor health status, (recurrent) myocardial infarction, and increased risk of mortality in cardiovascular patients [145]. As reported for anxiety, the link between Type D personality and worse cardiac outcome might be due to both biological and behavioral mechanisms. Adherence to medication, lifestyle modification, and post-event cardiac rehabilitation is at the forefront of treatment to prevent disease progression during the long-term follow-up of patients with CHD [59]. These behavioral pathways may be affected by a patient's Type D personality, thereby affecting cardiac prognosis. Additionally, direct biological pathways may be related to the progression of disease and the prognosis, with stress-related processes affecting pathophysiological processes. The understanding of these mechanisms may allow the implementation of personalized interventions, taking within-person risk factor profiles into account [145].

To date, there is no recommended psychological intervention for Type D personality. Nevertheless, stepwise psychotherapy to improve depressive symptoms was shown to be particularly beneficial for CHD patients with Type D personality [146]. A recent review also indicated that cardiac rehabilitation can significantly reduce anxiety and depression, as well as improve physical functioning and quality of life in people with Type D personality and CVD [144].

Personality Disorders and Cardiovascular Disease

Personality disorders can be defined as "pervasive, stiff, and maladaptive pattern of cognitive, emotional, and behavioral responses." These patterns develop early, typically in adolescence, becoming over a person's life his or her rigid way to feel, think, or act to interpersonal and social experiences, causing significant distress and disability [8]. Only a small amount of literature examined the link between personality disorders and the increased risk of developing CVD. In 2007, a national survey found that avoidant, obsessive-compulsive, and borderline personality disorders (BPD) were significantly associated with stroke. Moreover, ischemic heart disease was significantly associated with avoidant, paranoid, schizotypal, schizoid, and borderline personality disorders. The increased risk was not explained by differences in socioeconomic status or lifestyle [147].

Of note, borderline personality disorders (BPD) was the most frequently examined. BPD is characterized by marked instability in various areas, including affect regulation, interpersonal relationships, impulse control, and self-image abnormalities, and is often accompanied by self-harm and suicidal ideation [148]. One study found that women with BPD compared with age-matched healthy controls had greater intima-media thickness of common carotid arteries, a marker of atherosclerosis and cardiovascular risk [149]. Importantly, other findings suggest that body mass index (BMI) may account for this association of BPD with heart disease, arthritis, and obesity [150]. Another study conducted by Olssøn and Dahl [151] did not find significant differences in the prevalence of CVD between patients with and without personality disorders.

On the contrary, El-Gabalawy et al. [152] found the likelihood of a BPD diagnosis was associated with hypertension, hepatic disease, and even CVD. More recently, Chen and colleagues confirmed that patients with BPD had an elevated vulnerability to subsequent stroke and ischemic stroke compared to those without BPD [153].

It has been hypothesized that some characteristics of BPD may be associated with social risk factors and psychophysiological mechanisms known to promote the risk of developing a CVD. Specifically, BPD features are associated with elevated reactivity to conflict, a feature which has previously been found to predict the development of CVD [154]. Moreover, BPD is often present in comorbidity with substance use disorder (e.g., cocaine, alcohol) [155], which may further increase the risk of developing a CVD [156]. Further studies would be required to investigate the underlying mechanisms.

Cardioprotective Personality Traits

Few personality traits have been associated with positive health outcomes in subjects with CVD and can be regarded as cardioprotective personality traits [157]. Optimism, which is defined as the tendency to expect good experiences in the future, has been found to be a protective factor against the risk of CAD in elderly [158]. Additionally, it seemed to predict better physical health and reduction of depressive symptoms after an acute coronary syndrome, and has been associated with reduced pain intensity and physical symptom after coronary artery bypass graft surgery [159]. In contrast, pessimism has been found to be a substantial risk factor for cardiovascular mortality [160].

Openness to experience, a personality trait from the five-factor personality model that involves active imagination, artistic sensitivity, attentiveness to inner feelings, and intellectual curiosity, has also been found to be an independent protective factor for incident cardiovascular disease in the community after adjusting for all putative confounding factors including depression [161]. Of note, curiosity has been found to be associated with longevity, independent of medical risk factors and health behavior [162].

Finally, conscientiousness, which comprehends personality dispositions like sense of duty, organization, self-efficacy, organization, self-discipline, and cautiousness, has been regarded as a potential protective factor against heart disease [163]. In subjects with CVD, low conscientiousness has been evaluated as a risk factor for all-cause mortality due to CVD, stroke, and malignancies [164].

Conclusion

The evidence reviewed in this chapter clearly highlights that CVD can potentially represent the consequences of subclinical and clinical anxiety and of certain personality traits or disorders. Anxiety, anger, and personological traits might in fact represent important triggers for the development of heart disease. Given its unpredictable and widely fluctuating nature, the role of anxiety might in some cases be more unexpected and deadlier than other psychological factors, such as depression, causing sudden fatal events. Additionally, the onset and progression of CVD may be associated with the development of new anxiety disorders, which should certainly warrant appropriate psychological management. In this regard, it is desirable to better understand the mechanisms of this close interrelationship, as well as its appropriate treatment. It appears important to consider anxiety and personality while acting on primary and secondary prevention of heart diseases and their treatment.

Cross-References

- ▶ Adrenoceptor Blockers
- ▶ Borderline Personality Disorder and the Heart
- ▶ Cardiovascular Manifestations of Panic and Anxiety
- ▶ Distinguishing Cardiac from Psychological Somatic Symptoms
- ▶ Emotional Processing and Heart Activity

▶ The Relationship Between Psychological Distress and Bio-behavioral Processes in Cardiovascular Disease

References

1. Suls J. Toxic affect: are anger, anxiety, and depression independent risk factors for cardiovascular disease? Emot Rev. 2018;10(1):6–17.
2. Descartes R. The passions of the soul. 1649. Indianapolis: Hackett Publishing Company; 1989.
3. James W. The stream of consciousness. In: Psychology. Cambridge: MIT Press; 1892.
4. da Costa JM. ART. I. – on irritable heart; a clinical study of a form of functional cardiac disorder and its consequences. Am J Med Sci. 1871;61(121):2–52.
5. World Health Organization. The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines. Geneva: World Health Organization; 1992.
6. Friedman HS, Booth-Kewley S. The "disease-prone personality": a meta-analytic view of the construct. Am Psychol. 1987;42(6):539.
7. Booth-Kewley S, Friedman HS. Psychological predictors of heart disease: a quantitative review. Psychol Bull. 1987;101(3):343.
8. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-5®). Arlington: American Psychiatric Publications; 2013.
9. Spielberger CD. Manual for the state-trait anger expression inventory (STAXI), vol. 6. Odessa: Psychological Assessment Resources; 1988.
10. Remes O, Brayne C, Van Der Linde R, Lafortune L. A systematic review of reviews on the prevalence of anxiety disorders in adult populations. Brain Behav. 2016;6(7):e00497.
11. Perna G. Understanding anxiety disorders: the psychology and the psychopathology of defence mechanisms against threats. Riv Psichiatr. 2013;48(1):73–5. https://doi.org/10.1708/1228.13618.
12. Simpson HB, Neria Y, Lewis-Fernández R, Schneier F. Anxiety disorders: theory, research and clinical perspectives. Cambridge: Cambridge University Press; 2010.
13. Tully PJ, Cosh SM, Baumeister H. The anxious heart in whose mind? A systematic review and meta-regression of factors associated with anxiety disorder diagnosis, treatment and morbidity risk in coronary heart disease. J Psychosom Res. 2014;77(6):439–48. https://doi.org/10.1016/s0924-9338(15)30318-7.
14. Lichtman JH, Bigger JT Jr, Blumenthal JA, Frasure-Smith N, Kaufmann PG, Lespérance FO, et al. Depression and coronary heart disease: recommendations for screening, referral, and treatment: a science advisory from the American Heart Association Prevention Committee of the Council on Cardiovascular Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Interdisciplinary Council on Quality of Care and Outcomes Research: endorsed by the American Psychiatric Association. Circulation. 2008;118(17):1768–75.
15. Lee W, Wadsworth M, Hotopf M. The protective role of trait anxiety: a longitudinal cohort study. Psychol Med. 2006;36(3):345–51.
16. Parker G, Hyett M, Hadzi-Pavlovic D, Brotchie H, Walsh W. GAD is good? Generalized anxiety disorder predicts a superior five-year outcome following an acute coronary syndrome. Psychiatry Res. 2011;188(3):383–9.
17. Tully PJ, Harrison NJ, Cheung P, Cosh S. Anxiety and cardiovascular disease risk: a review. Curr Cardiol Rep. 2016;18(12):120.
18. Batelaan NM, Seldenrijk A, Bot M, Van Balkom AJ, Penninx BW. Anxiety and new onset of cardiovascular disease: critical review and meta-analysis. Br J Psychiatry. 2016;208(3):223–31.
19. Celano CM, Daunis DJ, Lokko HN, Campbell KA, Huffman JC. Anxiety disorders and cardiovascular disease. Curr Psychiatry Rep. 2016;18(11):101.
20. Fish F. The psychiatric aspects of paroxysmal tachycardia. Br J Psychiatry. 1964;110(465):205–10.
21. Miles HH, Cobb S. Neurocirculatory asthenia, anxiety and neurosis. N Engl J Med. 1951;245(19):711–9.
22. Weiss E, Dlin B, Rollin HR, Fischer HK, Bepler C. Emotional factors in coronary occlusion: 1. Introduction and general summary. Arch Intern Med. 1957;99(4):628–41.
23. Krantz DS, Manuck SB. Acute psychophysiologic reactivity and risk of cardiovascular disease: a review and methodologic critique. Psychol Bull. 1984;96(3):435.
24. Kawachi I, Sparrow D, Vokonas PS, Weiss ST. Decreased heart rate variability in men with phobic anxiety (data from the Normative Aging Study). Am J Cardiol. 1995;75(14):882–5.
25. Kamarck TW, Jennings JR. Biobehavioral factors in sudden cardiac death. Psychol Bull. 1991;109(1):42.
26. Bankier B, Barajas J, Martinez-Rumayor A, Januzzi JL. Association between C-reactive protein and generalized anxiety disorder in stable coronary heart disease patients. Eur Heart J. 2008;29(18):2212–7. https://doi.org/10.1093/eurheartj/ehn326.
27. Pitsavos C, Panagiotakos DB, Papageorgiou C, Tsetsekou E, Soldatos C, Stefanadis C. Anxiety in relation to inflammation and coagulation markers, among healthy adults: the ATTICA study. Atherosclerosis. 2006;185(2):320–6. https://doi.org/10.1016/j.atherosclerosis.2005.06.001.
28. Vogelzangs N, Beekman AT, de Jonge P, Penninx BW. Anxiety disorders and inflammation in a large adult cohort. Transl Psychiatry. 2013;3:e249. https://doi.org/10.1038/tp.2013.27.
29. Hohensinner PJ, Niessner A, Huber K, Weyand CM, Wojta J. Inflammation and cardiac outcome. Curr Opin Infect Dis. 2011;24(3):259–64. https://doi.org/10.1097/QCO.0b013e328344f50f.

30. Moyer CF, Sajuthi D, Tulli H, Williams JK. Synthesis of IL-1 alpha and IL-1 beta by arterial cells in atherosclerosis. Am J Pathol. 1991;138(4):951–60.
31. Hasper D, Hummel M, Kleber FX, Reindl I, Volk HD. Systemic inflammation in patients with heart failure. Eur Heart J. 1998;19(5):761–5.
32. Vasan RS, Sullivan LM, Roubenoff R, Dinarello CA, Harris T, Benjamin EJ, et al. Inflammatory markers and risk of heart failure in elderly subjects without prior myocardial infarction: the Framingham Heart Study. Circulation. 2003;107(11):1486–91.
33. Heitzer T, Schlinzig T, Krohn K, Meinertz T, Münzel T. Endothelial dysfunction, oxidative stress, and risk of cardiovascular events in patients with coronary artery disease. Circulation. 2001;104(22):2673–8.
34. Mercer DA, Lavoie KL, Ditto B, Pelletier R, Campbell T, Arsenault A, et al. The interaction between anxiety and depressive symptoms on brachial artery reactivity in cardiac patients. Biol Psychol. 2014;102:44–50. https://doi.org/10.1016/j.biopsycho.2014.07.012.
35. Narita K, Murata T, Hamada T, Takahashi T, Kosaka H, Yoshida H, et al. Association between trait anxiety and endothelial function observed in elderly males but not in young males. Int Psychogeriatr. 2007;19(5):947–54. https://doi.org/10.1017/s1041610206004571.
36. Davignon J, Ganz P. Role of endothelial dysfunction in atherosclerosis. Circulation. 2004;109(23_suppl_1):III-27–32.
37. Neumeister A, Bain E, Nugent AC, Carson RE, Bonne O, Luckenbaugh DA, et al. Reduced serotonin type 1A receptor binding in panic disorder. J Neurosci. 2004;24(3):589–91. https://doi.org/10.1523/jneurosci.4921-03.2004.
38. Strike PC, Magid K, Brydon L, Edwards S, McEwan JR, Steptoe A. Exaggerated platelet and hemodynamic reactivity to mental stress in men with coronary artery disease. Psychosom Med. 2004;66(4):492–500. https://doi.org/10.1097/01.psy.0000130492.03488.e7.
39. Levine SP, Towell BL, Suarez AM, Knieriem LK, Harris MM, George JN. Platelet activation and secretion associated with emotional stress. Circulation. 1985;71(6):1129–34.
40. Kokacya MH, Copoglu US, Kivrak Y, Ari M, Sahpolat M, Ulutas KT. Increased mean platelet volume in patients with panic disorder. Neuropsychiatr Dis Treat. 2015;11:2629–33. https://doi.org/10.2147/ndt.s94147.
41. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004;364(9438):937–52. https://doi.org/10.1016/s0140-6736(04)17018-9.
42. Bonnet F, Irving K, Terra J-L, Nony P, Berthezène F, Moulin P. Anxiety and depression are associated with unhealthy lifestyle in patients at risk of cardiovascular disease. Atherosclerosis. 2005;178(2):339–44.
43. Murray J, Craigs CL, Hill KM, Honey S, House A. A systematic review of patient reported factors associated with uptake and completion of cardiovascular lifestyle behaviour change. BMC Cardiovasc Disord. 2012;12(1):120.
44. Kawachi I, Sparrow D, Spiro A III, Vokonas P, Weiss ST. A prospective study of anger and coronary heart disease: the Normative Aging Study. Circulation. 1996;94(9):2090–5.
45. Roest AM, Martens EJ, de Jonge P, Denollet J. Anxiety and risk of incident coronary heart disease: a meta-analysis. J Am Coll Cardiol. 2010;56(1):38–46. https://doi.org/10.1016/j.jacc.2010.03.034.
46. Tully PJ, Cosh SM, Baune BT. A review of the affects of worry and generalized anxiety disorder upon cardiovascular health and coronary heart disease. Psychol Health Med. 2013;18(6):627–44.
47. Chalmers JA, Quintana DS, Abbott MJ, Kemp AH. Anxiety disorders are associated with reduced heart rate variability: a meta-analysis. Front Psychol. 2014;5:80.
48. Hammel JC, Smitherman TA, McGlynn FD, Mulfinger AM, Lazarte AA, Gothard KD. Vagal influence during worry and cognitive challenge. Anxiety Stress Coping. 2011;24(2):121–36.
49. Batelaan NM, ten Have M, van Balkom AJ, Tuithof M, de Graaf R. Anxiety disorders and onset of cardiovascular disease: the differential impact of panic, phobias and worry. J Anxiety Disord. 2014;28(2):252–8.
50. Albert CM, Chae CU, Rexrode KM, Manson JE, Kawachi I. Phobic anxiety and risk of coronary heart disease and sudden cardiac death among women. Circulation. 2005;111(4):480–7.
51. Haines A, Imeson J, Meade T. Phobic anxiety and ischaemic heart disease. Br Med J (Clin Res Ed). 1987;295(6593):297–9.
52. Brennan AM, Fargnoli JL, Williams CJ, Li T, Willett W, Kawachi I, et al. Phobic anxiety is associated with higher serum concentrations of adipokines and cytokines in women with diabetes. Diabetes Care. 2009;32(5):926–31.
53. Tully P, Turnbull D, Beltrame J, Horowitz J, Cosh S, Baumeister H, et al. Panic disorder and incident coronary heart disease: a systematic review and meta-regression in 1 131 612 persons and 58 111 cardiac events. Psychol Med. 2015;45(14):2909–20.
54. Kahn JP, Gorman JM, King DL, Fyer AJ, Liebowitz MR, Klein DF. Cardiac left ventricular hypertrophy and chamber dilatation in panic disorder patients: implications for idiopathic dilated cardiomyopathy. Psychiatry Res. 1990;32(1):55–61.
55. Coryell W, Noyes R, House JD. Mortality among outpatients with anxiety disorders. Am J Psychiatry. 1986;143(4):508–10.
56. Mansour VM, Thompson JM, Esler MD, Wilkinson DJ, Jennings GL, Schwarz RG. Panic disorder: coronary spasm as a basis for cardiac risk? Med J Aust. 1998;168(8):390–2.

57. Zafar MU, Paz-Yepes M, Shimbo D, Vilahur G, Burg MM, Chaplin W, et al. Anxiety is a better predictor of platelet reactivity in coronary artery disease patients than depression. Eur Heart J. 2010;31(13):1573–82.
58. Carey RM, Whelton PK. Prevention, detection, evaluation, and management of high blood pressure in adults: synopsis of the 2017 American College of Cardiology/American Heart Association hypertension guideline. Ann Intern Med. 2018;168(5):351–8.
59. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J. 2016;37(29):2315–81. https://doi.org/10.1093/eurheartj/ehw106.
60. Moschcowitz E. The psychogenic origin of organic diseases. N Engl J Med. 1935;212(14):603–11.
61. Moses L, Daniels GE, Nickerson JL. Psychogenic factors in essential hypertension; methodology and preliminary report. Psychosom Med. 1956;18:471.
62. Binger C. On so-called psychogenic influences in essential hypertension. Psychosom Med. 1951;13(5):273–6.
63. Liu M-Y, Li N, Li WA, Khan H. Association between psychosocial stress and hypertension: a systematic review and meta-analysis. Neurol Res. 2017;39(6):573–80. https://doi.org/10.1080/01616412.2017.1317904.
64. Pan Y, Cai W, Cheng Q, Dong W, An T, Yan J. Association between anxiety and hypertension: a systematic review and meta-analysis of epidemiological studies. Neuropsychiatr Dis Treat. 2015;11:1121–30. https://doi.org/10.2147/ndt.s77710.
65. Kivimäki M, Kawachi I. Work stress as a risk factor for cardiovascular disease. Curr Cardiol Rep. 2015;17(9):74.
66. Schnall PL, Landsbergis PA, Baker D. Job strain and cardiovascular disease. Annu Rev Public Health. 1994;15(1):381–411.
67. Dragano N, Siegrist J, Nyberg ST, Lunau T, Fransson EI, Alfredsson L, et al. Effort–reward imbalance at work and incident coronary heart disease: a multicohort study of 90,164 individuals. Epidemiology. 2017;28(4):619.
68. Timio M, Saronio P, Venanzi S, Gentili S, Verdura C, Timio F. Blood pressure in nuns in a secluded order: a 30-year follow-up. Miner Electrolyte Metab. 1999;25(1–2):73–9. https://doi.org/10.1159/000057424.
69. Esler M. Mental stress and human cardiovascular disease. Neurosci Biobehav Rev. 2017;74:269–76.
70. Colussi G, Catena C, Darsiè D, Sechi LA. Benzodiazepines: an old class of new antihypertensive drugs? Am J Hypertens. 2017;31(4):402–4.
71. Musman J, Paradis S, Panel M, Pons S, Barau C, Caccia C, et al. A TSPO ligand prevents mitochondrial sterol accumulation and dysfunction during myocardial ischemia-reperfusion in hypercholesterolemic rats. Biochem Pharmacol. 2017;142:87–95.
72. Erne P, Chiesi M, Longoni S, Fulbright J, Hermsmeyer K. Relaxation of rat vascular muscle by peripheral benzodiazepine modulators. J Clin Investig. 1989;84(2):493–8.
73. Kitajima T, Kanbayashi T, Saito Y, Takahashi Y, Ogawa Y, Sugiyama T, et al. Diazepam reduces both arterial blood pressure and muscle sympathetic nerve activity in human. Neurosci Lett. 2004;355(1–2):77–80.
74. Gupta R, Santha N, Upadya M, Manissery JJ. Effect of different dosages of intravenous midazolam premedication on patients undergoing head and neck surgeries-A Double Blinded Randomized Controlled Study. J Clin Diagn Res. 2017;11(8):UC01.
75. Grossman E, Nadler M, Sharabi Y, Thaler M, Shachar A, Shamiss A. Antianxiety treatment in patients with excessive hypertension. Am J Hypertens. 2005;18(9):1174–7.
76. Yilmaz S, Pekdemir M, Tural Ü, Uygun M. Comparison of alprazolam versus captopril in high blood pressure: a randomized controlled trial. Blood Press. 2011;20(4):239–43.
77. Mendelson N, Gontmacher B, Vodonos A, Novack V, Abu-AjAj M, Wolak A, et al. Benzodiazepine consumption is associated with lower blood pressure in ambulatory blood pressure monitoring (ABPM): retrospective analysis of 4938 ABPMs. Am J Hypertens. 2017;31(4):431–7.
78. Sato H. Tako-tsubo-like left ventricular dysfunction due to multivessel coronary spasm. In: Clinical aspects of myocardial injury: from ischemia to heart failure. Tokyo: Kagakuhyoronsha Publishing Company; 1990. p. 56–64.
79. Medeiros K, O'connor MJ, Baicu CF, Fitzgibbons TP, Shaw P, Tighe DA, et al. Systolic and diastolic mechanics in stress cardiomyopathy. Circulation. 2014;129(16):1659–67.
80. Suzuki H, Matsumoto Y, Kaneta T, Sugimura K, Takahashi J, Fukumoto Y, et al. Evidence for brain activation in patients with takotsubo cardiomyopathy. Circ J. 2014;78(1):256–8.
81. Wittstein IS, Thiemann DR, Lima JA, Baughman KL, Schulman SP, Gerstenblith G, et al. Neurohumoral features of myocardial stunning due to sudden emotional stress. N Engl J Med. 2005;352(6):539–48. https://doi.org/10.1056/NEJMoa043046.
82. Ruschitzka F, Ghadri J-R, Cammann VL, Templin C, Yoshida T, Manfredini R, et al. International expert consensus document on takotsubo syndrome (part II): diagnostic workup, outcome, and management. Eur Heart J. 2018;39(22):2047–62. https://doi.org/10.1093/eurheartj/ehy077.
83. Ghadri JR, Kato K, Cammann VL, Gili S, Jurisic S, Di Vece D, et al. Long-term prognosis of patients with

takotsubo syndrome. J Am Coll Cardiol. 2018;72 (8):874–82. https://doi.org/10.1016/j.jacc.2018.06.016.
84. Hanssen TA, Nordrehaug JE, Eide GE, Bjelland I, Rokne B. Anxiety and depression after acute myocardial infarction: an 18-month follow-up study with repeated measures and comparison with a reference population. Eur J Cardiov Prev Rehabil. 2009;16(6):651–9.
85. Versteeg H, Roest AM, Denollet J. Persistent and fluctuating anxiety levels in the 18 months following acute myocardial infarction: the role of personality. Gen Hosp Psychiatry. 2015;37(1):1–6.
86. Koivula M, Tarkka MT, Tarkka M, Laippala P, Paunonen-Ilmonen M. Fear and anxiety in patients at different time-points in the coronary artery bypass process. Int J Nurs Stud. 2002;39(8):811–22.
87. Easton K, Coventry P, Lovell K, Carter L-A, Deaton C. Prevalence and measurement of anxiety in samples of patients with heart failure: meta-analysis. J Cardiovasc Nurs. 2016;31(4):367.
88. Brouwers C, Denollet J, Caliskan K, de Jonge N, Constantinescu A, Young Q, et al. Psychological distress in patients with a left ventricular assist device and their partners: an exploratory study. Eur J Cardiovasc Nurs. 2015;14(1):53–62. https://doi.org/10.1177/1474515113517607.
89. Modica M, Ferratini M, Torri A, Oliva F, Martinelli L, De Maria R, et al. Quality of life and emotional distress early after left ventricular assist device implant: a mixed-method study. Artif Organs. 2015;39(3):220–7. https://doi.org/10.1111/aor.12362.
90. Magyar-Russell G, Thombs BD, Cai JX, Baveja T, Kuhl EA, Singh PP, et al. The prevalence of anxiety and depression in adults with implantable cardioverter defibrillators: a systematic review. J Psychosom Res. 2011;71(4):223–31.
91. Tully PJ, Cosh SM. Generalized anxiety disorder prevalence and comorbidity with depression in coronary heart disease: a meta-analysis. J Health Psychol. 2013;18(12):1601–16.
92. Roest AM, Zuidersma M, de Jonge P. Myocardial infarction and generalised anxiety disorder: 10-year follow-up. Br J Psychiatry. 2012;200(4):324–9. https://doi.org/10.1192/bjp.bp.111.103549.
93. Tully PJ, Winefield HR, Baker RA, Denollet J, Pedersen SS, Wittert GA, et al. Depression, anxiety and major adverse cardiovascular and cerebrovascular events in patients following coronary artery bypass graft surgery: a five year longitudinal cohort study. BioPsychoSoc Med. 2015;9(1):14.
94. Huffman JC, Pollack MH. Predicting panic disorder among patients with chest pain: an analysis of the literature. Psychosomatics. 2003;44(3):222–36.
95. Todaro JF, Shen B-J, Raffa SD, Tilkemeier PL, Niaura R. Prevalence of anxiety disorders in men and women with established coronary heart disease. J Cardpulm Rehabil. 2007;27(2):86–91.
96. Fleet R, Lavoie K, Beitman BD. Is panic disorder associated with coronary artery disease? A critical review of the literature. J Psychosom Res. 2000;48 (4–5):347–56.
97. Celano CM, Suarez L, Mastromauro C, Januzzi JL, Huffman JC. Feasibility and utility of screening for depression and anxiety disorders in patients with cardiovascular disease. Circulation. 2013;6(4):498–504.
98. Gomez-Caminero A, Blumentals WA, Russo LJ, Brown RR, Castilla-Puentes R. Does panic disorder increase the risk of coronary heart disease? A cohort study of a national managed care database. Psychosom Med. 2005;67(5):688–91.
99. Walters K, Rait G, Petersen I, Williams R, Nazareth I. Panic disorder and risk of new onset coronary heart disease, acute myocardial infarction, and cardiac mortality: cohort study using the general practice research database. Eur Heart J. 2008;29(24):2981–8.
100. Farquhar JM, Stonerock GL, Blumenthal JA. Treatment of anxiety in patients with coronary heart disease: a systematic review. Psychosomatics. 2018;59 (4):318–32. https://doi.org/10.1016/j.psym.2018.03.008.
101. Ostuzzi G, Turrini G, Gastaldon C, Papola D, Rayner L, Caruso R, et al. Efficacy and acceptability of antidepressants in patients with ischemic heart disease: systematic review and meta-analysis. Int Clin Psychopharmacol. 2019;34(2):65–75. https://doi.org/10.1097/yic.0000000000000248.
102. Alvarez W Jr, Pickworth KK. Safety of antidepressant drugs in the patient with cardiac disease: a review of the literature. Pharmacotherapy. 2003; 23(6):754–71.
103. Beach SR, Kostis WJ, Celano CM, Januzzi JL, Ruskin JN, Noseworthy PA, et al. Meta-analysis of selective serotonin reuptake inhibitor-associated QTc prolongation. J Clin Psychiatry. 2014;75(5):e441–9. https://doi.org/10.4088/JCP.13r08672.
104. Guck TP, Elsasser GN, Kavan MG, Barone EJ. Depression and congestive heart failure. Congest Heart Fail. 2003;9(3):163–9.
105. Serebruany VL. Selective serotonin reuptake inhibitors and increased bleeding risk: are we missing something? Am J Med. 2006;119(2):113–6. https://doi.org/10.1016/j.amjmed.2005.03.044.
106. Roweth HG, Cook AA, Moroi M, Bonna AM, Jung SM, Bergmeier W, et al. Two novel, putative mechanisms of action for citalopram-induced platelet inhibition. Sci Rep. 2018;8(1):16677. https://doi.org/10.1038/s41598-018-34389-5.
107. Kimmel SE, Schelleman H, Berlin JA, Oslin DW, Weinstein RB, Kinman JL, et al. The effect of selective serotonin re-uptake inhibitors on the risk of myocardial infarction in a cohort of patients with depression. Br J Clin Pharmacol. 2011;72(3):514–7. https://doi.org/10.1111/j.1365-2125.2011.04008.x.
108. Wernicke J, Lledo A, Raskin J, Kajdasz DK, Wang F. An evaluation of the cardiovascular safety profile of duloxetine. Drug Saf. 2007;30(5):437–55.
109. Batista M, Dugernier T, Simon M, Haufroid V, Capron A, Fonseca S, et al. The spectrum of acute

heart failure after venlafaxine overdose. Clin Toxicol. 2013;51(2):92–5.
110. Seldenrijk A, Vis R, Henstra M, Ho KP, Salomons T, Overmeire F, et al. Systematic review of the side effects of benzodiazepines. Ned Tijdschr Geneeskd. 2017;161:D1052.
111. Stonerock GL, Hoffman BM, Smith PJ, Blumenthal JA. Exercise as treatment for anxiety: systematic review and analysis. Ann Behav Med. 2015;49(4):542–56.
112. Stubbs B, Vancampfort D, Rosenbaum S, Firth J, Cosco T, Veronese N, et al. An examination of the anxiolytic effects of exercise for people with anxiety and stress-related disorders: a meta-analysis. Psychiatry Res. 2017;249:102–8.
113. Fiuza-Luces C, Santos-Lozano A, Joyner M, Carrera-Bastos P, Picazo O, Zugaza JL, et al. Exercise benefits in cardiovascular disease: beyond attenuation of traditional risk factors. Nat Rev Cardiol. 2018;15:731–743.
114. Camfield DA. Nutritional-based nutraceuticals in the treatment of anxiety. In: Evidence-based herbal and nutritional treatments for anxiety in psychiatric disorders. Cham: Springer; 2017. p. 81–101.
115. Cicero AFG, Colletti A. Nutraceuticals and dietary supplements to improve quality of life and outcomes in heart failure patients. Curr Pharm Des. 2017;23(8):1265–72. https://doi.org/10.2174/1381612823666170124120518.
116. Sosnowska B, Penson P, Banach M. The role of nutraceuticals in the prevention of cardiovascular disease. Cardiovasc Diagn Ther. 2017;7(Suppl 1):S21–31. https://doi.org/10.21037/cdt.2017.03.20.
117. Spielberger CD, Reheiser EC, Sydeman SJ. Measuring the experience, expression, and control of anger. Issues Compr Pediatr Nurs. 1995;18(3):207–32.
118. Smith TW. Concepts and methods in the study of anger, hostility, and health. In: Anger, hostility, and the heart. Hillsdale: Lawrence Erlbaum Associates; 1994. p. 23–42.
119. Miller TQ, Smith TW, Turner CW, Guijarro ML, Hallet AJ. Meta-analytic review of research on hostility and physical health. Psychol Bull. 1996;119(2):322.
120. Selye H. The stress of life. New York: McGraw-Hill Book Company; 1956.
121. Diamond EL. The role of anger and hostility in essential hypertension and coronary heart disease. Psychol Bull. 1982;92(2):410.
122. Gabbay FH, Krantz DS, Kop WJ, Hedges SM, Klein J, Gottdiener JS, et al. Triggers of myocardial ischemia during daily life in patients with coronary artery disease: physical and mental activities, anger and smoking. J Am Coll Cardiol. 1996;27(3):585–92.
123. Steptoe A, Brydon L. Emotional triggering of cardiac events. Neurosci Biobehav Rev. 2009;33(2):63–70.
124. Chida Y, Steptoe A. The association of anger and hostility with future coronary heart disease: a meta-analytic review of prospective evidence. J Am Coll Cardiol. 2009;53(11):936–46.
125. Pimple P, Shah A, Rooks C, Bremner JD, Nye J, Ibeanu I, et al. Association between anger and mental stress-induced myocardial ischemia. Am Heart J. 2015;169(1):115–21.e2. https://doi.org/10.1016/j.ahj.2014.07.031.
126. Chen H, Zhang B, Xue W, Li J, Li Y, Fu K et al. Anger, hostility and risk of stroke: a meta-analysis of cohort studies. J Neurol. 2019. https://doi.org/10.1007/s00415-019-09231-1.
127. Trudel-Fitzgerald C, Gilsanz P, Mittleman MA, Kubzansky LD. Dysregulated blood pressure: can regulating emotions help? Curr Hypertens Rep. 2015;17(12):92. https://doi.org/10.1007/s11906-015-0605-6.
128. Mezick EJ, Matthews KA, Hall M, Kamarck TW, Strollo PJ, Buysse DJ, et al. Low life purpose and high hostility are related to an attenuated decline in nocturnal blood pressure. Health Psychol. 2010;29(2):196–204. https://doi.org/10.1037/a0017790.
129. Friedman M, Rosenman RH. Association of specific overt behavior pattern with blood and cardiovascular findings: blood cholesterol level, blood clotting time, incidence of arcus senilis, and clinical coronary artery disease. JAMA. 1959;169(12):1286–96.
130. Spence JT, Helmreich RL, Pred RS. Impatience versus achievement strivings in the Type A pattern: differential effects on students' health and academic achievement. J Appl Psychol. 1987;72(4):522.
131. Kirkcaldy BD, Shephard RJ, Furnham AF. The influence of Type A behaviour and locus of control upon job satisfaction and occupational health. Personal Individ Differ. 2002;33(8):1361–71. https://doi.org/10.1016/S0191-8869(02)00018-1.
132. Ragland DR, Brand RJ. Type A behavior and mortality from coronary heart disease. N Engl J Med. 1988;318(2):65–9.
133. Friedman M. Type A behavior: its diagnosis and treatment. Boston: Springer Science & Business Media; 1996.
134. Cooper T, Detre T, Weiss S. Coronary-prone behavior and coronary heart disease: a critical review. Circulation. 1981;63(6 I):1199–215.
135. Myrtek M. Meta-analyses of prospective studies on coronary heart disease, Type A personality, and hostility. Int J Cardiol. 2001;79(2–3):245–51.
136. Gostautas A, Perminas A. Impact of the relationship between smoking and stressogenic behavior (Type A behavior) and their cumulative effect on development of myocardial infarction and mortality (25-year follow-up data). Medicina (Kaunas). 2004;40(3):265–71.
137. Šmigelskas K, Žemaitienė N, Julkunen J, Kauhanen J. Type A behavior pattern is not a predictor of premature mortality. Int J Behav Med. 2015;22(2):161–9.
138. Petticrew MP, Lee K, McKee M. Type A behavior pattern and coronary heart disease: Philip Morris's "crown jewel". Am J Public Health. 2012;102(11):2018–25.
139. Denollet J. Biobehavioral research on coronary heart disease: where is the person? J Behav Med. 1993;16(2):115–41.

140. Denollet J, De Potter B. Coping subtypes for men with coronary heart disease: relationship to well-being, stress and Type-A behaviour. Psychol Med. 1992;22(3):667–84.
141. Watson D, Pennebaker JW. Health complaints, stress, and distress: exploring the central role of negative affectivity. Psychol Rev. 1989;96(2):234.
142. Asendorpf JB. Social inhibition: a general-developmental perspective. Seattle: Hogrefe & Huber Publishers; 1993.
143. Mols F, Denollet J. Type D personality among non-cardiovascular patient populations: a systematic review. Gen Hosp Psychiatry. 2010;32(1):66–72.
144. Cao X, Wong EM, Chow Choi K, Cheng L, Ying Chair S. Interventions for cardiovascular patients with Type D personality: a systematic review. Worldviews Evid Based Nurs. 2016;13(4):314–23.
145. Kupper N, Denollet J. Type D personality as a risk factor in coronary heart disease: a review of current evidence. Curr Cardiol Rep. 2018;20(11):104. https://doi.org/10.1007/s11886-018-1048-x.
146. Herrmann-Lingen C, Beutel ME, Bosbach A, Deter HC, Fritzsche K, Hellmich M, et al. A stepwise psychotherapy intervention for reducing risk in coronary artery disease (SPIRR-CAD): results of an observer-blinded, multicenter, randomized trial in depressed patients with coronary artery disease. Psychosom Med. 2016;78(6):704–15. https://doi.org/10.1097/psy.0000000000000332.
147. Moran P, Stewart R, Brugha T, Bebbington P, Bhugra D, Jenkins R, et al. Personality disorder and cardiovascular disease: results from a national household survey. J Clin Psychol. 2007;68:69.
148. Leichsenring F, Leibing E, Kruse J, New AS, Leweke F. Borderline personality disorder. Lancet. 2011;377(9759):74–84.
149. Greggersen W, Rudolf S, Fassbinder E, Dibbelt L, Stoeckelhuber BM, Hohagen F, et al. Major depression, borderline personality disorder, and visceral fat content in women. Eur Arch Psychiatry Clin Neurosci. 2011;261(8):551–7.
150. Powers AD, Oltmanns TF. Borderline personality pathology and chronic health problems in later adulthood: the mediating role of obesity. J Pers Disord. 2013;4(2):152.
151. Olssøn I, Dahl A. Personality problems are considerably associated with somatic morbidity and health care utilisation. Eur Psychiatry. 2009;24(7):442–9.
152. El-Gabalawy R, Katz LY, Sareen J. Comorbidity and associated severity of borderline personality disorder and physical health conditions in a nationally representative sample. Psychosom Med. 2010;72(7):641–7.
153. Chen M-H, Hsu J-W, Bai Y-M, Su T-P, Li C-T, Lin W-C, et al. Risk of stroke among patients with borderline personality disorder: a nationwide longitudinal study. J Affect Disord. 2017;219:80–5.
154. Grove JL, Smith TW, Crowell SE, Williams PG, Jordan KD. Borderline personality features, interpersonal correlates, and blood pressure response to social stressors: implications for cardiovascular risk. Pers Individ Differ. 2017;113:38–47.
155. Carpenter RW, Wood PK, Trull TJ. Comorbidity of borderline personality disorder and lifetime substance use disorders in a nationally representative sample. J Personal Disord. 2016;30(3):336–50.
156. Hjorthøj C, Østergaard MLD, Benros ME, Toftdahl NG, Erlangsen A, Andersen JT, et al. Association between alcohol and substance use disorders and all-cause and cause-specific mortality in schizophrenia, bipolar disorder, and unipolar depression: a nationwide, prospective, register-based study. Lancet Psychiatry. 2015;2(9):801–8.
157. Sahoo S, Padhy SK, Padhee B, Singla N, Sarkar S. Role of personality in cardiovascular diseases: an issue that needs to be focused too! Indian Heart J. 2018;70:S471–S7. https://doi.org/10.1016/j.ihj.2018.11.003.
158. Kubzansky LD, Sparrow D, Vokonas P, Kawachi I. Is the glass half empty or half full? A prospective study of optimism and coronary heart disease in the normative aging study. Psychosom Med. 2001;63(6):910–6.
159. Ronaldson A, Molloy GJ, Wikman A, Poole L, Kaski J-C, Steptoe A. Optimism and recovery after acute coronary syndrome: a clinical cohort study. Psychosom Med. 2015;77(3):311.
160. Pänkäläinen M, Kerola T, Kampman O, Kauppi M, Hintikka J. Pessimism and risk of death from coronary heart disease among middle-aged and older Finns: an eleven-year follow-up study. BMC Public Health. 2016;16(1):1124.
161. Lee HB, Offidani E, Ziegelstein RC, Bienvenu OJ, Samuels J, Eaton WW, et al. Five-Factor Model Personality Traits as predictors of incident coronary heart disease in the community: a 10.5-year cohort study based on the Baltimore Epidemiologic Catchment Area Follow-Up Study. Psychosomatics. 2014;55(4):352–61.
162. Swan GE, Carmelli D. Curiosity and mortality in aging adults: a 5-year follow-up of the Western Collaborative Group Study. Psychol Aging. 1996;11(3):449.
163. Goldberg LR. The structure of phenotypic personality traits. Am Psychol. 1993;48(1):26.
164. Jokela M, Pulkki-Råback L, Elovainio M, Kivimäki M. Personality traits as risk factors for stroke and coronary heart disease mortality: pooled analysis of three cohort studies. J Behav Med. 2014;37(5):881–9.

Cardiovascular Manifestations of Panic and Anxiety

15

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Contents

Abstract

Anxiety disorders are prevalent in 10–23% of persons with coronary heart disease (CHD) and are therefore quite commonly encountered in typical cardiology practice settings. Because anxiety disorder patients frequently present to emergency departments and outpatient appointments for atypical cardiovascular symptoms, the accurate identification and treatment of anxiety is therefore a major priority for all persons involved in cardiovascular care. The substantial overlap in subjective cardiorespiratory symptoms shared between anxiety and cardiovascular diseases does little to improve our understanding of this complex association. Herein we describe the complex nature of anxiety disorders such as panic disorder in relation to CHD. Particular attention is paid to overviewing the empirical evidence demonstrating aetiological and prognostic links between anxiety disorders with incident

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*,
https://doi.org/10.1007/978-3-030-28008-6_23

and recurrent cardiovascular diseases, respectively. We also discuss potential biobehavioral mechanisms that lead to atherosclerosis and major cardiovascular event recurrence. This chapter also discusses the extant treatment approaches to anxiety, making suggestions for improving clinical interventions in the population with anxiety and comorbid CHD. After summarizing these facets of the anxiety-CHD link, suggestions are made for future research.

Keywords

Anxiety disorders · Panic disorder · Cardiovascular disease · Coronary heart disease · Myocardial infarction · Anxiety · Anxiolytic · Cognitive-behavioral therapy · Treatment · Review

Introduction

Anxiety disorders are among the most prevalent mental health disorders in the community [1]. Anxiety disorder patients commonly present to primary physicians, other medical specialists, and emergency departments with somatic complaints and comorbidities that are cardiovascular in nature [2, 3]. Globally, anxiety disorders pose a major public health burden in terms of economic costs [4–6], quality-adjusted life years, and disability worldwide [7]; and anxiety disorders persist across the lifespan if not adequately treated [8].

Unfortunately, misunderstandings of anxiety disorders, discrete anxiety subtypes, and the distinction from depression have led to a poor understanding of anxiety's role in coronary heart disease (CHD) [9], even though anxiety disorders have been linked with cardiovascular diseases for more than 100 years [10, 11]. Despite the inextricable relevance of anxiety to cardiovascular function, surprisingly, the etiological and prognostic links between anxiety disorders and CHD are only very recently emerging in the past decade. Recent empirical advances point to the likelihood that anxiety disorders increase the risk for developing CHD [12–14]; however, the potential mechanisms underlying the purported anxiety-cardiovascular function association are complex and poorly understood. In terms of prognosis among established CHD populations, anxiety symptoms and anxiety disorders confer a risk for recurrent major adverse coronary events (MACE, e.g., myocardial infarction [MI], left ventricular failure, coronary revascularization procedure, and stroke) [9, 12, 15], underscoring the importance of anxiety disorders to cardiology practice. In this review the epidemiological evidence relating to different anxiety disorders and CHD is described while closely examining anxiety disorders' association with clinical outcomes that are pertinent to cardiovascular function. We discuss potential mechanisms and also describe psychological and pharmacological intervention evidence that could benefit the population with anxiety and CHD.

Diagnosis and Symptom Overlap Between Anxiety and CHD

Anxiety is defined as apprehension, worry, and fear that is experienced across a continuum from a normal and even beneficial response to life's stressors, through to a clinical level, which is excessive, prolonged, persistent, and debilitating in important areas of functioning (e.g., occupational, social, educational, relational). This review concerns primarily the latter level of anxiety which is deemed clinically significant and often represents an anxiety disorder. Among the anxiety disorders, a particular focus here will be placed upon panic disorder given the substantial symptom overlap between panic disorder and CHD. Other disorders are mentioned by name when deemed relevant as are disorder-specific associations that are pertinent to the anxiety-CHD link.

Cases of anxiety can easily remain undetected or misdiagnosed in the population with known, suspected, or subclinical CHD. A survey of 114 medical specialists' understanding of panic disorder found only 51% correctly identified the features of panic disorder and its treatment, suggesting that these aspects were a significant gap in specialists' knowledge [16]. This knowledge gap underscores the necessity to be fully

aware of the characteristics of panic disorder and its hallmark diagnostic feature: recurrent and unexpected panic attacks accompanied by persistent concern or worry about additional panic attacks or their consequences or maladaptive behaviors including avoidance [17]. A clinical caveat however is that many symptoms characteristic of a panic attack overlap with the clinical presentation of CHD [18] as well as arrhythmias [19] and cardiomyopathies [20], making differential diagnosis difficult [9]. For example, chest pain and dyspnea are panic-like symptoms yet also overlap with those typical of a MI and angina pectoris (Table 1). The substantial overlap in subjective cardiorespiratory symptoms shared between anxiety and cardiovascular diseases does little to improve our understandings of such a complex association. Also, persons with panic disorder may be simply experiencing somatic symptoms of undiagnosed coronary conditions such as coronary spasm, microvascular angina, and coronary slow-flow [21, 22], in addition to CHD defined as $\geq$50% stenosis in a main coronary artery. Thus it is plausible that panic disorder partly represents a misdiagnosis at least in some patients [23]. As such some authors caution that many panic disorder cases could be misdiagnosed arrhythmias and have reported that panic-like symptoms resolve with arrhythmia rate or rhythm control [19]. Conversely, others suggest that cardiorespiratory symptoms not fully explained by cardiovascular system diseases should be evaluated for panic disorder [24] or hypochondriasis [25]. However, an anxiety disorder diagnosis does not preclude a true cardiovascular condition nor does the presence of high anxiety indicate the absence of CHD. In fact, concerns about the heart and its functioning are common prior to coronary catheterization [26] and coronary revascularization procedures [27]. Ideally, confirmation of anxiety diagnoses should be undertaken by an experienced mental health professional and appropriate referral made for treatment when anxiety causes distress or interferes with a patient's occupational or social functioning or other important areas of day-to-day functioning.

Prevailing psychiatric diagnostic taxonomies such as the *Diagnostic and Statistical Manual of Mental Disorders* and the *International Classification of Diseases* stipulate that a panic disorder diagnosis cannot be applied when panic symptoms are the direct result of a medical condition such as CHD [17]. Under such taxonomies, anxiety due to a general medical condition would be a

Table 1 List of possible symptoms experienced during a panic attack alongside common symptoms of heart disease

DSM-V panic disorder criteria	Corresponding symptoms of MI, CHD, or cardiomyopathy
Recurrent unexpected panic attacks, that is, an abrupt surge of intense fear or intense discomfort that reaches a peak within minutes, during which time four (or more) of the following symptoms occur:	
Palpitations, pounding heart, or accelerated heart rate	Palpitations, cardiac arrhythmia, (e.g., ventricular tachycardia, atrial fibrillation)
Sweating	Cold sweat
Trembling or shaking	
Sensations of shortness of breath or smothering	Dyspnea, orthopnea, breathlessness on exertion, wheezing
Feelings of choking	Jaw and neck pain, pressure, heaviness, tightness
Chest pain or discomfort	Angina, chest pain
Nausea or abdominal distress	Nausea
Feeling dizzy, unsteady, light-headed, or faint	Dizziness, light-headedness
Chills or heat sensations	Cold sweat
Paresthesias (numbness or tingling sensations)	
Derealization (feelings of unreality) or depersonalization (being detached from oneself).	
Fear of losing control or "going crazy"	
Fear of dying	Fear of dying

Panic disorder/panic attack symptoms adapted from the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition [17]. Adapted with permission from Elsevier [28]

more appropriate diagnosis. This distinction is primarily one of diagnostic nomenclature because treatment for heart-related anxiety is the same, regardless of diagnostic labels, when a diagnosis of CHD is confirmed [28]; and these important aspects of clinical care are discussed further in a later section.

In terms of identifying anxiety, our systematic review and meta-regression of 40 studies showed that clinical expertise is a source of heterogeneity in studies quantifying panic disorder prevalence among CHD populations. Specifically, panic disorder prevalence was lower in nonpsychiatric raters (4.74%; 95% CI 2.28–9.61) by comparison to psychiatric trained raters (9.92%; 95% CI 4.77–19.50) [9]. Moreover, panic disorder prevalence was lower in studies not reporting blinding to CHD status (5.89%; 95% CI 3.21–10.55) than studies in which the rater was blinded to CHD status (9.95%; 95% CI 3.77–23.74) [9]. As anxiety due to a general medical condition was not assessed in the original studies, it remains unclear if clinicians are more likely to attribute shared somatic symptoms to CHD.

A recent audit of 1,359,597 recorded hospitalizations for ST-elevated MI (STEMI) in the USA found that the prevalence of anxiety was lower among the population who underwent coronary revascularization than the STEMI patients who did not [29]. A similar study found that cardiac-specific anxiety was not significantly associated with either STEMI or troponins [30]. Likewise, we found that patients with anxiety disorder received fewer grafts during coronary artery bypass graft surgery [31]. Intriguingly, these studies suggest that anxiety symptoms are generally unrelated to the severity of coronary disease [32] and are perhaps analogous to subjective pain not being solely and reliably associated with the degree of physical injury [33]. One possible explanation for the lack of association between anxiety and severity of coronary disease is that panic disorder is characterized by anxiety sensitivity, generally defined as the fear of autonomic arousal-related sensations and symptoms [34]. Consequently, cardiorespiratory symptoms tend to be amplified by cognitive and behavioral processes including increased attentional focus, hypervigilance, catastrophizing, and avoidance which result in lowering the threshold for perceiving somatic sensations [35]. Indeed, the association between anxiety and subjective self-rated symptoms of CHD such as chest pain and dyspnea appears to be quite strong [36]. Unsurprisingly, patients with anxiety are more likely to perceive physical symptoms as serious and are more likely to attend emergency departments during a non-MI event such as a panic attack or non-cardiac chest pain (false-positive) [37]. However, recent evidence also suggests that anxious patients are more likely to attend emergency departments during a MI (true-positive) [38].

Prevalence of Anxiety in CHD

In populations with verified CHD, the prevalence of anxiety disorders is between 10 and 23% [9]. This estimate is based on a systematic review of 40 cohorts comprising of 7973 participants who underwent structured psychiatric interview to determine anxiety disorder status [9]. Among the most common anxiety disorders in CHD is panic disorder, the main topic of this chapter. Other common anxiety disorders include agoraphobia which frequently co-occurs with panic disorder, as well as generalized anxiety disorder (GAD), social phobia, specific phobia, and related disorders such as post-traumatic stress disorder (PTSD) and obsessive compulsive disorder [9, 39]. The prevalence estimates are depicted in Table 2. Past estimates of anxiety disorder prevalence from cross-sectional surveys utilizing self-reported CHD cannot be considered reliable [40] given the proclivity for anxiety disorder patients to misinterpret normal bodily sensations, catastrophize, and overreport their likelihood of having a medical condition [41].

From the prevalence estimates in Table 2, panic disorder, GAD, agoraphobia, and PTSD prevalence rates and their 95% confidence intervals (CI) exceed the 12-month prevalence rates in the general population from the US National Comorbidity Survey Replication [42]. The higher prevalence highlights the burden of anxiety disorders in CHD populations compared to the general

Table 2 Prevalence of common anxiety disorders in the CHD and general population

Disorder	Number of CHD studies in meta-analysis (pooled sample size)	Prevalence in CHD [10]	95% CI	Prevalence in general population [42]
Generalized anxiety disorder[a]	22 (5567)	7.97	5.42–11.57	3.1
Panic disorder[a]	29 (4713)	6.81	4.09–11.14	2.7
Agoraphobia[a]	17 (2885)	3.62	1.78–7.21	0.8
Social phobia	10 (1847)	4.62	2.31–9.02	6.8
Specific Phobia	11 (1795)	4.31	2.23–8.15	8.7
Obsessive compulsive disorder	6 (1558)	1.80	1.23–2.65	1.0
Post-traumatic stress disorder [39][a]	24 (2383)	12	9–16	3.5

Adapted with permission from Elsevier [9]
[a]Higher in CHD populations and related to CVD in etiological and prognostic studies; population estimates taken from the US National Comorbidity Survey Replication

population. Moreover, GAD, panic disorder, and PTSD have an etiological association with incident CHD and a prognostic association with recurrent MACE [9, 14, 39, 43], described in more depth in a later section. These etiological and prognostic links are especially noteworthy because most research has emphasized the role of depression in CHD, yet we found that 50% of CHD patients with a depression disorder also have an anxiety disorder [9]. Given that anxiety disorders are highly comorbid with depression disorders [44, 45], and that their comorbidity substantially hinders treatment outcomes [46, 47], the presence or suspicion of one disorder subtype should prompt a close examination of the other disorder subtype.

Etiological Links Between Anxiety and CHD

Etiological links between anxiety and incident CHD have been suspected for more than 100 years, and yet this association has only very recently been comprehensively investigated. Several large and adequately powered longitudinal studies and case-control studies have demonstrated that anxiety is associated with incident CHD, MI, and sudden cardiac death. A large case-control study [48] of 57,615 UK adults diagnosed with panic attacks/disorder and a random sample of 347,039 matched for sex/age reported a higher incidence of MI following new onset panic in people under 50 years of age, but not in older age groups. The incidence of MI in panic disorder patients under 50 years was increased by 38% (hazard ratio [HR] = 1.38; 95% CI 1.06–1.79) compared to no increased hazard of MI for those over 50 years (HR 0.92; 95% CI 0.82–1.03). Other studies have reported similar findings for the incident MI risk attributable to panic disorder in large and diverse samples including 355,999 persons from the Veteran's Affairs database [49], 75,861 persons from a national Danish research registry [50], 49,321 Swedish men examined for military service [51], a sample of 33,999 US male health professionals [52], and 33,696 residents from a national Taiwanese database [53]. Retrospective studies also estimate that elevated anxiety in the immediate 24-h period prior to a MI is associated with a two- to ninefold increased risk for MI, by comparison to earlier exposure to episodes of anxiety [54]. This finding might suggest that episodes of acute and excessive anxiety could aggravate underlying coronary plaques that rupture leading to coronary occlusion; however, the retrospective nature of such studies are prone to recall biases and should be interpreted with caution.

A recent systematic review of 12 studies comprising 1,131,612 persons and 58,111 incident CHD cases confirmed that panic disorder was associated with a 47% increase in incident CHD risk (Fig. 1). The association between panic and

	Events n	Analysis n	$_{adj}$HR (95% CI)	Weight %
Albert 2005	930	72,359	3.43 (1.27 – 9.26)	2.3
Bowen 2000	153	2,657	1.50 (1.10 – 2.05)	7.6
Bringager 2008	11	167	0.92 (0.29 – 2.92)	1.8
Chen 2009	1,249	33,696	1.62 (1.41 – 1.86)	9.5
Gomez- Camerino 2005	32,995	78,580	1.87 (1.83 – 1.91)	10.1
Jakobsen 2008	1,049	75,861	1.56 (1.35 – 1.80)	9.4
Jansky 2010	1,894	49,321	2.17 (1.28 – 3.68)	5.1
Kawachi 1994	168	33,999	2.66 (0.40 – 17.69)	0.7
Nabi 2010 (females)	209	14,298	1.47 (1.04 – 2.08)	7.1
Nabi 2010 (males)	NS	9,830	1.15 (0.92 – 1.44)	8.6
Rohacek 2010	7	191	0.31 (0.02 – 4.80)	0.4
Scherrer 2010 (PD + MD)	12,304	355,999	1.22 (1.07 – 1.39)	8.3
Scherrer 2010 (PD – MD)	NS	NS	1.43 (1.11 – 1.84)	9.6
Walters 2008 (age <50 yrs)	1,097	275,966	1.44 (1.25 – 1.65)	9.9
Walters 2008 (age >50 yrs)	6,045	128,677	1.11 (1.03 – 1.20)	9.5
Pooled data and effect	**58,111**	**1,131,612**	**1.47 (1.24 – 1.74)**	**100**
P for overall effect			**P<.00001**	**I^2 = 94**

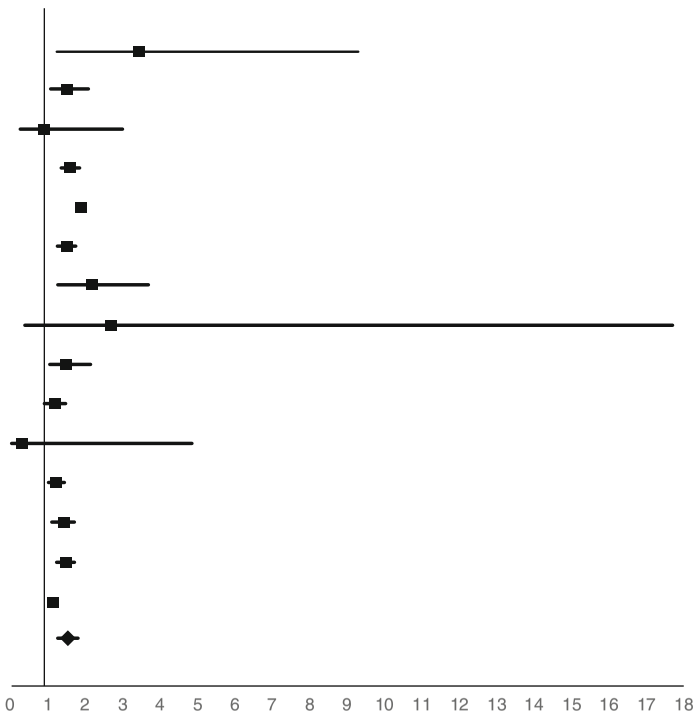

Fig. 1 Forest plot of adjusted and weighted hazard ratios for incident coronary heart disease (CHD) (primary endpoint). Adjusted hazard ratios (aHR) with 95% confidence intervals (CI) that exceed 1 (vertical line) indicate an increased CHD risk for persons with panic disorder (PD). GRADE assessment = low. GRADE, Grading of Recommendations Assessment, Development and Evaluation; *NS*, not specified; *MD*, major depression. Adapted with permission from Elsevier [14]

CHD persisted after excluding angina which is more subjective in nature. High to moderate quality evidence suggested an association with incident MACE and incident MI, and the risk remained significant after excluding depression and after depression adjustment [14]. Concurrent investigation of depression and anxiety disorders appears important, as disorder-specific and comorbidity specific patterns have been noted for etiological CHD risk [55]. Specifically, panic disorder without any depression comorbidity was significantly associated with cardiovascular disease, cerebrovascular disease, and peripheral vascular disease [56]. Stratifying anxiety disorders according to the presence of depression comorbidity suggests that anxiety confers a risk incident CHD that is on par with depression [57–59]. When interpreting etiological links, note that several authors have cautioned that reverse-causality cannot be ruled out due to most cohort studies not performing coronary angiography at baseline [14]. This opens up the possibility that subclinical CHD could be misdiagnosed as panic attacks, as opposed to true risk of incident MI [48] which is plausible in studies inclusive of participants in midlife. In the 37-year longitudinal follow-up study by Janszky et al. [51] where the risk ratio for incident CHD and MI was 2.17 (95% CI: 1.28–3.67) and 2.51 (95% CI: 1.38–4.55), respectively, all 49,321 participants were age 18–20 years at baseline, and therefore the presence of CHD at inception would be highly unlikely.

Prognostic Links Between Anxiety and CHD

Anxiety symptoms are associated with poorer outcome or MACE recurrence in populations with prevalent CHD [12] or MI [15]. Analyzing anxiety disorder subtypes has uncovered differential associations with CHD that primarily implicate GAD with adverse prognostic outcomes. This finding may, in part, be due to the limited prognostic research on verified anxiety disorders including panic disorder or PTSD. For example, our systematic review only retrieved three panic disorder studies (RR 0.87; (95% CI 0.37–2.02)) [9], one of which provided unpublished data pertaining to panic disorder [60]. Likewise, the systematic review by Edmondson et al. [39] also retrieved only three PTSD studies in acute coronary syndrome populations when finding a twofold increase risk for MACE (RR = 2.00; 95% CI, 1.69–2.37). Most other research has relied on medical records or anxiolytic medication to denote anxiety disorder status. Otherwise there remains some uncertainty as to whether anxiety disorders contribute to adverse CHD prognosis. Consequently both the American Heart Association [61] and German Heart Association [62] recommended that further research must strive to identify the independent contribution of anxiety disorders and its subtypes to cardiovascular prognosis.

Several longitudinal cohorts have demonstrated the prognostic importance of GAD to MACE recurrence. Among a sample of 804 acute coronary syndrome outpatients, the presence of GAD increased MACE risk approximately twofold over 2 years follow-up [60]. This association was subsequently corroborated in a large CHD outpatient sample of more than 900 patients over a mean of 5.6-year follow-up. The study showed that GAD was associated with a 74% increase in MACE risk [63]. GAD was associated with adverse cardiovascular and cerebrovascular outcomes at follow-up after coronary artery bypass graft surgery (HR = 2.79; 95% CI 1.00–7.80) [57, 64]. A pooled meta-analysis of GAD effect sizes indicated that a GAD diagnosis, determined during outpatient assessment, was associated with MACE (5 studies, 883 MACE events; RR = 1.25, 95% CI 1.01–1.47, $p = 0.04$, Fig. 2) [9]. Moreover, anxiety disorders determined during ACS hospitalization were not associated with poorer outcomes, reiterating the importance of accurate diagnosis and suggesting that inhospital anxiety disorder assessments post-ACS are unreliable.

Prognostic studies pertaining to anxiety symptoms have also supported a risk for recurrent MACE and mortality [65]. A systematic review of 12 studies using self-reported anxiety questionnaires post-MI found that the odds for MACE

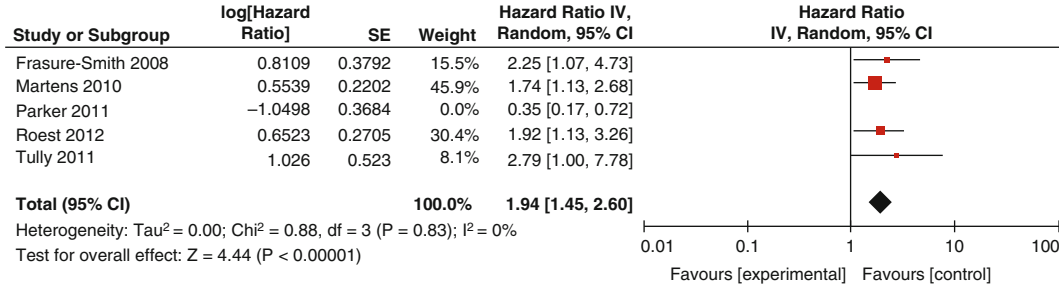

Fig. 2 Major adverse cardiac event risk in generalized anxiety disorder outpatient studies adjusted for covariates (random-effects). Forest plot showing the hazard ratio for major adverse cardiac events in outpatients with generalized anxiety disorder versus persons without generalized anxiety disorder. Hazard ratio values with 95% confidence intervals that exceed 1 (vertical line) indicate higher risk for major adverse cardiac events. Adapted with permission from Elsevier [9]

were increased 1.36 fold (95% CI 1.18–1.56) and the odds for cardiac-related mortality were also increased 1.23 fold (95% CI 1.03–1.47). Not all studies however support a positive association between anxiety and adverse MACE outcomes. Some studies have found a reduced risk for MACE [66], thus purporting a protective effect for anxiety. However, such findings appear to be a statistical artifact of multicollinearity between anxiety and depression, rather than anxiety truly being beneficial to cardiovascular prognosis.

Putative Biobehavioral Mechanisms Linking Anxiety and CHD

The biobehavioral mechanisms linking panic and CHD are complex, interacting, and poorly understood [67–71]. The biobehavioral risk factors moderating the relationship between anxiety and microvascular disorders such as coronary slow-flow [22], microvascular angina [72], and arterial stiffness [73] are poorly documented. Panic disorder may present with other pre-existing cardiometabolic risk factors including hypertension, hyperlipidemia, obesity, kidney disease, and diabetes [74–77], and therefore disentangling the association between anxiety and CHD would likely involve pathways shared between CHD and other chronic diseases.

With regard to behavioral mechanisms that could promote atherosclerosis, cross-sectional studies among anxiety disorder patients show a preponderance of behavioral risk factors including tobacco smoking [78]. A strong comorbid association between anxiety disorders with alcohol and substance abuse is consistently documented in national surveys [79–81]. The strong association between anxiety disorders and alcohol abuse implicates shared etiology or common risk factors [82] or alternatively impaired coping strategies [83]. Surprisingly, anxiety about one's health may not necessarily lead to a proactive approach to modifiable lifestyle factors such as exercise and diet as psychometric indices of health anxiety are associated with elevated risk for CHD [84].

Another behavioral risk factor directly relevant to CHD is cardiorespiratory fitness. Several longitudinal studies have demonstrated that low cardiorespiratory fitness is predictive of the onset of depression disorders in later life [85, 86]. A similar pathway could be speculated for anxiety disorders given that panic disorder patients with high levels of somatic anxiety were nearly threefold more likely to report low levels of physical activity measured by the Physical Activity Questionnaire compared to those with low somatic anxiety (OR 2.81; 95% CI 1.00–7.90) [87]. The example of cardiorespiratory fitness and physical activity however is more complicated in anxiety disorders compared to depression. What is becoming increasingly recognized is that anxiety disorder patients, especially those with panic, display exercise-avoidance behaviors [88, 89]. The overt avoidance of exercise is linked to high anxiety

sensitivity, or fear of somatic sensations, such as those produced by aerobic exercise. Support for this notion comes from cardiopulmonary exercise testing where panic disorder patients tend to be less willing to continue despite similar ventilation/VO_2 [90]. Patients exhibiting higher exercise avoidance also perform worse on cardiopulmonary exercise testing, including by comparison to patients with the respiratory subtype of panic disorder [88]. Exercise avoidance and fear of somatic sensations have clear consequences for CHD patients undergoing cardiac rehabilitation, and anxiety may pose a special barrier to engaging in physical activity post-cardiac event such as in a structured cardiac rehabilitation program [91]. Moreover, persistent anxiety and somatization are stronger predictors of reduced exercise capacity after cardiac rehabilitation [92], reiterating the importance of accurate diagnosis and self-report anxiety measures in CHD populations.

The CO_2 challenge test provides a common experimental paradigm to induce and quantify physiological symptoms in panic disorder. This task involves inhalation of a mixture of oxygen with 35% CO_2. The CO_2 test may stimulate breathlessness, dizziness, and minor anxiety in most participants and panic attacks in those with or at risk for panic disorder [93]. Self-reported ratings of panic symptomatology and subjective anxiety are higher among persons with panic disorder than control groups when exposed to the CO_2 challenge [94]. Also, autonomic correlates of panic disorder during treadmill testing have been documented which initially suggested very limited myocardial ischemia [95]. Indeed, much of the early empirical work on cardiorespiratory symptoms in panic disorder occurred in the population who were free from serious cardiovascular diseases [35, 96, 97].

In persons with CHD ascertained by positive nuclear exercise stress test, a 35% CO_2 challenge induced myocardial ischemia in 81% of CHD patients with comorbid panic disorder [98]. In a follow-up study [99], the authors tested patients with low risk CHD patients who underwent the 35% CO_2 panic challenge test and were injected with Tc-99m-tetrofosmin (Myoview) for nuclear imaging, upon inhalation. Single-photon emission computed tomography imaging was used to assess per-panic challenge reversible myocardial ischemia, and heart rate, blood pressure, and a 12-lead ECG were continuously measured during the procedure. Only 10% of patients in each group displayed myocardial ischemia per-panic challenge [99]. Because of the disparity in these findings [98, 99], it remains largely unclear whether panic attacks lead to reversible myocardial ischemia. Importantly, the myocardial ischemic effects of panic challenge in high risk CHD patients with panic disorder are undocumented.

Other work concerning cardiovascular response to panic has implicated the sympathetic nervous system as the mediating link between the heart and the brain [100–102]. The heightened sympathetic discharge during panic attacks has been linked with change in the QRS complex [103], especially the QT-interval [104–106] on ECG. A related body of work demonstrated a significant association between diminished heart rate variability (HRV) and anxiety disorders [107]. A meta-analysis of 36 articles, including 2086 patients with an anxiety disorder and 2294 controls, by Chalmers et al. [108] suggested anxiety disorders were associated with significantly lower time-domain HRV, as well as low- and high-frequency HRV [108]. Moderator analysis suggested no difference between the anxiety disorder subtypes, and the panic disorder effect sizes represented as Hedges' g were time-domain HRV −0.41 (95% CI −0.68 to −0.15), high-frequency HRV −0.22 (95% CI −0.42 to −0.02), and low-frequency HRV −0.11 (95% CI −0.47 to 0.25).

Other plausible mechanisms through which panic and anxiety promote atherosclerosis and recurrent MACE include upregulated inflammatory response which has been noted across the anxiety disorders including populations with comorbid CHD [75, 109, 110]. The most evidence for inflammatory markers in anxiety relates to C-reactive protein (CRP), an acute phase protein [69–71, 75, 111–114] which is clinically significant and increases the risk for incident CHD [69]. A large population study of 3719 Swiss persons aged between 35 and 75 years residing in Lausanne found that both current and lifetime

history of anxiety disorder were associated with higher CRP [114]. Other documented inflammatory markers across anxious populations with anxiety disorders include the interleukin group of cytokines [71, 111, 115], tumor necrosis factor-α [116], and adrenomedullin [117]. The increased trafficking of pro-inflammatory immune may lead to enhanced platelet aggregability and coronary plaque instability [118, 119].

Treatment of Anxiety in CHD Populations

Treatment options for panic disorder in persons with true manifestation of CHD have been largely neglected in the literature to the detriment of our understanding of anxiety disorders in CHD [9, 120]. Most treatment efficacy evidence relating to anxiety in fact comes from depression trials where anxiety is merely a secondary endpoint [121, 122] or from interventions utilizing only self-reported anxiety [123, 124]. Our 2014 systematic review [9] showed that no RCT had specifically targeted anxiety disorders in the CHD population and reports from other non-RCT interventions for anxiety disorders are uncommon [125]. Consequently anxiety disorder treatment remains a significant gap in the literature and clinical practice [126], and currently ongoing clinical trials in this field may provide clarity on anxiety treatment efficacy [127, 128].

The complex nature of panic disorder comorbid with CHD necessitates several adaptions to standard cognitive-behavioral therapy (CBT). Previously we highlighted that treating panic disorder comorbid with CHD or cardiomyopathy is challenging due to (a) diagnostic overlap between the symptoms experienced in anxiety and heart disease including those depicted in Table 1, (b) the high risk associated with ignoring chest pain symptoms and delaying seeking medical attention for a potential MI, (c) that CBT therapy based on catastrophic misinterpretation of bodily symptoms requires adaption to incorporate the element of cardiovascular risk, and (d) that certain interoceptive symptom induction experiments (e.g., hyperventilation) may be harmful, inducing myocardial ischemia, and are therefore fraught with potential legal liability because of the uncertainty in this area [28]. The rationale for revising panic symptom induction exercises was based on possible increase in stroke volume [129], acute coronary vasoconstriction and myocardial stunning [130], electrical changes increasing the risk for arrhythmias [73, 131], and potential head injury as a result of syncope [132]. Because of the nature of these issues, we recently developed the Panic Attack Treatment in Comorbid Heart Diseases (PATCHD) protocol [28], a panic disorder CBT model especially adapted for CHD patients and based on similar work in cardiopulmonary patients [133]. The PACTHD model is centered on enhancing coping skills, performing safe symptom induction interoceptive exposures and supervised exercise, and countering avoidance to reduce panic attack frequency.

Our real-world experiences with the PATCHD method demonstrated a significant reduction in cardiovascular hospital admissions and length of stay, panic attacks, general anxiety, as well as depression [28, 134]. A comprehensive outline of this treatment is provided elsewhere [28]. Another approach to anxiety treatment that could be beneficial is transdiagnostic CBT [127] and meta-cognitive therapy [128] that targets cognitive and behavioral processes common to anxiety and depression. As aforementioned, the findings from these ongoing clinical trials will provide valuable insight to anxiety disorder treatments in CHD [127, 128].

The most recent reviews of the literature have identified generally low effect sizes for treatment of anxiety and depression in CHD populations [123, 135] especially by comparison to other chronic disease populations such as diabetes [136]. Specifically, distinctly smaller depression treatment effect sizes are evident in CHD populations by comparison to diabetes (standardized mean difference [SMD] 0.30 vs. 0.60) [136–138]. Prior interventions including landmark RCTs in cardiology (e.g., ENRICHD, SADHART, CREATE) demonstrated the difficulty of treating depression and anxiety in CHD populations and have produced largely disappointing results in primary outcomes [139–141],

though secondary analyses suggest specific subgroups may benefit from psychological interventions [138, 142–144]. However, most prior RCTs were based on unitary interventions, testing either psychotropic drugs in isolation or psychotherapy in isolation. By contrast, multifaceted collaborative care interventions delivered by multidisciplinary healthcare providers and incorporating CBT, psychotropic drugs, structured reviews, and stepped-care have had a small but significant impact upon MACE and other important chronic disease outcomes [145, 146]. The collective findings point to the inherent challenges when treating anxiety and depression in CHD populations and raise the possibility that existing intervention approaches could be greatly improved [147, 148].

In terms of psychotropic drugs, the EUROASPIRE IV survey of 7589 patients from 24 European countries examined at a median of 1.4 years after hospitalization due to coronary heart disease events showed that anxiolytic medications were prescribed to only 2.4% of patients at hospital discharge and 2.7% of patients at follow-up [149]. This estimate is in line with other studies utilizing systematic depression and anxiety screening in cardiology where real-world evidence shows that psychotropic drugs are heavily favored over CBT or other psychotherapies. It is unclear if this relates to patient preference, clinician preference, or a lack of resources for initiating CBT [122, 150, 151]. Curiously, prescription of benzodiazepine after MI was found to be associated with a reduced risk for recurrent MI [152]. However, a "J curve" association was evident suggesting that small to medium doses of benzodiazepine is preferable to larger doses. Note that anxiolytic medications with tranquillizing effects such as benzodiazepines should be prescribed judiciously and is typically contraindicated in CBT [153]. Notwithstanding physical and psychological dependence issues, the rationale for this contraindication is that anxiolytic medication serves as a safety-behavior or maladaptive coping strategy, thereby hindering treatment, prolonging anxiety, and negatively reinforcing the need for medication during a panic attack or prior to anxiety inducing situations. Thus CBT is typically the preferred strategy for anxiety with more robust and durable term treatment gains in the longer term without relapse [154]. For these reasons, benzodiazepines are typically restricted in utility for CHD populations, and serotonergic drugs are the first-line pharmacological treatment of choice in CHD [155].

The efficacy of serotonergic drugs, including selective serotonin reuptake inhibitors (SSRI) and serotonin norepinephrine reuptake inhibitors (SNRI), to treat depression symptoms is established from depression RCT interventions among CHD populations SADHART and CREATE [140, 141]. The atypical antidepressant mirtazapine did not have a sustained impact on depression symptoms in the MIND-IT trial [156]. A systematic and pooled meta-analysis of pharmacological RCTs investigating SSRI versus placebo indicates that there is no risk reduction in mortality from antidepressant drugs [137, 157]. However, divergent findings were reported for hospital readmissions in systematic reviews. A Cochrane review found a reduced odds for hospital readmission (pooled OR 0.58, 95% CI 0.39–0.85) [137], whereas another review did not support reduced risk for hospital readmission when applying stringent criteria for properly randomized studies (risk ratio = 0.74, 95% CI 0.44–1.23) [157]. Although the potential benefits of serotonergic drugs are unclear for hard endpoints, possible pleiotropic effects of serotonergic drugs include reduced platelet aggregability and enhanced endothelial function [158, 159]. Potential side-effects include increased bleeding risk [160], while the SSRI escitalopram can prolong the QTc interval and should not be prescribed at doses higher than 40 mg/day.

In addition to standard first-line CBT and serotonergic drug interventions, some scholars have proposed that supervised aerobic exercise as one treatment modality for panic in CHD, which provides experiential and interoceptive exposure to heightened somatic sensations such as breathlessness, increased heart rate, and sweating [161]. The aerobic exercise component of structured cardiac rehabilitation provides exposure to somatic symptoms in safe and controlled environment which

may benefit patient's anxiety levels. For example, exposure to 12 sessions of aerobic exercise (25 min treadmill) was found to increase VO_2 max. in panic disorder patients versus a panic control group not exposed to the exercise intervention [54]. It is also postulated that regular physical activity may exert positive effects on anxiety disorder symptom via inflammation and oxidative and nitrogen stress pathways [162]. However, because persons with anxiety and depression are less likely to participate in cardiac rehabilitation [163], some of the benefits of exercise upon anxiety possibly represent a self-selected group and may not apply to exercise-avoidant persons. Accurate identification of anxiety among cardiac rehabilitation patients is paramount [164] and highly anxious, and avoidant patients would likely benefit from a concerted multidisciplinary approach to treatment, encompassing cardiology, cardiac nursing, exercise physiology, as well as clinical psychology and psychiatry [125].

Conclusions and Directions for the Future

This chapter has demonstrated that anxiety disorders are highly prevalent in the population with CHD and exceed prevalence estimates from the general population. There is substantial overlap between anxiety and CHD in terms of their characteristic cardiovascular symptoms. Patients with anxiety frequently present to primary physicians, other medical specialists, and emergency departments with somatic complaints. Panic disorder is strongly aetiologically linked to incident CHD, whereas prognostic associations tend to implicate GAD and self-reported anxiety because of the limited panic disorder research in verified CHD populations. Although the mechanisms linking anxiety and CHD are complex, interacting, and poorly understood, likely behavioral correlates include tobacco smoking, alcohol use, and exercise avoidance. Direct pathophysiological pathways include diminished HRV and an upregulated inflammatory response, especially the acute phase protein CRP. Unfortunately, no RCT has even attempted to treat anxiety disorders in CHD populations until very recently [127, 128, 165]. Consequently, the efficacy of psychological and pharmacological interventions is unclear [166] though we have proposed safe CBT alternatives for persons with panic attacks and CHD or cardiomyopathy [28]. Clearly, there is a large degree of scope to improve our understandings of the cardiovascular manifestations of anxiety as they relate to CHD. In future research, particular attention should focus on ruling out reverse-causality in aetiological studies, clarifying the extent of myocardial ischemia during panic attacks and stress testing in populations with CHD, illustrating panic disorder-specific prognostic links post-MI, and evaluating the efficacy of psychological and pharmacological interventions for persons with anxiety disorders where anxiety response is the primary outcome. The disappointing findings from past depression RCTs raise the possibility that the focus of our interventions are too narrow in scope and should be broadened to include anxiety and its discrete disorders. Nevertheless, the burden of anxiety disorders, irrespective of the association with cardiovascular prognosis, underscores the importance of early identification of anxiety disorders and their treatment in CHD. In fact, the level of clinical priority received by depression over the past 30 years should be extended to research and clinical intervention efforts in relation to anxiety [67].

References

1. Wittchen HU, Jacobi F, Rehm J, Gustavsson A, Svensson M, Jonsson B, et al. The size and burden of mental disorders and other disorders of the brain in Europe 2010. Eur Neuropsychopharmacol. 2011;21(9):655–79.
2. Roy-Byrne PP, Davidson KW, Kessler RC, Asmundson GJ, Goodwin RD, Kubzansky L, et al. Anxiety disorders and comorbid medical illness. Gen Hosp Psychiatry. 2008;30(3):208–25.
3. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. JAMA. 1999;282(18):1737–44.
4. Coley KC, Saul MI, Seybert AL. Economic burden of not recognizing panic disorder in the emergency department. J Emerg Med. 2009;36(1):3–7.

5. Lamb CE, Ratner PH, Johnson CE, Ambegaonkar AJ, Joshi AV, Day D, et al. Economic impact of workplace productivity losses due to allergic rhinitis compared with select medical conditions in the United States from an employer perspective. Curr Med Res Opin. 2006;22(6):1203–10.
6. Baumeister H, Haschke A, Munzinger M, Hutter N, Tully PJ. Inpatient and outpatient costs in patients with coronary artery disease and mental disorders: a systematic review. Biopsychosoc Med. 2015;9:11.
7. Baxter AJ, Vos T, Scott KM, Norman RE, Flaxman AD, Blore J, et al. The regional distribution of anxiety disorders: implications for the Global Burden of Disease Study, 2010. Int J Methods Psychiatr Res. 2014;23(4):422–38.
8. Kessler RC, Petukhova M, Sampson NA, Zaslavsky AM, Wittchen HU. Twelve-month and lifetime prevalence and lifetime morbid risk of anxiety and mood disorders in the United States. Int J Methods Psychiatr Res. 2012;21(3):169–84.
9. Tully PJ, Cosh SM, Baumeister H. The anxious heart in whose mind? A systematic review and meta-regression of factors associated with anxiety disorder diagnosis, treatment and morbidity risk in coronary heart disease. J Psychosom Res. 2014;77(6):439–48.
10. Miles HHW, Cobb S. Neurocirculatory asthenia, anxiety and neurosis. N Engl J Med. 1951;245 (19):711–9.
11. Walsh JJ. Psychotherapy: including the history of the use of mental influence, directly and indirectly in healing and the principles for the application of energies derived from the mind to the treatment of disease. New York: D. Appleton & Company; 1912. p. 819.
12. Suls J, Bunde J. Anger, anxiety, and depression as risk factors for cardiovascular disease: the problems and implications of overlapping affective dispositions. Psychol Bull. 2005;131(2):260–300.
13. Roest AM, Martens EJ, de Jonge P, Denollet J. Anxiety and risk of incident coronary heart disease: a meta-analysis. J Am Coll Cardiol. 2010;56(1):38–46.
14. Tully PJ, Turnbull DA, Beltrame JF, Horowitz JD, Cosh S, Baumeister H, et al. Panic disorder and incident coronary heart disease: a systematic review and meta-regression in 1,131,612 persons and 58,111 cardiac events. Psychol Med. 2015;45(14):2909–20.
15. Roest AM, Martens EJ, Denollet J, de Jonge P. Prognostic association of anxiety post myocardial infarction with mortality and new cardiac events: a meta-analysis. Psychosom Med. 2010;72(6):563–9.
16. Teng EJ, Chaison AD, Bailey SD, Hamilton JD, Dunn NJ. When anxiety symptoms masquerade as medical symptoms: what medical specialists know about panic disorder and available psychological treatments. J Clin Psychol Med Settings. 2008;15 (4):314–21.
17. American Psychiatric Association. The Diagnostic and statistical manual of mental disorders DSM-V. Washington, DC: American Psychiatric Association; 2013.
18. Carmin CN, Ownby RL, Wiegartz PS, Kondos GT. Women and non-cardiac chest pain: gender differences in symptom presentation. Arch Womens Ment Health. 2008;11(4):287–93.
19. Frommeyer G, Eckardt L, Breithardt G. Panic attacks and supraventricular tachycardias: the chicken or the egg? Neth Hear J. 2013;21(2):74–7.
20. Muller-Tasch T, Frankenstein L, Holzapfel N, Schellberg D, Lowe B, Nelles M, et al. Panic disorder in patients with chronic heart failure. J Psychosom Res. 2008;64(3):299–303.
21. Karatas MB, Sahan E, Ozcan KS, Canga Y, Gungor B, Onuk T, et al. Anxiety, depression, and general psychological distress in patients with coronary slow flow. Arq Bras Cardiol. 2015;105(4):362–70.
22. Vural M, Satiroglu O, Akbas B, Goksel I, Karabay O. Coronary artery disease in association with depression or anxiety among patients undergoing angiography to investigate chest pain. Tex Heart Inst J. 2009;36(1):17–23.
23. Beitman BD, Basha I, Flaker G, DeRosear L, Mukerji V, Trombka L, et al. Atypical or nonanginal chest pain. Panic disorder or coronary artery disease? Arch Intern Med. 1987;147(9):1548–52.
24. Esan OB, Baiyewu O. Panic disorder prevalence among patients referred for an electrocardiogram in a Nigerian teaching hospital. Psychosomatics. 2013;54(5):472–8.
25. Christoph M, Christoph A, Dannemann S, Poitz D, Pfluecke C, Strasser RH, et al. Mental symptoms in patients with cardiac symptoms and normal coronary arteries. Open Heart. 2014;1(1):e000093.
26. Delewi R, Vlastra W, Rohling WJ, Wagenaar TC, Zwemstra M, Meesterman MG, et al. Anxiety levels of patients undergoing coronary procedures in the catheterization laboratory. Int J Cardiol. 2017;228:926–30.
27. Hernandez-Palazon J, Fuentes-Garcia D, Falcon-Arana L, Roca-Calvo MJ, Burguillos-Lopez S, Domenech-Asensi P, et al. Assessment of preoperative anxiety in cardiac surgery patients lacking a history of anxiety: contributing factors and postoperative morbidity. J Cardiothorac Vasc Anesth. 2018;32(1): 236–44.
28. Tully PJ, Sardinha A, Nardi AE. A new CBT model of panic attack treatment in comorbid heart diseases (PATCHD): how to calm an anxious heart and mind. Cogn Behav Pract. 2017;24(3):329–41.
29. Carleton RN, Duranceau S, Freeston MH, Boelen PA, McCabe RE, Antony MM. "But it might be a heart attack": intolerance of uncertainty and panic disorder symptoms. J Anxiety Disord. 2014;28(5):463–70.
30. van Beek MH, Oude Voshaar RC, van Deelen FM, van Balkom AJ, Pop G, Speckens AE. Inverse correlation between cardiac injury and cardiac anxiety: a potential role for communication. J Cardiovasc Nurs. 2014;29(5):448–53.
31. Tully PJ, Newland RF, Baker RA. Cardiovascular risk profile before coronary artery bypass graft surgery in

relation to depression and anxiety disorders: an age and sex propensity matched study. Aust Crit Care. 2015;28(1):24–30.
32. Ali SS, Khan SA, Khosa F, Aneni EC, Jones A, St Leger AS, et al. Noninvasive assessment of subclinical atherosclerosis in persons with symptoms of depression. Atherosclerosis. 2017;264:92–9.
33. Clay FJ, Watson WL, Newstead SV, McClure RJ. A systematic review of early prognostic factors for persisting pain following acute orthopedic trauma. Pain Res Manag. 2012;17(1):35–44.
34. Vladan S, David B. Cognitive specificity of anxiety disorders: a review of selected key constructs. Depress Anxiety. 2006;23(2):51–61.
35. Salkovskis PM, Jones DR, Clark DM. Respiratory control in the treatment of panic attacks: replication and extension with concurrent measurement of behaviour and pCO_2. Br J Psychiatry. 1986;148:526–32.
36. Katon W, Lin EH, Kroenke K. The association of depression and anxiety with medical symptom burden in patients with chronic medical illness. Gen Hosp Psychiatry. 2007;29(2):147–55.
37. Fleet RP, Dupuis G, Marchand A, Burelle D, Arsenault A, Beitman BD. Panic disorder in emergency department chest pain patients: prevalence, comorbidity, suicidal ideation, and physician recognition. Am J Med. 1996;101(4):371–80.
38. Fang XY, Spieler D, Albarqouni L, Ronel J, Ladwig KH. Impact of generalized anxiety disorder (GAD) on prehospital delay of acute myocardial infarction patients. Findings from the multicenter MEDEA study. Clin Res Cardiol. 2018;107(6):471–8.
39. Edmondson D, Richardson S, Falzon L, Davidson KW, Mills MA, Neria Y. Posttraumatic stress disorder prevalence and risk of recurrence in acute coronary syndrome patients: a meta-analytic review. PLoS One. 2012;7(6):e38915.
40. Ormel J, Von Korff M, Burger H, Scott K, Demyttenaere K, Huang YQ, et al. Mental disorders among persons with heart disease – results from World Mental Health surveys. Gen Hosp Psychiatry. 2007;29(4):325–34.
41. Salkovskis PM, Clark DM, Gelder MG. Cognition-behaviour links in the persistence of panic. Behav Res Ther. 1996;34(5–6):453–8.
42. Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005;62(6):617–27.
43. Edmondson D, Kronish IM, Shaffer JA, Falzon L, Burg MM. Posttraumatic stress disorder and risk for coronary heart disease: a meta-analytic review. Am Heart J. 2013;166(5):806–14.
44. Tiller JW. Depression and anxiety. MJA Open. 2012;1 (Suppl 4):28–31.
45. Penninx BW. Depression and anxiety: their insidious dance. Lancet Psychiatry. 2015;2(6):479–80.
46. Westermair AL, Schaich A, Willenborg B, Willenborg C, Nitsche S, Schunkert H, et al. Utilization of mental health care, treatment patterns, and course of psychosocial functioning in northern German coronary artery disease patients with depressive and/or anxiety disorders. Front Psychol. 2018;9:75.
47. Celano CM, Mastromauro CA, Lenihan EC, Januzzi JL, Rollman BL, Huffman JC. Association of baseline anxiety with depression persistence at 6 months in patients with acute cardiac illness. Psychosom Med. 2012;74(1):93–9.
48. Walters K, Rait G, Petersen I, Williams R, Nazareth I. Panic disorder and risk of new onset coronary heart disease, acute myocardial infarction, and cardiac mortality: cohort study using the general practice research database. Eur Heart J. 2008;29(24):2981–8.
49. Scherrer JF, Chrusciel T, Zeringue A, Garfield LD, Hauptman PJ, Lustman PJ, et al. Anxiety disorders increase risk for incident myocardial infarction in depressed and nondepressed Veterans Administration patients. Am Heart J. 2010;159(5):772–9.
50. Jakobsen AH, Foldager L, Parker G, Munk-Jorgensen P. Quantifying links between acute myocardial infarction and depression, anxiety and schizophrenia using case register databases. J Affect Disord. 2008;109 (1–2):177–81.
51. Janszky I, Ahnve S, Lundberg I, Hemmingsson T. Early-onset depression, anxiety, and risk of subsequent coronary heart disease: 37-year follow-up of 49,321 young Swedish men. J Am Coll Cardiol. 2010;56(1):31–7.
52. Kawachi I, Colditz GA, Ascherio A, Rimm EB, Giovannucci E, Stampfer MJ, et al. Prospective study of phobic anxiety and risk of coronary heart disease in men. Circulation. 1994;89(5):1992–7.
53. Chen YH, Tsai SY, Lee HC, Lin HC. Increased risk of acute myocardial infarction for patients with panic disorder: a nationwide population-based study. Psychosom Med. 2009;71(7):798–804.
54. Buckley T, Hoo SYS, Fethney J, Shaw E, Hanson PS, Tofler GH. Triggering of acute coronary occlusion by episodes of anger. Eur Heart J Acute Cardiovasc Care. 2015;4(6):493–8.
55. Kubzansky LD, Cole SR, Kawachi I, Vokonas P, Sparrow D. Shared and unique contributions of anger, anxiety, and depression to coronary heart disease: a prospective study in the normative aging study. Ann Behav Med. 2006;31(1):21–9.
56. Tully PJ, Baune BT. Comorbid anxiety disorders alter the association between cardiovascular diseases and depression: the German National Health Interview and Examination Survey. Soc Psychiatry Psychiatr Epidemiol. 2014;49(5):683–91.
57. Tully PJ, Winefield HR, Baker RA, Denollet J, Pedersen SS, Wittert GA, et al. Depression, anxiety and major adverse cardiovascular and cerebrovascular events in patients following coronary artery bypass graft surgery: a five year longitudinal cohort study. Biopsychosoc Med. 2015;9:14.

58. Roest AM, de Jonge P, Lim CWW, Stein DJ, Al-Hamzawi A, Alonso J, et al. Fear and distress disorders as predictors of heart disease: a temporal perspective. J Psychosom Res. 2017;96:67–75.
59. Scott KM, de Jonge P, Alonso J, Viana MC, Liu Z, O'Neill S, et al. Associations between DSM-IV mental disorders and subsequent heart disease onset: beyond depression. Int J Cardiol. 2013;168(6): 5293–9.
60. Frasure-Smith N, Lespérance F. Depression and anxiety as predictors of cardiac events in patients with stable coronary artery disease. Arch Gen Psychiatry. 2008;65(1):62–71.
61. Lichtman JH, Froelicher ES, Blumenthal JA, Carney RM, Doering LV, Frasure-Smith N, et al. Depression as a risk factor for poor prognosis among patients with acute coronary syndrome: systematic review and recommendations: a scientific statement from the American Heart Association. Circulation. 2014;129 (12):1350–69.
62. Ladwig KH, Lederbogen F, Albus C, Angermann C, Borggrefe M, Fischer D, et al. Position paper on the importance of psychosocial factors in cardiology: update 2013. German Medical Science. 2014;12: Doc09.
63. Martens EJ, de Jonge P, Na B, Cohen BE, Lett H, Whooley MA. Scared to death? Generalized anxiety disorder and cardiovascular events in patients with stable coronary heart disease: the Heart and Soul Study. Arch Gen Psychiatry. 2010;67(7):750–8.
64. Goodwin RD, Davidson KW, Keyes K. Mental disorders and cardiovascular disease among adults in the United States. J Psychosom Res. 2009;43(3):239–46.
65. Strik JJ, Denollet J, Lousberg R, Honig A. Comparing depression and anxiety as predictors of cardiac events after myocardial infarction. J Am Coll Cardiol. 2003;42(10):1801–7.
66. Meyer T, Hussein S, Lange HW, Herrmann-Lingen C. Anxiety is associated with a reduction in both mortality and major adverse cardiovascular events five years after coronary stenting. Eur J Prev Cardiol. 2015;22(1):75–82.
67. Tully PJ, HN J, Cheung P, Cosh S. Anxiety and cardiovascular disease: a review. Curr Cardiol Rep. 2016;18(12):120.
68. Kubzansky LD, Kawachi I, Weiss ST, Sparrow D. Anxiety and coronary heart disease: a synthesis of epidemiological, psychological, and experimental evidence. Ann Behav Med. 1998;20(2):47–58.
69. Kollia N, Panagiotakos D, Georgousopoulou E, Chrysohoou C, Yannakoulia M, Stefanadis C, et al. Exploring the path between depression, anxiety and 10-year cardiovascular disease incidence, among apparently healthy Greek middle-aged adults: the ATTICA study. Maturitas. 2017;106:73–9.
70. Pierce GL, Kalil GZ, Ajibewa T, Holwerda SW, Persons J, Moser DJ, et al. Anxiety independently contributes to elevated inflammation in humans with obesity. Obesity (Silver Spring). 2017;25(2):286–9.
71. Vogelzangs N, de Jonge P, Smit JH, Bahn S, Penninx BW. Cytokine production capacity in depression and anxiety. Transl Psychiatry. 2016;6(5):e825.
72. Roy-Byrne PP, Schmidt P, Cannon RO, Diem H, Rubinow DR. Microvascular angina and panic disorder. Int J Psychiatry Med. 1989;19(4):315–25.
73. Cicek Y, Durakoglugil ME, Kocaman SA, Guveli H, Cetin M, Erdogan T, et al. Increased pulse wave velocity in patients with panic disorder: independent vascular influence of panic disorder on arterial stiffness. J Psychosom Res. 2012;73(2):145–8.
74. Chen YH, Lin HC. Patterns of psychiatric and physical comorbidities associated with panic disorder in a nationwide population-based study in Taiwan. Acta Psychiatr Scand. 2011;123(1):55–61.
75. Bankier B, Barajas J, Martinez-Rumayor A, Januzzi JL. Association between C-reactive protein and generalized anxiety disorder in stable coronary heart disease patients. Eur Heart J. 2008;29(18):2212–7.
76. van Reedt Dortland AK, Vreeburg SA, Giltay EJ, Licht CM, Vogelzangs N, van Veen T, et al. The impact of stress systems and lifestyle on dyslipidemia and obesity in anxiety and depression. Psychoneuroendocrinology. 2013;38(2):209–18.
77. van Reedt Dortland AK, Giltay EJ, van Veen T, Zitman FG, Penninx BW. Longitudinal relationship of depressive and anxiety symptoms with dyslipidemia and abdominal obesity. Psychosom Med. 2013;75(83–89):83–9.
78. Isensee B, Wittchen HU, Stein MB, Hofler M, Lieb R. Smoking increases the risk of panic: findings from a prospective community study. Arch Gen Psychiatry. 2003;60(7):692–700.
79. Hoertel N, Le Strat Y, De Maricourt P, Limosin F, Dubertret C. Are subjects in treatment trials of panic disorder representative of patients in routine clinical practice? Results from a national sample. J Affect Disord. 2013;146(3):383–9.
80. Grant BF, Stinson FS, Dawson DA, Chou SP, Dufour MC, Compton W, et al. Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Arch Gen Psychiatry. 2004;61(8):807–16.
81. Wagner JA, Pietrzak RH, Petry NM. Psychiatric disorders are associated with hospital care utilization in persons with hypertension: results from the National Epidemiologic Survey on alcohol and related conditions. Soc Psychiatry Psychiatr Epidemiol. 2008;43(11):878–88.
82. Grant BF, Goldstein RB, Chou SP, Huang B, Stinson FS, Dawson DA, et al. Sociodemographic and psychopathologic predictors of first incidence of DSM-IV substance use, mood and anxiety disorders: results from the Wave 2 National Epidemiologic Survey on Alcohol and Related Conditions. Mol Psychiatry. 2009;14(11):1051–66.
83. Buckner JD, Schmidt NB. Understanding social anxiety as a risk for alcohol use disorders: fear of scrutiny,

not social interaction fears, prospectively predicts alcohol use disorders. J Psychiatr Res. 2009;43(4): 477–83.
84. Berge LI, Skogen JC, Sulo G, Igland J, Wilhelmsen I, Vollset SE, et al. Health anxiety and risk of ischaemic heart disease: a prospective cohort study linking the Hordaland Health Study (HUSK) with the Cardiovascular Diseases in Norway (CVDNOR) project. BMJ Open. 2016;6(11):e012914.
85. Willis BL, Leonard D, Barlow CE, Martin SB, DeFina LF, Trivedi MH. Association of midlife cardiorespiratory fitness with incident depression and cardiovascular death after depression in later life. JAMA Psychiat. 2018;75(9):911–917.
86. Åberg MAI, Waern M, Nyberg J, Pedersen NL, Bergh Y, Åberg ND, et al. Cardiovascular fitness in males at age 18 and risk of serious depression in adulthood: Swedish prospective population-based study. Br J Psychiatry. 2012;201(5):352–9.
87. Belem da Silva CT, Schuch F, Costa M, Hirakata V, Manfro GG. Somatic, but not cognitive, symptoms of anxiety predict lower levels of physical activity in panic disorder patients. J Affect Disord. 2014;164:63–8.
88. Muotri RW, Bernik MA. Panic disorder and exercise avoidance. Rev Bras Psiquiatr. 2014;36:68–75.
89. Sardinha A, Araújo CGS, Soares-Filho GLF, Nardi AE. Anxiety, panic disorder and coronary artery disease: issues concerning physical exercise and cognitive behavioral therapy. Expert Rev Cardiovasc Ther. 2011;9(2):165–75.
90. Ramos PS, Sardinha A, Nardi AE, Araújo CG. Cardiorespiratory optimal point: a submaximal exercise variable to assess panic disorder patients. PLoS One. 2014;26(9(8)):e104932.
91. Daniel M, Agewall S, Berglund F, Caidahl K, Collste O, Ekenback C, et al. Prevalence of anxiety and depression symptoms in patients with myocardial infarction with non-obstructive coronary arteries. Am J Med. 2018;131:1118.
92. Kazukauskiene N, Burkauskas J, Macijauskiene J, Duoneliene I, Gelziniene V, Jakumaite V, et al. Mental distress factors and exercise capacity in patients with coronary artery disease attending cardiac rehabilitation program. Int J Behav Med. 2018;25(1):38–48.
93. Vickers K, Jafarpour S, Mofidi A, Rafat B, Woznica A. The 35% carbon dioxide test in stress and panic research: overview of effects and integration of findings. Clin Psychol Rev. 2012;32(3):153–64.
94. Woznica A, Vickers K, Koerner N, Fracalanza K. Reactivity to 35% carbon dioxide in bulimia nervosa and panic disorder. Psychiatry Res. 2015;228(3):571–5.
95. Taylor CB, King R, Ehlers A, Margraf J, Clark D, Hayward C, et al. Treadmill exercise test and ambulatory measures in panic attacks. Am J Cardiol. 1987;60(18):48J–52J.
96. Clark DM, Salkovskis PM, Chalkley AJ. Respiratory control as a treatment for panic attacks. J Behav Ther Exp Psychiatry. 1985;16(1):23–30.
97. Salkovskis PM, Warwick HM, Clark DM, Wessels DJ. A demonstration of acute hyperventilation during naturally occurring panic attacks. Behav Res Ther. 1986;24(1):91–4.
98. Fleet R, Lesperance F, Arsenault A, Gregoire J, Lavoie K, Laurin C, et al. Myocardial perfusion study of panic attacks in patients with coronary artery disease. Am J Cardiol. 2005;96(8):1064–8.
99. Fleet R, Foldes-Busque G, Grégoire J, Harel F, Laurin C, Burelle D, et al. A study of myocardial perfusion in patients with panic disorder and low risk coronary artery disease after 35% CO_2 challenge. J Psychosom Res. 2014;76(1):41–5.
100. Esler M. Mental stress and human cardiovascular disease. Neurosci Biobehav Rev. 2017;74(Pt B):269–76.
101. Herrmann-Lingen C, al'Absi M. Exploring the association of hypertension with risk for depression: evidence for tamed neurobehavioral arousal versus central emotional dysregulation. Psychosom Med. 2018;80(6):504–7.
102. Tully PJ, Tzourio C. Psychiatric correlates of blood pressure variability in the elderly: the Three City cohort study. Physiol Behav. 2017;168:91–7.
103. Yeragani VK, Pohl R, Bar KJ, Chokka P, Tancer M. Exaggerated beat-to-beat R amplitude variability in patients with panic disorder after intravenous isoproterenol. Neuropsychobiology. 2007;55(3–4):213–8.
104. Sullivan GM, Kent JM, Kleber M, Martinez JM, Yeragani VK, Gorman JM. Effects of hyperventilation on heart rate and QT variability in panic disorder pre- and post-treatment. Psychiatry Res. 2004;125(1): 29–39.
105. Yeragani VK, Pohl R, Balon R, Jampala VC, Jayaraman A. Twenty-four-hour QT interval variability: increased QT variability during sleep in patients with panic disorder. Neuropsychobiology. 2002;46(1):1–6.
106. Pohl R, Yeragani VK. QT interval variability in panic disorder patients after isoproterenol infusions. Int J Neuropsychopharmacol. 2001;4(1):17–20.
107. Yeragani VK, Pohl R, Berger R, Balon R, Ramesh C, Glitz D, et al. Decreased heart rate variability in panic disorder patients: a study of power-spectral analysis of heart rate. Psychiatry Res. 1993;46(1):89–103.
108. Chalmers J, Quintana DS, Abbott MJ, Kemp AH. Anxiety disorders are associated with reduced heart rate variability: a meta-analysis. Front Psychol. 2014;5:80.
109. Fangauf SV, Herbeck Belnap B, Meyer T, Albus C, Binder L, Deter HC, et al. Associations of NT-proBNP and parameters of mental health in depressed coronary artery disease patients. Psychoneuroendocrinology. 2018;96:188–94.
110. Meyer T, Herrmann-Lingen C. Natriuretic peptides in anxiety and panic disorder. Vitam Horm. 2017;103:131–45.
111. Memon AA, Sundquist K, Ahmad A, Wang X, Hedelius A, Sundquist J. Role of IL-8, CRP and epidermal growth factor in depression and anxiety

patients treated with mindfulness-based therapy or cognitive behavioral therapy in primary health care. Psychiatry Res. 2017;254:311–6.
112. Tang Z, Ye G, Chen X, Pan M, Fu J, Fu T, et al. Peripheral proinflammatory cytokines in Chinese patients with generalised anxiety disorder. J Affect Disord. 2018;225:593–8.
113. Tayefi M, Shafiee M, Kazemi-Bajestani SMR, Esmaeili H, Darroudi S, Khakpouri S, et al. Depression and anxiety both associate with serum level of hs-CRP: a gender-stratified analysis in a population-based study. Psychoneuroendocrinology. 2017;81:63–9.
114. Glaus J, Vandeleur CL, von Kanel R, Lasserre AM, Strippoli MP, Gholam-Rezaee M, et al. Associations between mood, anxiety or substance use disorders and inflammatory markers after adjustment for multiple covariates in a population-based study. J Psychiatr Res. 2014;58:36–45.
115. Moons WG, Shields GS. Anxiety, not anger, induces inflammatory activity: an avoidance/approach model of immune system activation. Emotion. 2015;15 (4):463–76.
116. Abbott R, Whear R, Nikolaou V, Bethel A, Coon JT, Stein K, et al. Tumour necrosis factor-alpha inhibitor therapy in chronic physical illness: a systematic review and meta-analysis of the effect on depression and anxiety. J Psychosom Res. 2015;79(3):175–84.
117. Meyer T, Herrmann-Lingen C, Chavanon ML, Pieske B, Wachter R, Edelmann F. Plasma mid-regional pro-adrenomedullin levels are inversely associated with anxiety but unrelated to depression: results from the observational DIAST-CHF study in patients with cardiovascular risk factors. Psychoneuroendocrinology. 2015;62:227–32.
118. Hoirisch-Clapauch S. Anxiety-related bleeding and thrombosis. Semin Thromb Hemost. 2018;44(7): 656–661.
119. Zafar MU, Paz-Yepes M, Shimbo D, Vilahur G, Burg MM, Chaplin W, et al. Anxiety is a better predictor of platelet reactivity in coronary artery disease patients than depression. Eur Heart J. 2010;31(13):1573–82.
120. Sardinha A, Nardi AE, Zin WA. Are panic attacks really harmless? The cardiovascular impact of panic disorder. Rev Bras Psiquiatr. 2009;31(1):57–62.
121. Kang HJ, Bae KY, Kim SW, Shin IS, Hong YJ, Ahn Y, et al. Effects of escitalopram on anxiety in patients with acute coronary syndrome: a randomized controlled trial. Clin Psychopharmacol Neurosci. 2017;15(2):126–31.
122. Rollman BL, Belnap BH, LeMenager MS, Mazumdar S, Houck PR, Counihan PJ, et al. Telephone-delivered collaborative care for treating post-CABG depression: a randomized controlled trial. JAMA. 2009;302(19):2095–103.
123. Richards SH, Anderson L, Jenkinson CE, Whalley B, Rees K, Davies P, et al. Psychological interventions for coronary heart disease: cochrane systematic review and meta-analysis. Eur J Prev Cardiol. 2018;25(3):247–59.
124. Huffman JC, Mastromauro CA, Beach SR, Celano CM, Dubois CM, Healy BC, et al. Collaborative care for depression and anxiety disorders in patients with recent cardiac events: the Management of Sadness and Anxiety in Cardiology (MOSAIC) randomized clinical trial. JAMA Intern Med. 2014;174(6): 927–36.
125. Tully PJ, Selkow T, Bengel J, Rafanelli C. A dynamic view of comorbid depression and generalized anxiety disorder symptom change in chronic heart failure: discrete effects of cognitive behavioral therapy, exercise rehabilitation, and psychotropic medication. Disabil Rehabil. 2015;37(7):585–92.
126. Tully PJ, Wittert GA, Selkow T, Baumeister H. The real world mental health needs of heart failure patients are not reflected by the depression Randomized Controlled Trial Evidence. PLoS One. 2014;9 (1):e85928.
127. Tully PJ, Turnbull D, Horowitz JD, Beltrame JF, Selkow T, Baune BT, et al. Cardiovascular Health in Anxiety or Mood Problems Study (CHAMPS): study protocol for a RCT. Trials. 2016;17(1):18.
128. Wells A, McNicol K, Reeves D, Salmon P, Davies L, Heagerty A, et al. Improving the effectiveness of psychological interventions for depression and anxiety in the cardiac rehabilitation pathway using group-based metacognitive therapy (PATHWAY Group MCT): study protocol for a randomised controlled trial. Trials. 2018;19(1):215.
129. Oldenburg O, Spiesshofer J, Fox H, Bitter T, Horstkotte D. Cheyne-Stokes respiration in heart failure: friend or foe? Hemodynamic effects of hyperventilation in heart failure patients and healthy volunteers. Clin Res Cardiol. 2015;104(4):328–33.
130. Wittstein IS, Thiemann DR, Lima JA, Baughman KL, Schulman SP, Gerstenblith G, et al. Neurohumoral features of myocardial stunning due to sudden emotional stress. N Engl J Med. 2005;352(6):539–48.
131. Yavuzkir M, Atmaca M, Dagli N, Balin M, Karaca I, Mermi O, et al. P-wave dispersion in panic disorder. Psychosom Med. 2007;69(4):344–7.
132. Ricci F, De Caterina R, Fedorowski A. Orthostatic hypotension: epidemiology, prognosis, and treatment. J Am Coll Cardiol. 2015;66(7):848–60.
133. Cully JA, Paukert A, Falco J, Stanley M. Cognitive-behavioral therapy: innovations for cardiopulmonary patients with depression and anxiety. Cogn Behav Pract. 2009;16(4):394–407.
134. Tully PJ. A good time to panic? Premorbid and postmorbid panic disorder in heart failure affects cardiac and psychiatric cause admissions. Australas Psychiatry. 2015;23(2):124–7.
135. Sommaruga M, Angelino E, Della Porta P, Abatello M, Baiardo G, Balestroni G, et al. Best practice in psychological activities in cardiovascular prevention and rehabilitation: Position Paper. Monaldi Arch Chest Dis. 2018;88(2):966.
136. Baumeister H, Hutter N, Bengel J. Psychological and pharmacological interventions for depression in

patients with diabetes mellitus: a systematic Cochrane review. Diabet Med. 2014;31:773.
137. Baumeister H, Hutter N, Bengel J. Psychological and pharmacological interventions for depression in patients with coronary artery disease. Cochrane Database Syst Rev. 2011;9:CD008012.
138. Dickens C, Cherrington A, Adeyemi I, Roughley K, Bower P, Garrett C, et al. Characteristics of psychological interventions that improve depression in people with coronary heart disease: a systematic review and meta-regression. Psychosom Med. 2013;75 (2):211–21.
139. Berkman LF, Blumenthal J, Burg M, Carney RM, Catellier D, Cowan MJ, et al. Effects of treating depression and low perceived social support on clinical events after myocardial infarction: the Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) Randomized Trial. J Am Med Assoc. 2003;289(23):3106–16.
140. Glassman AH, O'Connor CM, Califf RM, Swedberg K, Schwartz P, Bigger JT Jr, et al. Sertraline treatment of major depression in patients with acute MI or unstable angina. JAMA. 2002;288(6):701–9.
141. Lesperance F, Frasure-Smith N, Koszycki D, Laliberte MA, van Zyl LT, Baker B, et al. Effects of citalopram and interpersonal psychotherapy on depression in patients with coronary artery disease: the Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) trial. JAMA. 2007;297(4):367–79.
142. Saab PG, Bang H, Williams RB, Powell LH, Schneiderman N, Thoresen C, et al. The impact of cognitive behavioral group training on event-free survival in patients with myocardial infarction: the ENRICHD experience. J Psychosom Res. 2009; 67(1):45–56.
143. Scherrer JF, Chrusciel T, Garfield LD, Freedland KE, Carney RM, Hauptman PJ, et al. Treatment-resistant and insufficiently treated depression and all-cause mortality following myocardial infarction. Br J Psychiatry. 2012;200(2):137–42.
144. Taylor CB, Youngblood ME, Catellier D, Veith RC, Carney RM, Burg MM, et al. Effects of antidepressant medication on morbidity and mortality in depressed patients after myocardial infarction. Arch Gen Psychiatry. 2005;62(7):792–8.
145. Stewart JC, Perkins AJ, Callahan CM. Effect of collaborative care for depression on risk of cardiovascular events: data from the IMPACT randomized controlled trial. Psychosom Med. 2014;76(1):29–37.
146. Davidson KW, Rieckmann N, Clemow L, Schwartz JE, Shimbo D, Medina V, et al. Enhanced depression care for patients with acute coronary syndrome and persistent depressive symptoms: coronary psychosocial evaluation studies randomized controlled trial. Arch Intern Med. 2010;170(7):600–8.
147. Tully PJ, Baumeister H. Collaborative care for comorbid depression and coronary heart disease: a systematic review and meta-analysis of randomized controlled trials. BMJ Open. 2015;5(12):e009128.
148. Huang Y, Wei X, Wu T, Chen R, Guo A. Collaborative care for patients with depression and diabetes mellitus: a systematic review and meta-analysis. BMC Psychiatry. 2013;13(1):1–11.
149. Pogosova N, Kotseva K, De Bacquer D, von Känel R, De Smedt D, Bruthans J, et al. Psychosocial risk factors in relation to other cardiovascular risk factors in coronary heart disease: results from the EUROASPIRE IV survey. A registry from the European Society of Cardiology. Eur J Prev Cardiol. 2017;24(13):1371–80.
150. Wade V, Cheok F, Schrader G, Hordacre AL, Marker J. Depression after cardiac hospitalisation – the identifying depression as a comorbid condition (IDACC) study. Aust Fam Physician. 2005;34(11):985–9.
151. Czarny MJ, Arthurs E, Coffie DF, Smith C, Steele RJ, Ziegelstein RC, et al. Prevalence of antidepressant prescription or use in patients with acute coronary syndrome: a systematic review. PLoS One. 2011;6(11):e27671.
152. Wu CK, Huang YT, Lee JK, Jimmy Juang JM, Tsai CT, Lai LP, et al. Anti-anxiety drugs use and cardiovascular outcomes in patients with myocardial infarction: a national wide assessment. Atherosclerosis. 2014;235(2):496–502.
153. Clark DB, Taylor CB, Roth WT, Hayward C, Ehlers A, Margraf J, et al. Surreptitious drug use by patients in a panic disorder study. Am J Psychiatry. 1990;147(4):507–9.
154. Clark DM, Salkovskis PM, Hackmann A, Middleton H, Anastasiades P, Gelder M. A comparison of cognitive therapy, applied relaxation and imipramine in the treatment of panic disorder. Br J Psychiatry. 1994;164(6):759–69.
155. Sowden GL, Huffman JC. The impact of mental illness on cardiac outcomes: a review for the cardiologist. Int J Cardiol. 2009;132(1):30–7.
156. van Melle JP, de Jonge P, Honig A, Schene AH, Kuyper AMG, Crijns HJGM, et al. Effects of antidepressant treatment following myocardial infarction. Br J Psychiatry. 2007;190(6):460–6.
157. Pizzi C, Rutjes AW, Costa GM, Fontana F, Mezzetti A, Manzoli L. Meta-analysis of selective serotonin reuptake inhibitors in patients with depression and coronary heart disease. Am J Cardiol. 2011;107(7):972–9.
158. van Zyl LT, Lesperance F, Frasure-Smith N, Malinin AI, Atar D, Laliberte MA, et al. Platelet and endothelial activity in comorbid major depression and coronary artery disease patients treated with citalopram: the Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy Trial (CREATE) biomarker sub-study. J Thromb Thrombolysis. 2009;27(1):48–56.
159. Serebruany VL, Suckow RF, Cooper TB, O'Connor CM, Malinin AI, Krishnan KR, et al. Relationship between release of platelet/endothelial biomarkers

and plasma levels of sertraline and N-desmethylsertraline in acute coronary syndrome patients receiving SSRI treatment for depression. Am J Psychiatry. 2005;162(6):1165–70.
160. Labos C, Dasgupta K, Nedjar H, Turecki G, Rahme E. Risk of bleeding associated with combined use of selective serotonin reuptake inhibitors and antiplatelet therapy following acute myocardial infarction. CMAJ. 2011;183(16):1835.
161. Gomes RM, Sardinha A, Soares de Araújo CG, Nardi AE, Deslandes AC. Aerobic training intervention in panic disorder: a case-series study. Med Express. 2014;1(4):195–201.
162. Moylan S, Eyre HA, Maes M, Baune BT, Jacka FN, Berk M. Exercising the worry away: how inflammation, oxidative and nitrogen stress mediates the beneficial effect of physical activity on anxiety disorder symptoms and behaviours. Neurosci Biobehav Rev. 2013;37(4):573–84.
163. Pedersen SS, von Kanel R, Tully PJ, Denollet J. Psychosocial perspectives in cardiovascular disease. Eur J Prev Cardiol. 2017;24(3_suppl):108–15.
164. Abberger B, Haschke A, Tully PJ, Forkmann T, Berger J, Wirtz M, et al. Development and validation of parallel short forms PaSA-cardio for the assessment of general anxiety in cardiovascular rehabilitation patients using Rasch analysis. Clin Rehabil. 2017;31(1):104–14.
165. Blumenthal JA, Feger BJ, Smith PJ, Watkins LL, Jiang W, Davidson J, et al. Treatment of anxiety in patients with coronary heart disease: rationale and design of the UNderstanding the benefits of exercise and escitalopram in anxious patients WIth coroNary heart Disease (UNWIND) randomized clinical trial. Am Heart J. 2016;176:53–62.
166. Rollman BL, Huffman JC. Treating anxiety in the presence of medical comorbidity: calmly moving forward. Psychosom Med. 2013;75(8):710–2.

Depression and Cardiovascular Diseases

16

Isabella Masci, Sergio Merlino, and Grazia Rutigliano

Contents

Abstract

Cardiovascular diseases (CVD) and depression share a common epidemiology, thus suggesting a mutual link between these two disorders. Growing evidence supports the detrimental influence of depression on cardiovascular risk factors and outcomes. Reciprocally, depression rates in patients with known CVD are higher than in the general population. Heart and brain seem to be intertwined in a psycho-neuro-hormonal-cardiovascular axis. Their disorders emerge from pathophysiological derangements in the same fundamental mechanisms, including inflammation, platelet reactivity, autonomic dysregulation, circadian rhythm and sleep disruption, hormone imbalance, and neurotrophins. In addition, common unhealthy lifestyle habits, mainly poor diet, low physical activity, and tobacco use, might

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*,
https://doi.org/10.1007/978-3-030-28008-6_18

help explain the association between depression and CVD. Notwithstanding this, depression is grossly under-detected and undertreated in patients with CVD. The application of pharmacological and nonpharmacological approaches to the treatment of depression might help physicians to optimize health outcomes and quality of life for their CVD patients.

Keywords

Inflammation · Platelet reactivity · Endothelial dysfunction · Autonomic imbalance · Circadian rhythm · Renin-angiotensin-aldosterone system · Vasopressin · Hypothalamic-pituitary-adrenal axis · Neurotrophins · Antidepressants

Introduction

Cardiovascular diseases (CVD) refers to those conditions that affect the heart and blood vessels, including coronary heart disease, cerebrovascular disease, and peripheral artery disease. CVD is the primary cause of mortality and is considered one of the highest economic costs in many countries. In a recent report, the American Heart Association estimated that medical costs and productivity losses of CVD are expected to grow from $555 billion in 2015 to $1.1 trillion in 2035. In many developing countries, mortality and morbidity from CVD have increased exponentially. It is estimated that in 2008 about 7.3 million global deaths resulted from CVD, which account for one in every six deaths. There were significant differences by sex, age, ethnicity, and geographic region in the proportion of persons who had been diagnosed with CVD. Men were more likely than women to be diagnosed with CVD. Non-Hispanic whites were more likely than any other ethnic groups to be diagnosed with CVD (39.1%). Physical activity, healthy diet, and lifestyle are probably the most crucial ways to prevent CVD.

Depression is a common mental disease. It is estimated that major depressive episodes have a prevalence of 14.6% in high-income countries and 11.1% in developing countries. Depression became the second leading cause of disability in 2010. According to current international classifications (International classification of disease, ICD-10 and diagnostic and statistical manual of mental disorders, DSM 5), a major depressive episode is defined by five or more of the following nine symptoms lasting for at least 2 weeks nearly every day. One of these symptoms must be depressed mood or anhedonia (loss of interest in activities or pleasure). Other symptoms are: significant decrease or increase in weight or appetite; insomnia or hypersomnia, fatigue, psychomotor agitation, or retardation; diminished ability to concentrate or make decisions; feelings of worthlessness or inappropriate guilt; and recurrent thoughts of death or suicidal ideation. Depressive symptoms and major depressive episodes are among the building blocks of "Mood disorders," a chapter of the previous editions of the DSM, which has been split into "Depressive disorders" and "Bipolar and related disorders" in the DSM 5. It is beyond the scope of this chapter to provide a detailed description of the diagnostic criteria for depressive and bipolar disorders. Briefly, a diagnosis of major depressive disorder (MDD) can be made in presence of one or more major depressive episodes, with no lifetime (hypo)manic episodes. Nonetheless, a major depressive episode is often the first presentation of bipolar disorders, and it is not rare that an initial diagnosis of MDD transitions to bipolar disorder. Also, depressive presentations not reaching the diagnostic threshold for a major depressive episode in terms of either duration or symptom count may be present in other depressive (persistent depressive disorder, disruptive mood dysregulation disorder, premenstrual dysphoric disorder) or bipolar (cyclothymic disorder, other specified bipolar and related disorders) disorders. In this chapter we will mainly refer to depression as a psychopathological dimension. When data is presented which is relevant for a specific diagnostic category, this will be specified.

Biological and psychosocial factors contribute to the emergence of depression, especially in the elderly. Genetic vulnerability may make some people more susceptible to depression. Among

biological risk factors are old age and female sex. In the elderly, according to the so-called "vascular depression" hypothesis, depression has been linked to vascular brain lesions, chronic inflammation, and atherosclerosis, which is also the leading cause of CVD. Similarly to CVD, poor lifestyle habits, such as smoking and alcohol use, are important risk factors for depression, especially in the elderly. Some authors suggest that depression could be prevented by improving lifestyle habits, such as exercise, diet, smoking cessation. Furthermore, treatment for hypertension, hypercholesterolemia, and hyperglycemia, conditions traditionally related to CVD, could ameliorate depression as well.

In the present chapter, we will review the pathophysiological mechanisms underlying the interaction between CVD and depression. We hope to convince physicians of the uttermost importance of monitoring the cardiovascular state of depressed patients and, reciprocally, assessing the mood profile in patients suffering from CVD. Also, a more thorough understanding of this association could help developing novel lines of interventions.

The Reciprocal Association Between Depression and CVD

Evidence accumulated of a reciprocal association between depression and CVD. Psychosocial risk factors, including depression and anxiety, have been found to be strongly and consistently correlated to a worse outcome of CVD [1]. On the other hand, CVD can increase the risk of developing depressive symptoms and disorders through either biological, bodily, or psychosocial changes. In fact, the association between depression and CVD can be considered a downward spiral in which depression and CVD reinforce each other [2]. Incidence rates of depression in patients with CVD reach up to 20–40% [3]. Reciprocally, depression increases the risk of cardiac death by 3–4 times [4]. Depression and anxiety are common symptoms among patients who have suffered an acute cardiac event and sometimes can persist for months or even for years, influencing patients' quality of life [5]. Moreover, depression may lead to complications, as depressed patients have a reduced pharmacological compliance and have more difficulty coping with the distress of a disease [4]. In summary, depression has a major impact on mortality, morbidity, and functional recovery in patients with CVD.

The socio-psycho-biological model of modern medicine suggests that CVD may be viewed as a part of a psycho-neuro-hormonal-cardiovascular axis, which links the brain and the heart. Several biological mechanisms might be involved, including inflammation, platelet reactivity, autonomic dysregulation, circadian rhythm and sleep disruption, hormone imbalance, neurotrophins, lifestyle, and metabolic syndrome.

Inflammation

Atherosclerosis is a chronic inflammatory disease, orchestrated by endothelial and white blood cells through numerous cytokines. Chronic inflammation in CVD results from an oxidative/anti-oxidative imbalance, which determines an accumulation of oxidized low-density lipoproteins (LDL) in the arterial wall. This generates an inflammatory response in the subendothelial space, through the release of proinflammatory molecules, such as tumor necrosis factor alpha (TNF-α) and interleukin (IL)-1, from the endothelial cells and monocytes. The release of other cytokines, such as IL-10 and IL-6, and the increased synthesis of acute phase proteins as C-reactive protein (CRP) by the liver, perpetuates the inflammatory response.

Similarly, a link exists between depression and some diseases characterized by chronic inflammation with increased levels of inflammatory cytokines. For instance, depression is common in people with rheumatoid arthritis [6]. Also, about 30–50% of patients with hepatitis C virus will develop depression after treatment with interferon [7]. Intriguingly, experimental studies showed that inducing inflammation in healthy volunteers, e.g., with a typhoid vaccine, which increases circulating IL-6 levels, leads to depressive symptoms and reduced cognitive performance [8].

Furthermore, systematic reviews and meta-analyses found that the levels of circulating pro-inflammatory cytokines, such as IL-6, IL-1β, TNF-α, and CRP, rise in acutely depressed patients, to then largely normalize after recovery [9]. As some studies showed that patients resistant to SSRI and other antidepressants continue to show elevated levels of IL-6, CRP, and other inflammatory markers, it has been hypothesized that elevated serum concentrations of cytokines might predict poor response to antidepressants [10].

Platelet Reactivity

Blood platelets are primarily known for their role in hemostasis and thrombosis, but they also have a role in inflammation and immune system. Platelets contain three different types of storage granules: dense granules, alpha granules, and lysosomes. Alpha granules store pro-inflammatory and immune-modulatory markers, such as CD62P (P-selectin), platelet factor 4 (PF-4), β-thromboglobulin (β-TG), adhesion molecules (intercellular adhesion molecule-1, ICAM-1; platelet/endothelial adhesion molecule-1, PECAM-1; the matrix-metalloproteinases type 2 and 9, MMP-2 and MMP-9), and the immune-modulatory molecule CD40L. Alpha granules are found mainly in the cytosol of platelets, are released when platelets are activated, and are responsible for the formation of platelet-monocyte aggregates. The secretion of these molecules allows for the interaction with other platelets, immune cells, and endothelial cells. Platelet degranulation is usually followed by a conformational change and aggregation. Platelets contribute largely to the development of potentially fatal ischemic events in the late stages of CVD. After adhesion to the damaged loci of the blood vessels walls, platelets promote the growth of the chronic atherosclerotic plaques and trigger the onset of arterial thrombosis consequent to the rupture of the atherosclerotic plaque. Furthermore, they maintain a local pro-atherothrombotic condition, through specific alterations of the arterial wall. On the other hand, the relationship between depression and platelet reactivity is still controversial. Some studies reported higher levels of PF-4, β-TG, and P-selectin, increased activation of platelet glycoprotein IIb/IIIa receptors, and increased platelet reactivity in patients with depression [11], while others were not able to find any difference in platelet reactivity between depressed and nondepressed patients [12].

Platelets share many biochemical similarities with the neuronal monoamine systems, mainly about the uptake, storage, and metabolism of serotonin (5-HT). The platelet and brain 5-HT transporters (SERTs) are substantially identical except for a slightly different extent of glycosylation. The role of 5-HT in depression is well established. Lower concentrations of 5-HT and 5-hydroxyindoleacetic acid (5-HIAA), its major metabolite, have been reported in the cerebrospinal fluid and the postmortem brain tissue of depressed and/or suicidal patients [13, 14]. Postmortem brains of depressed/suicidal patients showed: (i) reduced number of serotonin binding sites in the SERT [13, 14] and (ii) increased density of 5-HT2A receptors [15]. Similar findings were reported in the platelets of suicide victims, which presented: (i) decreased maximal velocity of the SERT [16] and (ii) upregulation of 5-HT2A [17]. These alterations persist even after therapy with antidepressants and clinical improvement [18]. The gold standard treatment of depression includes the administration of drugs that affect 5-HT neurotransmission, among which selective serotonin reuptake inhibitors (SSRIs). SSRIs, in particular sertraline and citalopram, were found to normalize platelet activity indices (especially β-TG and E-selectin) [19, 20]. On the other side, a recent study demonstrated that some drugs used for angina pectoris like trimetazidine could regulate central and peripheral 5-HT in rats with myocardial infarction combined with depression [21].

Endothelial Dysfunction

Endothelial dysfunction is characterized by an alteration of nitric oxide (NO)-dependent vasodilation. Endothelial damage is a hallmark of acute cardiovascular events, where an increase of

circulating endothelial cells and a reduction of endothelial progenitor cells have been described. More surprisingly, an association between endothelial dysfunction and depressed mood was demonstrated via measures of flow-mediated dilation [22] and of plasma levels of endothelium related markers [23]. There is recent evidence of reduced levels of circulating endothelial progenitor cells in patients with coexisting depression and acute coronary syndromes [24].

Autonomic Dysregulation

The autonomic nervous system (ANS) encompasses two branches: the sympathetic nervous system, which drives physiological responses to acute stress (*fight-or-flight*); and the parasympathetic system with complementary *rest-and-digest* actions at rest. The balance between the two divisions of the ANS is fundamental. Heart rate variability (HRV), a noninvasive marker of the ANS function, refers to the beat-to-beat variations in heart rate, measured by electrocardiogram. HRV results from the balance between the two branches of the ANS at the sinus node, the parasympathetic (vagus) and the sympathetic nerves, with slowing and accelerating effects, respectively. High parasympathetic tone, by increasing the HRV, has a protective effect against possible adverse cardiac events, while high sympathetic tone, typical of situations of stress, either emotional or physical, reduces the HRV, thereby increasing the risk of malignant arrhythmias and sudden cardiac death. From a psychological perspective, while high HRV is associated with cheerfulness and calm, motivation for social commitment, resilience and well-being, low HRV is related to cognitive and affective dysregulation and psychological inflexibility, strong psychological risk factors for psychopathology. Consistently, a reduction in HRV has been found in many psychiatric disorders, such as schizophrenia, bipolar disorder (BD), conduct disorder, and autism spectrum disorders. An inverse association exists between depression severity and HRV, meaning that the more severe the depression, the lower the HRV. It is suggested that in MDD there is a relative state of sympathetic hyper-tone [25]. To support this, hallmark symptoms of depression, such as reduced social engagement, poorly flexible behavioral response to environmental changes, and somatomotor deficits, are all linked to low vagal activity since the vagus and the other cranial nerves control the peripheral structures involved in the behavioral expression of emotions [26]. In addition, patients with MDD in comorbidity with generalized anxiety disorder show the most consistent reductions in vagal activity at rest [27]. Probably, chronic worry and hypervigilance to threat may underpin chronic withdrawal of vagal activity resulting in increased morbidity and mortality. The HRV could represent an important link between MDD and CVD. The reduction of vague-mediated cardiovascular control in depression could have a disinhibiting effect on sympathetic excitatory inputs, with consequent impairment in flexibility and reactivity to environmental demands. Reciprocally, the reduction in vagal tone (and HRV) deriving from myocardial infarction could be responsible for a progressive worsening of depressive symptoms.

Although HRV changes have been found in drug-naïve depressed patients, many antidepressants, can exert diverse effects on the HRV, depending on their mechanism of action. Antidepressants with a prominent stimulation of noradrenergic neurotransmission, such as tricyclic antidepressants (TCA) and selective noradrenaline and serotonin reuptake inhibitors (SNRIs), decrease the already lower HRV seen in depression, contributing an unfavorable cardiovascular profile. In the case of TCAs, the adrenergic effect is further exacerbated by the anticholinergic properties deriving from the blockade of muscarinic cholinergic receptors. Furthermore, changes in serotonergic and dopaminergic transmission may also affect HRV. Globally, SSRIs seem to have no significant impact on HRV, regardless the response to therapy. Regarding alternative treatments, agomelatine, that blocks the 5-HT2C receptor and stimulates the melatonergic MT1 and MT2 receptors, has a significant effect on vagal tone, resulting in increased HRV; ketamine, a N-methyl-D-aspartate (NMDA) receptor antagonist, increases the sympathetic effects on the

heart thereby decreasing HRV; therefore, dose studies are needed to better assess its impact on the ANS. Transcranial magnetic stimulation (rTMS) has been shown to improve HRV in patients with MDD. Controversial data have emerged from studies that have examined the impact of electroconvulsive therapy (ECT) on HRV, requiring additional research. The vagus nerve stimulation (VNS), consisting of a surgical implant of a bipolar electrode connected to a subcutaneous generator to repeatedly stimulate the vagus nerve, improves autonomic control and reverses HRV reduction.

Strategies to increase HRV (exercise, smoking cessation, dietary changes, weight loss, intake of omega-3 fatty acids and vitamin D, stress and worry reduction, meditation) should be warmly recommended to patients with depression, especially if treated with antidepressants, to lessen their cardiovascular risk.

Sleep and Circadian Rhythm Disruption

The association between depression and sleep disorder is evident, as sleep disturbances are part of the diagnostic criteria for mood disorders. Then, it is not surprising that complaints of poor sleep occur in an estimated 50% to 90% of individuals diagnosed with depression. However, sleep alterations, such as short (< 6 h/day) or long (>8 h/day) sleep duration, and various sleep disturbances, appear to be significant determinants of CVD as well [28]. This association seems to be mediated by the impact of sleep problems on major CVD risk factors, including obesity, hypertension, diabetes, and inflammation [29]. It is known that both short and long sleep duration negatively impact upon fasting glucose levels, and short sleep is linked to increased waist circumference and triglyceride levels, independently of depressive symptoms [30]. However, a synergistic model of sleep and psychopathology in cardiovascular and metabolic disease risk has been proposed. For instance, Vgontzas et al. recently reported that short sleep duration is related to higher body mass index (BMI) in individuals reporting high emotional distress, but not in those reporting low emotional distress [31]. Similarly, subjects with both long sleep and elevated depressive symptoms developed hypertension [32].

What are the pathophysiological mechanisms called into question? Both sleep and depression are associated with unhealthy behaviors important to cardiometabolic disease risk, including smoking and physical inactivity. For instance, epidemiologic and experimental evidence shows that sleep disturbances (poor quality, polysomnography (PSG) indices of continuity, and decreased duration) are related to smoke and physical inactivity. Then, disrupted sleep influences (i) inflammation, (ii) hypothalamic-pituitary-adrenal axis, and (iii) autonomic output. First, short sleep duration and poor sleep continuity have been related to increased levels of inflammatory markers, such as IL-6 and CRP. In one study of patients with MDD, it was found that IL-6 elevation could be predicted by sleep latency and rapid eye movement (REM) density measured with all-night PSG, to suggest that disturbances of sleep initiation found in depressed patients might be partially responsible for the elevation of inflammatory markers [33]. Second, a strong link has been observed between insomnia with objective short sleep duration and both activation of the hypothalamic-pituitary-adrenal (HPA) axis and increased neurocognitive-physiologic arousal. Insomnia, jointly with HPA over-activation and consistent PSG alterations (low amounts of slow wave sleep, a short REM latency, and a high REM density), characterizes the melancholic subtype of depression, while HPA under-activation and inconsistent or inexistent sleep disturbances were found in atypical depression. Furthermore, while the alteration of HPA activity emerged as a state feature, as it tended to normalize during remission or recovery, sleep disturbances were trait features, independent of the depressive status.

Some evidence suggests that the covariation among sleep parameters, depressive symptoms, and CVD may be due to genetic influences. For example, twin studies show that common genetic variants account for significant portions of the

phenotypic correlations between depression and sleep problems in children and between depressive symptoms and coronary artery disease. These variants might be related to the bio-behavioral pathways summarized in this chapter (e.g., inflammation, HPA, autonomic imbalance); an interesting class of possibly relevant genes are the core clock genes, which are thought to regulate the endogenous circadian rhythmicity, either in the realm of glucose metabolism, adipocyte function, and vascular function or in mood regulation. A reciprocal interaction between the circadian clock system and metabolic pathways has been shown. It was demonstrated that a dysregulation of the circadian rhythm in humans is closely associated with the development of metabolic diseases, including nonalcoholic fatty liver disease (NAFLD), obesity, and type 2 diabetes. Animals deficient for clock genes or for aryl hydrocarbon receptor nuclear translocator-like protein-1 (BMAL1) go on to develop hyperlipidemia, hepatic steatosis, and defective gluconeogenesis [34, 35]. A survey of nuclear receptor mRNA profiles in metabolic tissues suggested that approximately half of the known nuclear receptors and transcriptional regulators exhibit rhythmic expression [36]. Improved knowledge of the associations between sleep and depression in relation to these mechanisms will contribute to etiological models of CVD and may provide new preventative strategies.

The Renin-Angiotensin-Aldosterone System and Neurohypophysis

The renin-angiotensin-aldosterone system (RAAS) is an endocrine system best known for its role in hydromineral balance and blood pressure regulation. As such, the RAAS system plays a fundamental role in the progression of heart failure (HF). The pathophysiology of HF is indeed characterized by the activation of different neurohormonal systems. In the early stages of HF, the sympathetic branch of the ANS and the RAAS play a compensatory role, aimed at supporting cardiac output and increasing peripheral vasoconstriction to maintain circulatory homoeostasis. However, the prolonged activation of the two systems becomes detrimental and contributes to the progression and worsening of HF, eventually leading to congestion. HF may be conceptualized as a state of neurohormonal imbalance, which cannot be counteracted even by the massive activation of the natriuretic peptide (NP) system (mostly the atrial natriuretic peptide, ANP and the B-type natriuretic peptide, BNP). The effector peptide of the renin-angiotensin system (RAS) is angiotensin-II (Ang-II). There are evidences supporting a role for the angiotensin receptor in stress-related diseases. Both physiological and psychological stressors elicit the activation of the RAS through the angiotensin type-1a receptor (AT1aR), which potentiates the intensity of stress responding. Acute stress triggers an array of neuroendocrine, autonomic, and behavioral responses, which serve as an evolutionary mechanism towards survival. However, the chronic activation of these systems has psychological, cardiovascular, and metabolic detrimental consequences. Recently, the group led by Dr. Krause has sought to elucidate the mechanisms underlying the AT1aR involvement in stress responses using the Cre-recombinarse/IoxP system and optogenetic technology in mice. They found a high expression of AT1aR in neurons within the neurosecretory subdivision of the paraventricular nucleus of the hypothalamus (PVN), projecting mostly to the exterior portion of the median eminence. Most of these neurons, which are robustly activated by a restraint stress, are glutamatergic and co-synthesize the corticotropin releasing hormone (CRH) or the thyrotropic releasing hormone (TRH). Their optical stimulation increases systolic blood pressure and circulating levels of adrenal corticotropic hormone (ACTH), corticosterone, thyroid-stimulating hormone (TSH), and thyroxine (T4). Also, their optogenetic inhibition has an anxiolytic effect, which parallels the suppression of the hypothalamic-pituitary-adrenal/thyroid axis [37]. These results point to a population of AT1aR-expressing neurons in the PVN as orchestrators of the stress response, and potential targets of treatments to alleviate stress-related diseases.

Furthermore, Ang-II increases the secretion of the antidiuretic hormone or vasopressin (ADH) from the paraventricular (PVN) and supraoptic (SON) nuclei of the hypothalamus. The ADH is mainly an osmotic regulator, causing water retention, and stimulating thirst to cause water repletion. However, ADH – and the related hormone oxytocin (OT) – also act on multiple brain regions as neuromodulators and influence a range of neurophysiological processes and behaviors, including feeding, anxiety, aggression, social recognition, and the stress/fear response to social stimuli. These neuropeptides are associated with complex social and emotional processing in healthy people which, if impaired, may account for some of the symptoms present in psychiatric disorders. Several studies assessed whether these neuropeptides could serve as biomarkers of psychiatric disorders. These have been recently summarized in a meta-analysis, which found no convincing evidence for significant alterations in the two neuropeptides in psychiatric disorders, mainly because of high heterogeneity across individual studies, low quality, and significant methodological limitations [38]. However, preclinical and clinical data reported the association between ADH and affective disorders (BD and MDD), probably mediated by the overactivation of the HPA axis. Postmortem brains of patients with MDD contain a greater number of ADH-immunoreactive neurons in the hypothalamic PVN. Therefore, antagonists of the ADH receptor V1b have been developed and tested in rodents as potential new strategies for the treatment of affective disorders, whose efficacy in humans does still need clarification.

Hypothalamic-Pituitary-Adrenal Axis Dysregulation

The onset, symptom severity, and the course of MDD is closely associated with psychosocial stressors. Since the HPA axis is crucially involved in the stress response, its hyperactivity has been investigated as a maintaining factor of MDD. As known, the CRH released from the hypothalamus stimulates the secretion of the ACTH from the anterior pituitary gland, and eventually the release of cortisol into the blood from the adrenal cortex. Cortisol levels show a peak in the first 30–40 min after awakening and then gradually decrease during the day, in line with a normal circadian rhythm associated with the sleep-wake cycle. Psychological or physical stressors result in HPA hyperactivity, thereby increasing plasma cortisol levels. Interestingly, individuals with depression show hypercortisolism either basal or in response to stress or after awakening, similarly to other psychiatric diseases, such as schizophrenia and BD. It has been indeed proposed that cortisol receptor antagonists and cortisol synthesis inhibitors, such as methirone, aminoglutethimide, or ketoconazole, can also be used effectively in the treatment of major depression. HPA-axis hyperactivity was also observed among the offspring of depressed patients, suggesting that it could partly reflect a marker of genetic vulnerability or an endophenotype of depression. Alterations of mineralocorticoid and glucocorticoid receptors, which act as transcriptional factors, can lead to chronic activation of the stress response resulting in atrophy of the hippocampal neurons, reduced neurogenesis and synaptic plasticity, and altered monoaminergic signaling: these alterations may lead to a depressive state. Other authors have studied the altered sensitivity of the hypothalamus to feedback signals (such as the dexamethasone suppression) in depressed patients: they found, at least in the most severe cases (depression with psychotic symptoms), a reduced or absent response to cortisol suppression.

The dysregulation of the HPA axis could be responsible for the cardiovascular somatic symptoms of depression (e.g., hypertension, tachycardia) and has also been associated with other medical conditions such as hypertension, high lipids, insulin resistance, and obesity. It is known that patients with HF have high circulating corticosteroids due to neuroendocrine activation. Higher serum and salivary levels of both cortisol and aldosterone are independent, complementary, and incremental predictors of all-cause mortality risk in patients with systolic and nonsystolic

chronic or acute HF of any cause and severity. Aldosterone participates in numerous detrimental processes that lead to HF progression such as inflammation, fibrosis, endothelial dysfunction, hypertrophy, hypertension, and arrhythmia. Cortisol acts primarily through the glucocorticoid receptor: mineralocorticoid receptor has equal affinity for both cortisol and aldosterone, but since cortisol concentrations are 100 to 1000 times higher than aldosterone, it is hypothesized that the mineralocorticoid receptor is predominantly occupied from cortisol in those tissues that are not classically a target of aldosterone such as cardiac muscle. Generally, cortisol acts as a mineralocorticoid receptor antagonist, but in HF, there is a high cellular oxidative stress and cortisol can act as a mineralocorticoid receptor agonist. Chronic hypercortisolism, as in Cushing's syndrome, can have deleterious cardiovascular effects and affected patients often develop central obesity, hypertension, and diabetes mellitus, in turn cardiovascular risk factors. Antagonists of mineralocorticoid receptors (such as spironolactone or eplerenone), used in the treatment of patients with HF, effectively reduce adverse cardiac remodeling and hospitalization, with improved survival.

Neurotrophins

Neurotrophins (NTs) are a large family of dimeric polypeptides that include four similar proteins: nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT-3), and neurotrophin 4/5 (NT-4/5). The activity of these factors has been implicated in axonal growth, synaptic plasticity, survival, differentiation, and myelination. BDNF in the brain is active in the hippocampus, cortex, and basal forebrain areas, vital to learning, memory, and higher thinking.

It has been shown that serum/plasma levels of BDNF are lower in patients with MDD than in healthy controls and increase in response to antidepressant treatment or ECT. Therefore, BDNF can be considered as state rather than a trait marker of MDD. A possible pathogenetic theory correlates chronic stress with BDNF; chronic stress is an environmental trigger of several psychiatric disorders, including depression. It is demonstrated that chronic stress has neurotoxic effects, including damage to hippocampal cells that may underlie symptoms of depression. Also, several studies reported a correlation between polymorphisms of BDNF and depression. The rs6265 G/A variant, in which a valine changes to a methionine in position 66 of the BDNF protein (Val66Met), is related to a higher risk of depression: individuals with the Val/Val (G/G) genotype have a stronger depressive trait [39]. However, more recently, the Val66Met variant was found to correlate not to MDD risk per se, but with late-life depression. Plausibly, Val66Met in the BDNF gene predicts the response to antidepressants in MDD, in fact serum plasma levels of BDNF in patients with MDD increase after antidepressant treatment or ECT.

In addition to its important role in the CNS, there is increasing evidence that BDNF is also involved in cardiovascular development and pathophysiology. BDNF is known to play a protective role in the heart by inducing angiogenesis and vascular remodeling, by the upregulation of pro-survival factors, and by promoting the neovascularization of ischemic tissue by recruiting endothelial cells and regulating the survival of cardiomyocytes. BDNF and its receptors are expressed in various tissues, including the heart, endothelial cells, macrophages, vascular smooth muscle cells, and atherosclerotic coronary arteries. Recent studies showed BDNF to have a regulatory impact on cardiac progenitor cells, contribute to cardiac repair and attenuate cardiac dysfunction [40]. Moreover, in a recent investigation, plasma BDNF concentration was found to be negatively associated with the levels of triglyceride, LDL-cholesterol and fibrinogen, presence of diabetes mellitus, male sex and age, and positively with high-density lipoprotein cholesterol (HDL) level and platelet count in people with angina pectoris [41]. Consequently, it seems that a higher serum level of BDNF can be associated with a lower risk of CVD. Carriers of the Val66Met variant have higher BMI and CRP levels than Met carriers.

Lifestyle and Metabolic Syndrome

The association between depression and CVD is thought to be mediated the so-called metabolic syndrome, encompassing obesity, diabetes, hypertension, and dyslipidemia. The exact mechanisms linking depression and metabolic syndrome remain largely unclear. Some suggest that metabolic syndrome could represent the outcome of many unhealthy lifestyle habits of depressed patients, such as poor diet, physical inactivity, tobacco and alcohol use. Indeed, adjusting for lifestyle-related factors reduced the association between depression and adverse lipoprotein patterns (lower HDL level and higher triglyceride level). Depressed patients are more prone to inadequate diets that are often characterized by an excessive intake of highly palatable food with high content of sugar, starches, and fat, and a low consumption of fish, vegetables, and cereals. A protective potential against depression is yielded by the adherence to the Mediterranean dietary pattern, which improves endothelial function, decreases pro-inflammatory cytokines, reduces plasma homocysteine levels, and induces favorable changes in insulin/glucose homeostasis. The high content in fruits, nuts, vegetables, beans, cereals, olive oil, and fish, and the low content in meat and dairy products, ensures the adequate intake of nutrients with a key role in the CNS. Vitamins B6 and B12, together with folic acids, are fundamental in the homocysteine cycle. Their deficit may impair the synthesis of catecholamines, serotonin, and other monoamine neurotransmitters. Moreover, it determines an accumulation of homocysteine and its metabolites, with excitotoxic effect on NMDA glutamate receptors. Additionally, fish consumption, rich in v3-polyunsaturated fatty acids (v3-PUFA), seems to inhibit the synthesis of pro-inflammatory cytokines, particularly TNF-α and IL-β. Olive oil is a good source of monounsaturated fatty acids (MUFAs, oleic acid), which have antioxidant properties, increase the d-9 desaturase enzyme activity, crucial for the properties of neuronal membranes, and improve the binding of serotonin to its receptor. A recent line of research suggests that dietary barley (1.3) beta-D-glucan (β-D-glucan), a water-soluble polysaccharide, increases the levels of histone H4 acetylation, thereby ameliorating glucose tolerance, mood, anxiety, and cognition in obese mice exposed to chronic psychosocial stress. This is accompanied by the upregulation of the hippocampal BDNF and its receptor, the tropomyosin-related kinase B TrkB [42].

Also, a sedentary lifestyle and a negative self-perception due to the stigmatization of obesity could lead to an increased risk of depression. Growing evidence suggests that exercise reduces depressive symptoms in CVD patients, especially aerobic exercise, which seems to be effective by the end of a 16-week intervention. Exercise may be effective in part because it involves behavioral activation, a key component of cognitive-behavioral therapy (CBT) for depression. Exercise has well-documented cardiovascular benefits. Exercise training is associated with several beneficial physiologic changes, such as improvements in ANS and HPA-axis functioning, endothelial function, hypertension, dyslipidemia, insulin resistance, and inflammation. Exercise affects depression, CVD risk factors, and CVD outcomes so that it seems a promising intervention for depression, together with good dietary habits. Furthermore, exercise has been proven to revert the downregulation of the BDNF/TrkB signaling in the prefrontal cortex of obese male mice [43].

Increased smoking and alcohol consumption are well documented in depression. Park and Lee reported that current smokers are 3.99 times more likely to suffer from depression than those who had never smoked. In addition, depressed people smoke more cigarettes and are less likely to quit smoking. Nicotine might cause depression through direct or indirect influences on neurotransmission (noradrenergic neurotransmission and/or hippocampal BDNF). Alcohol consumption is associated with an increase in the prevalence of depression as well, particularly in women in relation to reduced alcohol tolerance, as compared to men. It is biologically plausible that alcohol can act as a depressant of the CNS;

reciprocally, depression itself can induce alcohol consumption.

However, some authors reported that the association between (i) low HDL cholesterol and melancholic depression, and (ii) high total and LDL cholesterol and atypical depression, remained even after adjusting for covariates. A hypothesis is that depression and metabolic syndrome would share common pathophysiologic mechanisms, such as the above described alterations of the stress system, including the HPA-axis, the ANS, the immune system, and platelet and endothelial function.

From an epidemiological perspective, obese subjects (defined as high BMI or high abdominal circumference) are 55% more likely to develop depression over time. Like depression, obesity can be viewed as a low grade inflammatory state. The white adipose tissue, especially in the abdominal area, is an active endocrine organ that produces cytokines with paracrine functions, such as TNF-α, resistin, IL-6, and CRP. IL-6 and TNF-α have important effects in glucose and lipid metabolism and regulation, such as: (i) inhibition of the action of lipoprotein lipase and stimulation of lipolysis, leading to dyslipidemia; (ii) phosphorylation of both the insulin receptor and its substrate, IRS-1, leading to impairment of the insulin signaling pathway. Elevated levels of IL-6 and TNF-α may be responsible for alterations in vasodilation of resistance vessels and ultimately hypertension, by inducing endothelial expression of chemokines and adhesion molecules. Furthermore, adipocytes secrete leptin, a hormone which acts at the hypothalamic level as an anorexigenic signal. Leptin has been shown to influence hippocampal and cortical structure through its actions on neurogenesis, axon growth, synaptogenesis, and regulation of dendritic morphology. Leptin-deficient mice (ob/ob), jointly with an obese phenotype, exhibit neurodegenerative changes – lower brain weight and cortical volume, and reduced expression of total neuronal and glial proteins – which can be rescued by leptin replacement [44]. Animal models of chronic stress posit an antidepressant-like role for leptin [44]. Also, more depressive behaviors were observed in diet-induced obese mice fed a high-fat diet, with respect to a control diet. However, in this model leptin seemed to lose its antidepressant-like effect: only diet substitution from high-fat diet to control diet improved the depressive state [45]. This in in line with the hypothesis that depressed people, similarly to obese people, although having high circulating levels of leptin in proportion to their greater fat mass, might develop a resistance to the effects of leptin. Intriguingly, leptin could modulate the synaptic availability of 5-HT and dopamine, neurotransmitters classically involved in depression, given the high proportion of 5-HT and dopamine neurons, respectively, in the raphe nuclei and in the VTA, which express leptin receptors. Another peripheral hormone participating in either homeostatic or stress-induced feeding behavior is ghrelin, a gut-derived orexigenic hormone, acting at the level of its receptors (GHSR) in the hypothalamic circuits. Evidence has emerged about the role of ghrelin in depression: (i) elevated levels of ghrelin were observed in animal models of depression; (ii) peripheral administration of ghrelin to wild-type animals reverted depressive behavior; (iii) Ghrs-null mice exhibited more depressive-like symptoms than wild-type littermates. Interestingly, wild-type mice, but not Ghrs−/− mice, showed hyperphagia in response to social stress [46]. The activation of ghrelin signaling pathways in response to chronic stress could represent a homeostatic adaptation that helps an individual coping with stress, but at the expense of increased caloric intake. Of note, ghrelin cells are stimulated by stress-induced catecholamines. As described for leptin, ghrelin has emerged as a potent modulator of the mesolimbic dopaminergic circuits.

Moreover, depression is in turn predictive of the development of obesity through long-term activation of the HPA axis, as cortisol inhibits the enzymes mobilizing lipids in the presence of insulin, a process mediated by glucocorticoid receptors found in fat stores, especially in intra-abdominal visceral fat.

Identification and Treatment of Depression in Patients with CVD

The American Heart Association recommends that CVD patients are routinely screened for depression. The answers to two simple questions – "*During the past month, have you often been bothered by feeling down, depressed, or hopeless?*" and "*During the past month, have you often been bothered by little interest or pleasure in doing things?*" – yield a 90% sensitivity and 69% specificity and a negative likelihood ratio of 0.14, essentially ruling out depression. Alternately, instruments with good diagnostic characteristics, such as the depression module of the Patient Health Questionnaire (PHQ-9), can be introduced in the routine vital sign gathering of CVD patients. Notwithstanding this, in general practice depression is recognized and diagnosed in less than 25% of patients with CVD, the remaining being at risk of more severe clinical outcomes.

Diagnosis should be then followed by initiation of an adequate antidepressant treatment. Effective treatments for depression in CVD include pharmacological (antidepressant medications), nonpharmacological somatic (e.g., ECT), and evidence-based psychotherapeutic strategies (e.g., CBT, interpersonal therapy [IPT]). Current guidelines for antidepressant treatment suggest 6–12 weeks of acute treatment followed by a continuation phase of 3–9 months to maintain therapeutic benefit. However, antidepressant drugs are associated with a potential for cardiac toxicity, often related to the presence of preexisting cardiac disease or other factors that might independently increase the risk of arrhythmia. The cardiovascular safety profile will be specifically discussed for the different classes of antidepressants.

SSRIs, such as citalopram, sertraline, and paroxetine, are recommended as first-line drug therapy, due to their effectiveness, safety profile, cost-effectiveness, and best supporting data in CVD populations. Among them, sertraline has been the most commonly studied and is often considered to be the first-line drug of choice in patients with ischemic heart disease. At therapeutic doses, the most common side effects of SSRIs are sexual dysfunction and weight gain. Also, adverse effects might be generated from the inhibition of the 2D6 isoenzyme of the cytochrome P-450 by fluoxetine and paroxetine. SSRIs are unlikely to be associated with cardiovascular adverse events. Nonetheless, there are reports of orthostatic hypotension, mild bradycardia, and conduction abnormalities under SSRIs therapy. Some SSRIs, such as citalopram and escitalopram, are known to cause a dose-dependent QTc prolongation. Therefore, their use should be accompanied by QTc monitoring and avoided in presence of QTc prolongation. In a large population of CVD patients, major adverse cardiac events have been reported to be 1.5-fold more common in patients taking SSRIs. Since SSRIs are known to alter platelet activation and aggregation leading to impairment in hemostasis, their use could potentially increase the risk of perioperative bleeding, transfusion, morbidity, and mortality in cardiac surgical patients. However, a recent study found no significant differences in perioperative outcomes between patients under SSRIs and matched controls and concluded that SSRIs interruption to reduce the risk of perioperative bleeding and transfusion is unwarranted to and may risk destabilization of patients' psychiatric condition.

Second-line therapy for depression includes SNRIs, trazodone, mirtazapine, and bupropion. SNRIs seem able to increase sympathetic tone, with consequent modest increase of heart rate, increase of arterial pressure, and increase of sympathetic influence on the HRV. Venlafaxine could block the cardiac conductance of the sodium channel and at toxic doses could increase the systemic blood pressure and cause a QTc prolongation. Duloxetine has been less studied, and no clear indications are given in relation to CVD. Although a study of a large population of CVD patients found fewer adverse cardiac events than expected in patients taking SNRIs, caution is required in geriatric populations. Bupropion and mirtazapine are often used in clinical practice, but remain largely unstudied. Aside the risk of hypertension, bupropion was found to be safe in patients with cardiac conduction disease and left ventricular systolic dysfunction. Mirtazapine has

been noted to cause weight gain and increased body fat mass, but no association with CVD was found.

TCAs and monoamine oxidase inhibitors are contraindicated in CVD patients. In a large population of CVD patients, major adverse cardiac events occurred with 2.5 times higher frequency in patients under TCAs. TCAs can cause significant inhibition of central cholinergic neurotransmission and reduced neuronal reabsorption of norepinephrine, which cause alterations in the sympathovagal balance. TCAs also block alpha-adrenergic receptors, reducing systemic vascular resistance and causing (orthostatic) hypotension. TCAs also inhibit the conductance of the sodium channel, resulting in slower conduction within the His fibers-Purkinje and of the ventricular myocardium and in prolongation of the QRS.

Although pharmacologic-based approaches to treat depression have a significant beneficial impact on platelet/endothelial activation markers, inflammation, and sympathovagal balance, trials of antidepressant pharmacotherapy in patients with CVD failed to demonstrate a clear impact on cardiovascular events and outcomes. On the other hand, randomized and observational trials showed that pharmacotherapy for depression might decrease the risk of future cardiovascular events.

Nonpharmacological somatic therapies are often useful in clinical practice to treat severe form of depression or drug-resistant depression; among them ECT is one of the most effective. The ECT is associated with significant changes in cardiovascular physiology and has a significant implication in patients suffering from a CVD. The ECT causes a generalized seizure activity, which induces an initial parasympathetic activity, that coincides with the tonic phase of the seizure, followed by a generalized sympathetic activity, associated with catecholamine release during the clonic phase. The double activation of the two branches of the ANS has a significant hemodynamic impact. Due to the sympathetic discharge, tachycardia and hypertension may develop. The sudden increase of the rate/pressure product may place the myocardium at risk for ischemia by a sudden increase in myocardial oxygen consumption. Despite this, ECT is administered safely even in patients with cardiac risk factors, although it is generally recommended to wait for a period of 90 days following an acute coronary event to initiate ECT.

To maximize improvements in health outcomes and quality of life, CVD patients with depression may benefit most from interventions that simultaneously target both depression and cardiovascular risk factors. Studies about non-pharmacological treatment of depression and CVD are relatively small and the findings are equivocal. In a recent review and meta-analysis, CBT resulted more effective than usual care at improving depression and quality of life in patients with HF. It was demonstrated that CBT-based interventions reduced ischemia and prevented cardiac events in the following months [47]. It is also possible that other psychosocial interventions, such as IPT, may prove to be effective, but further research is needed to address these questions.

Finally, collaborative care models emerged in several studies as promising interventions to ameliorate depression, mental health status, medication adherence, cardiac risk factors (cholesterol and blood pressure), and cardiac symptoms.

Conclusions

In 1628, William Harvey, the pioneer of blood circulation, warned that mental suffering and anxiety could disturb the heart and the circulatory system. For him, “The heart of animals is the foundation of their life, the sovereign of everything within them, the sun of their microcosm, that upon which all growth depends, from which all power proceeds.” The symbolism of myth, poetry and holy has put the heart at the center of the body, as the headquarter of the mental and spiritual life in humans. The link between the heart and emotions is also revealed by transcultural linguistic expressions, such as “sick at heart,” “heartbroken,” or by the depressed patients frequently complaining of pain in their chest. Here, we showed that the relationship between brain and heart, far from being just metaphorical, lies in a

psycho-neuro-hormonal-cardiovascular axis. We described the overlapping pathophysiological mechanisms involved in the association between depression and CVD, which include inflammation, platelet reactivity, autonomic dysregulation, circadian rhythm and sleep disruption, hormone imbalance, neurotrophins, lifestyle, and metabolic syndrome. We strongly recommend physicians to explore depressive symptoms in people with CVD and to assess the cardiovascular function in subjects presenting with depression. Interventions that simultaneously target both depression and cardiovascular risk factors might indeed substantially improve health outcomes and quality of life.

References

1. Chauvet-Gelinier JC, Bonin B. Stress, anxiety and depression in heart disease patients: a major challenge for cardiac rehabilitation. Ann Phys Rehabil Med. 2017;60(1):6–12.
2. Penninx BW. Depression and cardiovascular disease: Epidemiological evidence on their linking mechanisms. Neurosci Biobehav Rev. 2017;74(Pt B):277–86.
3. Whooley MA. Depression and cardiovascular disease: healing the broken-hearted. JAMA. 2006;295(24): 2874–81.
4. Bradley SM, Rumsfeld JS. Depression and cardiovascular disease. Trends Cardiovasc Med. 2015;25(7): 614–22.
5. Grace SL, et al. Prospective examination of anxiety persistence and its relationship to cardiac symptoms and recurrent cardiac events. Psychother Psychosom. 2004;73(6):344–52.
6. Dickens C, Creed F. The burden of depression in patients with rheumatoid arthritis. Rheumatology (Oxford). 2001;40(12):1327–30.
7. Bonaccorso S, et al. Depression induced by treatment with interferon-alpha in patients affected by hepatitis C virus. J Affect Disord. 2002;72(3):237–41.
8. Harrison NA, et al. Inflammation causes mood changes through alterations in subgenual cingulate activity and mesolimbic connectivity. Biol Psychiatry. 2009;66(5): 407–14.
9. Goldsmith DR, Rapaport MH, Miller BJ. A meta-analysis of blood cytokine network alterations in psychiatric patients: comparisons between schizophrenia, bipolar disorder and depression. Mol Psychiatry. 2016;21(12):1696–709.
10. Carvalho LA, et al. Lack of clinical therapeutic benefit of antidepressants is associated overall activation of the inflammatory system. J Affect Disord. 2013;148(1): 136–40.
11. Brydon L, Magid K, Steptoe A. Platelets, coronary heart disease, and stress. Brain Behav Immun. 2006;20(2):113–9.
12. Parakh K, et al. Platelet function in patients with depression. South Med J. 2008;101(6):612–7.
13. Leake A, et al. Studies on the serotonin uptake binding site in major depressive disorder and control postmortem brain: neurochemical and clinical correlates. Psychiatry Res. 1991;39(2):155–65.
14. Owens MJ, Nemeroff CB. Role of serotonin in the pathophysiology of depression: focus on the serotonin transporter. Clin Chem. 1994;40(2):288–95.
15. Hrdina PD, et al. 5-HT uptake sites and 5-HT2 receptors in brain of antidepressant-free suicide victims/depressives: increase in 5-HT2 sites in cortex and amygdala. Brain Res. 1993;614(1–2):37–44.
16. Stain-Malmgren R, et al. Serotonergic function in major depression and effect of sertraline and paroxetine treatment. Int Clin Psychopharmacol. 2001;16(2):93–101.
17. Hrdina PD, et al. Serotonergic markers in platelets of patients with major depression: upregulation of 5-HT2 receptors. J Psychiatry Neurosci. 1995;20(1):11–9.
18. Hrdina PD, et al. Platelet serotonergic indices in major depression: up-regulation of 5-HT2A receptors unchanged by antidepressant treatment. Psychiatry Res. 1997;66(2–3):73–85.
19. Serebruany VL, et al. Platelet/endothelial biomarkers in depressed patients treated with the selective serotonin reuptake inhibitor sertraline after acute coronary events: the Sertraline AntiDepressant Heart Attack Randomized Trial (SADHART) Platelet Substudy. Circulation. 2003;108(8):939–44.
20. van Zyl LT, et al. Platelet and endothelial activity in comorbid major depression and coronary artery disease patients treated with citalopram: the Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy Trial (CREATE) biomarker substudy. J Thromb Thrombolysis. 2009;27(1):48–56.
21. Zhang LJ, et al. Psychocardiological disorder and brain serotonin after comorbid myocardial infarction and depression: an experimental study. Neurol Res. 2018;40:1–8.
22. Cooper DC, et al. Depressed mood and flow-mediated dilation: a systematic review and meta-analysis. Psychosom Med. 2011;73(5):360–9.
23. van Sloten TT, et al. Endothelial dysfunction is associated with a greater depressive symptom score in a general elderly population: the Hoorn Study. Psychol Med. 2014;44(7):1403–16.
24. Felice F, et al. Influence of depression and anxiety on circulating endothelial progenitor cells in patients with acute coronary syndromes. Hum Psychopharmacol. 2015;30(3):183–8.
25. Licht CM, et al. The association between depressive disorder and cardiac autonomic control in adults 60 years and older. Psychosom Med. 2015;77(3):279–91.
26. Porges SW. The polyvagal theory: phylogenetic substrates of a social nervous system. Int J Psychophysiol. 2001;42(2):123–46.

27. Kemp AH, Quintana DS. The relationship between mental and physical health: insights from the study of heart rate variability. Int J Psychophysiol. 2013;89(3):288–96.
28. Schwartz S, et al. Insomnia and heart disease: a review of epidemiologic studies. J Psychosom Res. 1999;47(4):313–33.
29. Deng HB, et al. Short sleep duration increases metabolic impact in healthy adults: a population-based cohort study. Sleep. 2017;40(10):zsx130.
30. Hall MH, et al. Self-reported sleep duration is associated with the metabolic syndrome in midlife adults. Sleep. 2008;31(5):635–43.
31. Vgontzas AN, et al. Short sleep duration and obesity: the role of emotional stress and sleep disturbances. Int J Obes. 2008;32(5):801–9.
32. Mezick EJ, Hall M, Matthews KA. Are sleep and depression independent or overlapping risk factors for cardiometabolic disease? Sleep Med Rev. 2011;15(1):51–63.
33. Motivala SJ, et al. Inflammatory markers and sleep disturbance in major depression. Psychosom Med. 2005;67(2):187–94.
34. Rudic RD, et al. BMAL1 and CLOCK, two essential components of the circadian clock, are involved in glucose homeostasis. PLoS Biol. 2004;2(11):e377.
35. Shimba S, et al. Deficient of a clock gene, brain and muscle Arnt-like protein-1 (BMAL1), induces dyslipidemia and ectopic fat formation. PLoS One. 2011;6(9):e25231.
36. Yang X, et al. Nuclear receptor expression links the circadian clock to metabolism. Cell. 2006;126(4): 801–10.
37. de Kloet AD, et al. A unique "Angiotensin-Sensitive" neuronal population coordinates neuroendocrine, cardiovascular, and behavioral responses to stress. J Neurosci. 2017;37(13):3478–90.
38. Rutigliano G, et al. Peripheral oxytocin and vasopressin: biomarkers of psychiatric disorders? A comprehensive systematic review and preliminary meta-analysis. Psychiatry Res. 2016;241:207–20.
39. Licinio J, Dong C, Wong ML. Novel sequence variations in the brain-derived neurotrophic factor gene and association with major depression and antidepressant treatment response. Arch Gen Psychiatry. 2009;66(5):488–97.
40. Samal R, et al. Brain derived neurotrophic factor contributes to the cardiogenic potential of adult resident progenitor cells in failing murine heart. PLoS One. 2015;10(3):e0120360.
41. Tasci I, Kabul HK, Aydogdu A. Brain derived neurotrophic factor (BDNF) in cardiometabolic physiology and diseases. Anadolu Kardiyol Derg. 2012;12(8):684–8.
42. Agrimi J, et al. Long term intake of barley beta-D-glucan attenuates glucose intolerance, mood disorders and cognitive decline in high-fat diet-induced obese mice exposed to chronic psychosocial stress. The FASEB J. 2017;31(1_supplemet):lb1–1091.2
43. Baranowski B, Peppler WT, MacPherson REK. Acute exercise rescues cortex BDNF signaling in high fat fed male mice. The FASEB J. 2017;31(1_supplement): lb1–1091.2
44. Lu XY. The leptin hypothesis of depression: a potential link between mood disorders and obesity? Curr Opin Pharmacol. 2007;7(6):648–52.
45. Yamada N, et al. Impaired CNS leptin action is implicated in depression associated with obesity. Endocrinology. 2011;152(7):2634–43.
46. Lutter M, et al. The orexigenic hormone ghrelin defends against depressive symptoms of chronic stress. Nat Neurosci. 2008;11(7):752–3.
47. Jeyanantham K, et al. Effects of cognitive behavioural therapy for depression in heart failure patients: a systematic review and meta-analysis. Heart Fail Rev. 2017;22(6):731–41.

Bipolar Disorder

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Risk for Cardiovascular Disease?

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Contents

Abstract

In recent years, epidemiologic research has consistently documented a significant clustering of medical and psychiatric conditions. In most cases, this comorbidity has been shown to enhance morbidity, loss of quality of life, and mortality, presenting a considerable challenge to clinical management, interdisciplinary communication, and healthcare costs. On the other hand, recognizing unique patterns of association between medical and psychiatric illnesses has born the chance of shading a new light on the mechanisms underpinning both kinds of morbidity.

The relationship between cardiovascular diseases (CVDs) and mood disorders (MDs) is one that gained growing interest in the last decades. In many instances, MDs were considered consequential to CVDs, especially when depression was involved. However, research has also begun to test the hypothesis that a common underlying process might be linking together CVDs and MDs, which may likely be the case of bipolar disorder (BPD). However, a third possibility may also hold true: BPD may increase the risk of developing CVDs, either directly or promoting the development of classical cardiovascular risk factors. Whatever is the case, it seems unlikely that the association between CVDs and BPD merely represents the co-occurrence of two

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*,
https://doi.org/10.1007/978-3-030-28008-6_22

simultaneous but independent conditions. From this perspective, the present chapter aims to review and summarize recent knowledge on the relationship among BPD and CVDs, devoting special attention to factors that may contribute to both diseases, as manifestations of a complex, systemic pathological process.

Keywords

Bipolar disorder · Mood disorders · Cardiovascular disease · Coronary heart disease · Pathophysiology · Behavioral risk factors · Cardiovascular risk factors

Introduction

CVDs are the leading cause of death worldwide. According to the World Health Organization, 17.7 million people died from CVDs in 2015, the equivalent of one third of all global deaths, with coronary heart disease (CHD) accounting for at least 40% of these deaths [1]. Mental disorders are also notable contributors to global burden of disease and are expected to become the leading cause of disability in the next two decades [2, 3]. Overall, they account for about 7.4% of disease burden and for approximately 14.3% of all deaths worldwide. Despite BPD is relatively rare compared to other mental conditions, with 48.8 million estimated cases globally, it ranked in the top 20 leading causes of disability worldwide in 2013, accounting for 5.7% of the burden due to mental and substance use disorders.

According to the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5) [4], BPD is a chronic mood disorder, defined by the recurrence of one or more manic or hypomanic episodes, which can be accompanied by a major depressive episode. A manic episode is characterized by elevated, expansive, or irritable mood for at least 1 week, while a hypomanic episode is characterized by symptoms of a manic episode which are less severe for at least 4 days. A major depressive episode is characterized by depressed mood for at least 2 weeks [4]. Prevalence estimates of all type BPD range from 1.8% to 3.9%, with higher estimates (between 2.7% and 5.9%) reported among young adults [4, 5]. The age of onset for BPD varies across countries. Approximately one third of the subjects in European countries and more than a half in the USA have an early onset, namely, below the age of 19 years, while the majority of cases in Europe and one third in the USA have onset during 20s or later [6]. The focus on specific age ranges is particularly important with respect to the prognostic significance, since it has been shown that cases with an early onset tend to have a poor outcome for what concerns number of episodes, impairment in global functioning, therapy response, and psychiatric and medical comorbidities.

Epidemiology of the Comorbidity Between BPD and CVDs

Among mental diseases, BPD represents the one with the higher prevalence of medical comorbidities [7], overall occurring in up to 80% of BPD patients [3] and mainly including CVDs, diabetes mellitus, obesity, hypertension, autoimmune disorders, and thyroid dysfunction [8]. In the framework of this heterogeneous range of physical comorbidities, CVDs – as well as pathological conditions favoring them, such as hypertension, metabolic syndrome (MetS), and obesity – are strongly prevalent and potentially avoidable as contributors to premature death [9]. A recent meta-analysis involving more than three million subjects with severe mental illnesses, including BPD, found a CVD prevalence of 8.4% among BPD patients. While CVDs were not significantly associated with BPD in cross-sectional studies, they were so in longitudinal ones, with a hazard ratio of 1.57. However, no association was found with coronary heart disease (CHD) [10]. Consistently, in a more recent nationally representative cohort study involving more than 17,000 subjects with BPD from 2000 to 2014, a significant hazard ratio of 1.41 for CVDs was found compared with the general population. Importantly, smoking, hypercholesterolemia, hypertension, BMI, and diabetes mellitus did not

fully explain the increased rates, with a still significant hazard ratio of 1.26 after adjustment for these confounders. Moreover, especially in the years after 2010, the elevated CVD risk translated into increased mortality for CVDs with a hazard ratio of 1.77 relative to the general population comparison group [9]. Importantly, the association with CVD might be stronger in BPD than in other mood spectrum disorders. Indeed, a recent prospective study comparing the 3-year incidence of CVDs in patients suffering from BPD or major depressive disorder (MDD) found an almost threefold risk of new-onset CVDs in patients with BPD and a twofold risk in the MDD group compared with healthy subjects, with a significant difference between BPD and MDD groups as well [11].

It has been widely described that patients suffering from BPD show a critically reduced life expectancy. In some recent studies this reduction has been quantified in about 10 years if compared to general population, clearly indicating that people with BPD are at high risk of premature death [7, 12]. Noteworthy, unnatural death causes, namely, suicide and accidents, play an important but minor role, while the medical comorbidities justify most of the aforementioned life-year loss [13]. Strong evidences indicate that CVDs are the leading cause of death among people with BPD, both in clinical and epidemiological samples. In a recent population-based study in Sweden, 38% of BPD subjects died by CVDs, while unnatural deaths accounted for only 18%. Mortality rate ratio for CHD and acute myocardial infarction (MI) were twice as high in persons with BPD compared to the general population [13]. Moreover, if mortality rate ratio was increased for patients with BPD across all ages, it was particularly pronounced in the young age groups, and death for MI, CHD, and cerebrovascular disease was shown to occur significantly earlier in BPD patients than in the general population. Interestingly, later data derived from the same Sweden cohort indicate that despite the mortality due to CVDs decreased between 1987 and 2010 in both the general population and people with severe mental illness, the relative excess of mortality in the latter group remained unchanged, with BPD showing the thinner decline compared to schizophrenia and MDD [14]. Noteworthy, in studies with a focus on early adulthood, it has been observed an even higher risk-gap, with a standardized mortality ratio that reaches 8 among BPD patients younger than 40 [1]. This suggests that people suffering from BPD are not only more likely to develop CVDs but may also begin earlier to suffer from it. More specifically, the prospective study quoted above quantified the gap between the mean age of the participants with or without a BPD at the onset of CVD in 17 years [15]. Accounting for these data, a statement by the American Heart Association (AHA) included juvenile BPD among the moderate risk conditions associated with accelerated atherosclerosis and early CVD. In this framework, the AHA statement highlighted a necessity for increasing awareness about the clinical and epidemiological relevance of this association, as well as for the systematic risk assessment and management. This point is of overwhelming importance if we consider that while BPD usually onsets in a young age, patients suffering from BPD who develop a CVD showed a poor prognosis for both the psychiatric and the cardiovascular condition [11].

Possible Reasons for Excessive and Premature CVDs Among BPD Sufferers

The growing epidemiological and clinical evidence of the strong association between BPD and CVD has encouraged to deepen the inquiry into the etiology and pathophysiology of this link, that could be seen as a prototypical bond between psychiatric condition and medical comorbidity [16]. Even though the results of observational studies do not imply causality, they prove solid ground to hypothesize that mood disorder spectrum is related to a highly significant increase in CVD risk.

The vascular-bipolar link has often been traced back to the clustering of a number of traditional risk factors, such as hypertension, obesity, diabetes, smoking, sedentary lifestyle, and substance use, which usually affect patients suffering

from BPD. At the same time, this approach has been challenged by some studies, consistently enlightening the fact that the increase of CVD risk is higher than that which one would expect if only the aforementioned risk sources were involved [17]. This point granted, considering the risk-gap merely as consequence of medications and unhealthy lifestyle would definitely be an understatement. Accordingly, recent findings from studies conducted on young BPD patients indicate that the development of medical comorbidities is precocious and that the increase of risk is detectable also in patients who have never been treated and have been exposed to traditional risk factors just for a short time span [18, 19]. As a matter of fact, despite it has been clearly demonstrated that metabolic side effects of psychopharmacological treatment play a significant role in CVD risk [20], it has to be taken into account that weight gain and impairment in glucose metabolism may occur also in treatment-naive patients [21]. On the other hand, it is noteworthy that an increase in CVD risk has been found also in the relatives of bipolar patients who have no mood disorders, clearly drawing the attention onto a genetic perspective [22, 23]. In this framework, the high quota of medical comorbidities in patients with BPD represents a milestone for increasing integration of psychiatry and medicine [24].

All this makes it crucial to clarify the biological processes that underlie the BD-CVD association, to define the directionality of this link, and to identify the pathophysiologic features shared by BPD and medical comorbidities.

Pathophysiological Factors

Currently, several aspects of the BPD etiopathology remain partially understood, although different perspectives of research coexist: on one hand, there are models highlighting the key role of systemic imbalances in inflammation, mitochondrial dysfunction, and neurotrophic factors; on the other, there are brain-focused models pinpointing abnormalities in neural function and neurochemistry [16]. Furthermore, a link between systemic processes and brain alterations in BPD has emerged in recent studies, which investigated whether the mentioned alterations are the result of a common diathesis, or rather represent a physiopathological bridge between mental illness and medical comorbidities – and, if the latter is the case, it is also necessary to clarify the directionality of this link [25, 26]. A list of some of the physiopathological mechanisms detected in BD and potentially involved in the pathogenesis of medical comorbidities follows [11]: abnormalities of HPA axis functioning; adrenal medulla hyperactivity; autonomic dysfunction; increased platelet activation; endothelial dysfunction; abnormalities in neurotrophic factors, such as BDNF; genetic aspects; inflammation; and oxidative stress. Among these several mechanisms, however, excessive inflammation and oxidative stress have been assumed to be two of the main links between BD and CVD, since both pathologies present similar association with these physiopathological alterations [19]. Accordingly, in what follows we shall expand on these two issues.

Inflammation

The role of inflammation in the pathogenesis and course of mood disorders has gained great interest in the last two decades. In this respect, it is important to mention the macrophagic theory of depression [27], which was formulated with the aim to provide a systematic framework to the existing evidence of a role of the cytokines in the generation of depressive symptoms. On the other hand, it is well-known that inflammation has a causal role in neuronal damage, neurodegeneration [28], and adverse changes in neurotransmitter metabolic pathways, such as a decrease in the availability of tryptophan [29, 30]. Consistently, further studies have detected increased cytokine levels in the serum and in cerebrospinal fluid of patients suffering from mood disorder [31, 32]: the levels of inflammatory mediator were correlated to the symptomatic burden and to cognitive impairment [33]. Indeed, recent large meta-analyses have confirmed the existence of pro-inflammatory imbalance during symptomatic episodes of BPD with higher levels

of pro-phlogistic cytokines (IL-2, IL-6; IL-4; TNF) and elevation of acute-phase protein, such as C-reactive protein (CRP), among patients compared to healthy controls [34]. These alterations undergo modification in the different phases of BPD: the peripheral levels of pro-inflammatory markers are elevated during maniacal and depressive episodes [35–37]. Furthermore, while at the beginning of bipolar disease these immune-inflammatory alterations regress to the level of healthy controls during euthymia, in multi-episodic illness the allostatic load weakens the homeostatic mechanisms, and immunological alterations seem to become permanent [38].

Moreover, several studies have shown that bipolar patients seem to have an inflammation prone genotype, with an aberrant expression of pro-phlogistic genes in the 88% of patients with BPD [39]. More specifically, a cluster of alterations in genes strictly related to inflammatory response was detected in a series of studies: the alterations especially affected the IL-1, Il-6, IL-8, and IFN pathways and transcriptional factors that take part in inflammatory response, such as STAT [40]. The relation between inflammatory mediators and mood disorder symptoms seems to be bidirectional: patients undergoing cytokine-based therapy against cancer were prone to develop depression [41, 42], while patients treated for other medical conditions with infliximab (a drug that antagonize the pro-phlogistic effect of TNFa) underwent a significant reduction in depressive symptoms [43].

Such evidence overall suggests that immune dysfunction not only plays a role in the physiopathology of BPD, to the point that BPD can be considered a multi-system inflammatory disease [44–46] but could also embody a key link between BPD and medical-inflammatory comorbidities [16]. Consistently, among bipolar patients there is a high prevalence of medical conditions characterized by a phlogistic diathesis and/or immunological dysfunction, such as migraines, asthma, arthritis, diabetes, and thyroid diseases [44]. On the other hand, it has been demonstrated that obesity, being a common finding among bipolar patients, can be in its turn considered as a chronic phlogistic condition [47]: a recent study has indicated that BMI is even stronger as a predictor of inflammation than recent mood episodes [48]. The same applies also to insulin resistance and diabetes, which are usually strictly related to metabolic syndrome (MetS). This latter is a clustering of metabolic alterations, being highly prevalent among patients with mood disorder and associated with a low-grade chronic inflammatory response [49]. In consequence, it has been hypothesized that a common inflammatory process can underpin both bipolar and cardiovascular disorder [44]. From this point of view, systemic and brain inflammatory processes have a role in triggering and propagating atherosclerosis, diabetes, obesity, and hypertension, which are traditional cardiovascular risk factors [50].

On the other hand, inflammation is directly associated with the main CVD proxy: the atherosclerosis. A huge number of studies have enlightened the strong impact of ongoing inflammation response in the mechanisms of atherogenesis, clarifying its pathogenetic role in mediating all stages of atherosclerotic disease. The inflammatory response plays a key role in the initiation of an atheroma, in the lesion's progression, and ultimately in the atherothrombosis, which is the last cause of acute cardiovascular events such as MI or stroke [51]. Consistently, several studies have shown that leukocyte recruitment and expression of pro-inflammatory cytokines are constant findings during the early atherogenesis, and the lesion's cells display feature of ongoing inflammation [52]. This proflogistic imbalance is one of the most important determining factors of the plaque vulnerability and in consequence of the plaque-associated thrombotic risk. Moreover, it is well-known that inflammation has also a detrimental action on the endothelium in as much as it causes oxidative stress, vasoconstriction, and prothrombotic state [53]. From this starting point, an increasing interest in defining the predictive and prognostic role of phlogistic biomarkers has emerged. In this respect, level of pro-inflammatory cytokines – such as IL-1, IL-4, IL-6, and TNF-a – has been found to rise during mania; similarly, some studies have found a relation between mood episodes and

the level of CRP, which is an acute-phase protein and a well-known risk indicator for CVD [39, 44, 54, 55]. Trophic factors might be another putative link among inflammation, BPD, and CVD: the inflammation induces a decrease in brain-derived neurotrophic factor (BDNF), which not only affects neurogenesis and neuronal repair, but is also associated with vascular endothelial dysfunction and CVD [56].

Therefore, it may be reasonable to hypothesize that inflammation subserves the CVD-BD link [11]. From this perspective, general medical comorbidities in BPD may be regarded as the final outcome of a complex interplay of pathways, acting synergistically and exerting a pervasive influence on the course of BPD and on the development and prognosis of medical comorbidities, such as CVD. Still, further studies are needed to better seize the directionality of the observed findings. Indeed, the role of inflammatory changes related to the general comorbidities affecting bipolar patients could be either causal (with BPD-induced inflammation leading to CVD) or consequential (with traditional risk factors commonly associated with BPD, such as MetS, increasing the vulnerability of bipolar patients to CVD). Alternatively, BPD and CVD may represent two expressions of the same diathesis rooted in immune dysfunction [25]. Similarly, further longitudinal studies would allow us to understand how inflammation fluctuates with symptomatic episodes and what is the relation among these fluctuations, atherosclerosis, and CVD over time. Finally, further research is necessary in order to define the potential role of therapeutic approach targeting this aspect [57].

Oxidative Stress

Oxidative stress (OS) is the consequence of a systemic imbalance between the generation of oxidant species – such as reactive oxygen species (ROS), thiobarbituric reactives, nitric oxide (NO), lipid peroxidation – and antioxidant defense system, such as glutathione peroxidase (GHS-Px), superoxide dismutase (SOD), catalases, and many other anti-oxidant enzymes and dietary or endogenous scavengers, such as vitamins A, C, E, or glutathione [58, 59]. The OS plays a key role in a large variety of pathophysiological processes, and there is evidence that the OS pathway may represent one of the main mechanisms underpinning the shared pathophysiology of CVD and BPD [60–62].

A large number of studies demonstrated that an imbalance in the redox homeostasis can lead to irreversible cellular damage, plays a key role in tissue senescence, and is robustly associated with increased risk of CVD. Indeed, OS is significantly associated with CVD because of its detrimental effect on vascular structure and functioning, which include an accelerated vascular aging, endothelial dysfunction, impairment in NO production, induction of subendothelial inflammation, and increasing of shear stress [63, 64]. Moreover, it has been demonstrated that OS is linked to a considerable worsening of metabolic profile in as much as it is associated with lower levels of high-density lipoproteins (HDL), higher levels of low-density lipoproteins (LDL), higher body mass index (BMI), altered glucidic homeostasis, and hypertension. Finally, it mediates various signaling pathways that underlie vascular inflammation in atherogenesis. For all these reasons, OS can be considered as a unifying mechanism for many CVD risk factors [64].

On the other hand, a growing number of studies have been emphasizing the role of OS in the pathophysiology of mood disorders up to the point of regarding it as a leading putative biomarker of BPD [65, 66]. It has been demonstrated that patients suffering from BPD have significantly different levels of antioxidant enzymes, lipid perodixations, NO, and thiobarbituric reactives compared to healthy controls [67, 68]. Moreover, the antioxidant level seems to increase in the later stage of BPD course, possibly as a delayed expression of a compensatory mechanism [59]. Furthermore, some studies detected a correlation between symptom burden, functional impairment, and the level of OS markers [69].

Consistently, researches have been focusing on the trigger of OS among bipolar patients: some studies have enlightened the potential role of a mitochondrial dysfunction in the pathophysiology

of BPD [70, 71]. In this sense, massive evidence indicates the involvement of mitochondrial dysfunction in BPD: for instance, reduced expression of several mitochondrial electron transport chain subunits, increased mtDNA deletion and mutation, reduced pH, and decreased levels of high-energy phosphates in the brain of BPD patients [72]. The importance of these findings can be easily understood if one considers that the mitochondria are the main source of free radicals.

All this given, an important point to take into account is the bidirectional and strict link between OS and inflammation. Inflammatory process induces the activation of OS pathways along with the related generation of ROS and nitrogen species. This leads to the damaging of the cell wall, mitochondria, and nucleic acids, such as DNA and RNA, and these structural alterations can eventually result in apoptosis and cell death, and in turn the structural damage perpetuates the inflammatory response by creating a variety of new epitopes, which are highly immunogenic [62]. Overall, these stressors constitute an "allostatic load": they produce an irreversible physiological modification induced by the cumulative effect of acute and chronic endogenous and/or exogenous stress, and by this way they overwhelm the homeostatic mechanisms and lead to progressive neurostructural changes, cognitive impairment, and medical comorbidities [73].

Autonomic Dysfunction

It has been suggested that dysfunction of the autonomic nervous system may be the primary pathological factor linking mood disorders and CVD. Under normal conditions, the parasympathetic activity of the autonomic nervous system is responsible for neurovegetative functions, whereas the sympathetic division prepares the body to respond to a challenge by promoting coagulation and platelet activation, constricting arteries and vessels, and increasing hepatic production of glucose to transport to the muscles. Sympathetic nervous system overactivity has been shown in depressed subjects, as suggested by elevated plasma norepinephrine and excess catecholamine response to orthostatic challenge [74, 75]. More recently, in order to estimate autonomic system dysfunction, most studies used the resting beat-to-beat variability in heart rate (HRV), which may easily reveal sympathetic overactivity or imbalance between the activity of the sympathetic and parasympathetic nervous systems. Besides a large amount of data indicating a reduction in HRV in depression [76–78], a handful of studies suggested that autonomic nervous system functioning is also impaired in patients with BPD compared to those without [79–81]. Although autonomic dysfunction (i.e., reduced HRV) is supposed to be directly associated with a worse prognosis in patients with CVD [82, 83], it is likely to contribute to CVD risk also indirectly, by enhancing the development of other CVD risk factors. For instance, impaired autonomic nervous system function is associated with incident hypertension, and sympathetic activation plays a critical role in the persistence of hypertension through altered arterial baroreflex receptivity and by the promotion of renal dysfunction [84]. Moreover, autonomic system dysfunction is also associated with diabetes mellitus, where lower HRV is associated with incident clinical cardiovascular events [85, 86].

Genetic Factors

Besides the above pathophysiological mechanisms likely underlying BPD and CVD comorbidity, a parallel line of research has developed with the aim of unraveling molecular underpinnings of these commonly affected mechanisms. A recent systematic review evaluated candidate pleiotropic genes that are likely to be shared among mood disorders, CVD, and metabolic disorders [87]. Overall, genes encoding for molecules involved in HPA-axis activity, circadian rhythm, inflammation, neurotransmission, metabolism, and energy balance were found to have a pivotal role in the relationship between mood disorders and CVD. For instance, genetic variants of the genes for BDNF, CREB1, GNAS, and POMC, all belonging to corticotrophin-releasing hormone signaling, which is the principal regulator of the HPA axis, have been found to be associated with BPD, obesity, and hypertension

[88–91]. A second main genetic underpinning may relate to the adenosine monophosphate-activated protein kinase (AMPK) signaling pathway, which regulates the intercellular energy balance. Variations in one or more of the contributing genes in the AMPK pathway, such as ADRA2A, ADRB1, LEP, CREB1, and GNAS, can easily impair energy homeostasis in the brain. Parallel, AMP activation, for instance, during stress, has been shown to induce insulin resistance and to promote MetS, obesity, diabetes, and CVD [92, 93].

Other strong candidate mechanisms underlying mood disorders and CVD are the serotonin and dopamine receptors signaling pathways. Serotonin modulates several physiological processes in the SNC, including mood, appetite, sleep, body temperature, and metabolism. Dysregulation of serotonergic neurotransmission, which may occur through genes involved in the serotonin receptor-signaling pathway, such as SLC18A1, HTR1A, and GNAS, has been suggested to contribute to the pathogenesis of mood disorders [94]. On the other hand, animal studies have consistently shown that the products of beta-islet cells regulate the expression of genes that synthesize serotonin, while serotonin conversely plays a role in the synthesis of insulin in the beta-islet cells [95]. The dopamine receptors pathway also appears to be involved in the relationship between mood disorders and CVD. Dopamine has important roles in movement, motivation, positive reinforcement, and, in the periphery, as a modulator of renal, cardiovascular, and endocrine systems. The dopamine-signaling pathway further induces the dopamine-DARPP32 Feedback in cAMP signaling. The central regulator of this pathway is the PPP1R1B gene that encodes a bifunctional signal transduction molecule called the dopamine and cAMP-regulated neuronal phosphoprotein (DARPP-32). Moreover, the CACNA1D gene, also belonging to dopamine receptors pathway, encodes the alpha-1D subunit of the calcium channels that mediates the entry of calcium ions into excitable cells. Calcium channel proteins are involved in a variety of calcium-dependent processes, including hormone or neurotransmitter release and gene expression [96].

Behavioral and Environmental Factors

In addition to direct pathophysiological aspects, several behavioral and environmental factors frequently occurring in patients with BPD are associated with increased cardiovascular risk [11]. Most of them are thought to exert an indirect effect on CVD, in the sense that they promote a cascade of pathophysiological changes that in turn increase the susceptibility to classical cardiovascular risk factors, ultimately enhancing the risk of CVD.

Weight gain is one of the most frequently experienced problems in patients with BPD [11], and it is thought to play a central role in the development of MetS, a constellation of several metabolic alterations, including abdominal obesity, insulin resistance (IR), dyslipidemia, and elevated blood pressure, frequently affecting subjects with BPD. All components of the MetS have been recognized as independent risk factors for CVD, and the presence of MetS is associated with other comorbidities such as the prothrombotic state, pro-inflammatory state, and atherosclerosis [97]. While increased calorie intake, sedentary lifestyles, and smoking habits have been implicated in the development of MetS in the general population as well as in certain patient groups, including BPD subjects, the latter have an even greater predisposition to MetS, and so that to CVD, due to the prolonged exposure to pharmaceutical treatments that have been shown to have side effects targeting the cardiovascular system.

Medication-Related Factors

Lithium and Anticonvulsant Drugs

Two of the most common mood stabilizers prescribed in the treatment of BPD, valproic acid and lithium salts, have been both associated with weight gain [98], which is in turn related to a number of adverse events, such as hypertension, type 2 diabetes mellitus (T2DM), and CVD. Although patients on treatment with valproic acid seem to gain more weight than those with lithium, this relationship does not appear to be clearly dose dependent, while in the case of

lithium the weight increase is associated with the employment of higher doses, corresponding to plasma levels>0.8 mmol/L [99, 100]. Conversely, other mood stabilizers such as lamotrigine or carbamazepine appear to have little effect on weight [101, 102]. Significant weight gain may also convey additional risk for dyslipidemia. While lithium is not directly associated with dyslipidemia, [103] its effects on lipid metabolism may occur in relationship with lithium-induced hypothyroidism, which adversely impacts weight and lipids [104]. As for valproic acid, a number of studies have shown an increase in triglyceride levels in treated patients, despite no significant changes in cholesterol levels have been found [105, 106]. Valproic acid may also be responsible of hyperinsulinemia and IR in those with BPD, despite it is not clear whether hyperinsulinemia and IR is the result of valproic acid-induced weight gain or a factor contributing to it [107]. Furthermore, valproic acid has been associated with hypertension in 1–5% of patients [108], while data provided by animal studies demonstrated an antihypertensive effect of lithium [109] exerted through its renal effects, which are similar to those reported in humans [110].

Antipsychotic Agents

Both first- and second-generation antipsychotics (AP) can be associated with QTc prolongation and/or torsade de pointes [111, 112], as well as with sudden death due to cardiac arrhythmias [113]. However, the major cardiovascular risk conveyed by AP might be related to their metabolic adverse effects. AP are associated with changes in lipid and glucose metabolism, with some of them also inducing significant weight gain as well as other metabolic abnormalities, such as obesity, T2DM and MetS [114]. A broad literature suggests that metabolic effects are more pronounced for second generation AP, with clozapine and olanzapine posing the higher risk of overweight, dyslipidemia, and T2DM, while quetiapine, sertindole, and risperidone may exert intermediate-low effects (except for an intermediate-high effect of quetiapine regarding triglycerides and cholesterol) and ziprasidone, amisulpride, and aripiprazole the least effects [115–120]. A meta-analysis conducted by Smith and colleagues (2008) reported that second generation AP have a 1.3-fold higher diabetogenic risk than first-generation ones [121]. However, among the latter, some low-potency agents too may be associated with significant metabolic effects, so that patients taking any AP should have their metabolic parameters routinely monitored [122]. As for most recent AP, it appears that lurasidone is closer in its effects to those that have been observed with aripiprazole, amisulpride, and ziprasidone, while asenapine, iloperidone, and paliperidone probably confer an intermediate risk of weight gain, comparable to risperidone and quetiapine, and a metabolic risk comparable to risperidone [123].

Furthermore, although several AP may directly block central and peripheral adrenoreceptors, leading to vasodilation and hypotension [124, 125], a hypertensive effect may actually occur during treatment with AP (especially clozapine) as a result of therapy-induced weight gain as well as of dopamine receptor effect on sympathetic nervous system and sodium excretion [126].

Behavioral Factors

Tobacco Smoking and Substance Abuse

Cigarette smoking is the most significant behavioral contributor to overall cardiovascular risk, and several studies showed a direct dose-dependent correlation between cigarette smoke exposure and the severity of CVD risk [127]. Tobacco smoking has been shown to contribute to all phases of atherosclerosis (from endothelial dysfunction to acute cardiovascular events) by enhancing thrombosis, inflammation, and oxidation of low-density lipoprotein cholesterol [128]. Overall, up to 70% of people with BPD report current tobacco use being from two to ten times more likely to be smokers and less likely to successfully quit smoking compared to the general population. Moreover, BPD patients are more likely to be heavy smokers than both people with major depressive disorder and the general population [129].

Alcohol and illegal drug use are also frequently associated with BPD. The increased risk of

substance abuse in patients with BPD compared to non-bipolar individuals has been acknowledged by many investigations [130–135]. Roughly, up to 60% of BPD population have lifetime substance abuse (about 48% for alcohol and almost 43% for illicit drugs), with higher rates in patients with early-onset disease [127, 136]. Whereas few studies evaluated the impact of alcohol and other substance misuse on CVD risk among subjects with BPD, a recent meta-analysis included alcohol, cocaine, and marijuana exposure among factors that are more likely to trigger acute myocardial infarction in the general population, with cocaine abuse bearing the higher odd ratio. Besides inducing acute myocardial events, cocaine represents a significant threat to the integrity of the cardiovascular system, being able to affect it by many different pathophysiological pathways, and subsequently is considered as a risk factor for many cardiovascular diseases like hypertension, aortic dissection, myocardial ischemia, cardiomyopathy, myocarditis, arrhythmias, and stroke.

Sedentary Lifestyle and Unhealthy Eating Habits

Sedentary lifestyle is known to increase the risk of developing CVD, while physical activity decreases cardiovascular risk through multiple pathways, including reducing body weight and improving endothelial and immune function as well as blood pressure [137]. BPD usually features a chronic course, characterized by recurrent depressive and manic phases, often lasting for several weeks. This means that patients go through recurrent periods of depression, lack of interests, and inactivity, followed by periods of intense activity irritability, and physical exhaustion that can have a significant impact on self-confidence, self-efficacy, and health-related decisions [138]. As a matter of fact, people with depressive symptoms are more likely to be sedentary compared to those without [139, 140] and physical inactivity has been identified as an independent predictor of premature mortality among people with BD and significantly increases their risk of CVD [141]. Due to the frequent mood swings and to the intense distress, people with BPD often fail in pursuing healthy habits and may end up having disordered eating. In a study of 1046 Australian women, poor diet quality was associated with twice the odds for BPD [142]. In another study comparing 2032 participants with BPD in the general population, having BPD was associated with significantly poorer eating behaviors, including fewer daily meals and difficulty obtaining or cooking food, as well as increased appetite and caloric intake. Complicating this and supporting an integrated approach, people at risk for one adverse health behavior are at greater risk for others [143].

Miscellaneous

Several studies have linked sleep disturbances to an increased risk of dyslipidemia and, generally, to MetS [144–147]. Based on the observation that BPD patients show a broad range of sleep disturbances both during acute and remitting phases [148–150], it has been hypothesized that disturbances in the sleep-wake cycle may add to classical risk factors for CVDs in BPD population [151].

Nutrition as well could play a role in the association between BPD and cardiovascular risk. Fish oils, specifically omega-3 fatty acids, have received particular attention for secondary prevention of CVD in the general population [152]. On the other hand, omega-3 supplementation showed positive outcomes in the treatment of depression among both bipolar subjects [153, 154] and unipolar patients with CVD [155]. Intriguingly, despite provisionally, observational data suggest that greater seafood consumption is associated with lower rates of BPD [156] and omega-3 deficits have been reported among adults with BPD [157, 158].

Conclusion/Summary

The relationship between BPD and CVD appears to be complex and multifaceted. Bipolar subjects are clearly prone to develop CVD, and this risk may be evident early in life, also having a significant impact on life expectancy of this patient group. Still, further studies are needed to better

characterize the observed association. Indeed, the broad range of alterations bridging BPD and CVD could either imply a direct causal link between the two (but, if so, the directionality has to be determined) or an indirect, consequential relationship, with BPD leading to the development of a range of traditional cardiovascular risk factors and ultimately to CVD. However, a third, intriguing hypothesis is making his way in recent literature, that is to say that BPD and CVD may represent two expressions of a same diathesis rooted elsewhere. While research makes advance in the complex link between BPD and CVD, health practitioners need to keep in mind that there may be more to CVD risk, besides the contribution of usual risk factors. Mental health providers are especially expected to assess and target CVD risk and to develop more effective prevention and treatment strategies in order to reduce the excess burden of morbidity and mortality of people with BPD. If BPD-associated risk is invariable so far, it also holds true that BPD onset usually occurs before CVD, providing clinicians with the opportunity to slow CVD progression by early assessing and treating modifiable risk factors. Until more clear insight on BPD-CVD relationship is gained, we must consider BPD subjects as a high risk group, in which classical CVD risk factors should be referred to more stringent benchmarks and treated prematurely.

References

1. World Health Organization (WHO). Fact sheet. 2017.
2. Grant BF, Stinson FS, Hasin DS, Dawson DA, Chou SP, Ruan WJ, Huang B. Prevalence, correlates, and comorbidity of bipolar I disorder and axis I and II disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. J Clin Psychiatry. 2005;66(10):1205–15.
3. Kilbourne AM, Cornelius JR, Han X, Pincus HA, Shad M, Salloum I, Conigliaro J, Haas GL. Burden of general medical conditions among individuals with bipolar disorder. Bipolar Disord. 2004;6(5):368–73.
4. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Washington, DC: Author; 2013.
5. Merikangas KR, Akiskal HS, Angst J, Greenberg PE, Hirschfeld RM, Petukhova M, Kessler RC. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. Arch Gen Psychiatry. 2007;64(5):543–52.
6. Post RM, Luckenbaugh DA, Leverich GS, Altshuler LL, Frye MA, Suppes T, Keck PE, McElroy SL, Nolen WA, Kupka R, Grunze H, Walden J. Incidence of childhood-onset bipolar illness in the USA and Europe. Br J Psychiatry. 2008;192(2):150–1.
7. Westman J, Hällgren J, Wahlbeck K, Erlinge D, Alfredsson L, Ösby U. Cardiovascular mortality in bipolar disorder: a population-based cohort study in Sweden. BMJ Open. 2013;4(3):e002373.
8. Kupfer J. The increasing medical burden in bipolar disorder. JAMA. 2005;293(20):2528–30.
9. Walker ER, McGee RE, Druss BG. Mortality in mental disorders and global disease burden implications: a systematic review and meta-analysis. JAMA Psychiat. 2015;72:334–41.
10. Correll CU. Elevated cardiovascular risk in patients with bipolar disorder: when does it start and where does it lead? J Clin Psychiatry. 2008;69(12): 1948–52.
11. Goldstein BI, Carnethon MR, Matthews KA, McIntyre RS, Miller GE, Raghuveer G, Stoney CM, Wasiak H, McCrindle BW. Major depressive disorder and bipolar disorder predispose youth to accelerated atherosclerosis and early cardiovascular disease. A scientific statement from the American Heart Association. Circulation. 2015;132:965–86.
12. De Hert M, Detraux J, Vncampfort D. The intriguing relationship between coronary heart disease and mental disorders. Dialogues Clin Neurosci. 2018; 20(1):31–40.
13. Kessing LV, Vradi E, Andersen PK. Life expectancy in bipolar disorder. Bipolar Disord. 2015;17:543–8.
14. Osby U, Brandt L, Correia N, Ekbom A, Sparn P. Excess mortality in bipolar and unipolar disorder in Sweden. Arch Gen Psychiatry. 2001;58:844–50.
15. Sharma R, Markar HR. Mortality in affective disorder. J Affect Disord. 1994;31:91–6.
16. Goldstein B. Bipolar disorder and the vascular system: mechanisms and new prevention opportunities. Can J Cardiol. 2017;33(12):1565–157.
17. Callaghan RC, Khizar A. The incidence of cardiovascular morbidity among patients with bipolar disorder: a population-based longitudinal study in Ontario. J Affect Disord. 2010;122(1–2):118–23.
18. Fiedorowicz JG, Solomon DA, Endicott J, Leon AC, Li C, Rice JP, Coryell WH. Manic/hypomanic symptom burden and cardiovascular mortality in bipolar disorder. Psychosom Med. 2009;71(6):598–606.
19. Hatch JK, Scola G, Olowoyeye O, Collins JE, Andreazza AC, Moody A, Levitt AJ, Strauss BH, Lanctot KL, Goldstein BI. Inflammatory markers and brain-derived neurotrophic factor as potential bridges linking bipolar disorder and cardiovascular risk among adolescents. J Clin Psychiatry. 2017;78 (3):286–93.
20. Kessing LV, Vradi E, McIntyre RS, Andersen PK. Causes of decreased life expectancy over the life

span in bipolar disorder. J Affect Disord. 2015; 180:142–7.
21. Allison DB, Newcomer JW, Dunn AL, Blumenthal JA, Fabricatore AN, Daumit GL, Cope MB, Riley WT, Vreeland B, Hibbeln JR, Alpert JE. Obesity among those with mental disorders: a National Institute of mental health meeting report. Am J Prev Med. 2009;36:341–50.
22. Mannie ZN, Williams C, Diesch J, Steptoe A, Leeson P, Cowen PJ. Cardiovascular and metabolic risk profile in young people at familial risk of depression. Br J Psychiatry. 2013;203:18–23.
23. Rottenberg J, Yaroslavsky I, Carney RM, Freedland KE, George CJ, Baji I, Dochnal R, Gádoros J, Halas K, Kapornai K, Kiss E, Osváth V, Varga H, Vetr A, Kovacs M. The association between major depressive disorder in childhood and risk factors for cardiovascular disease in adolescence. Psychosom Med. 2014;76:122–7.
24. Muller AH, Manji HM. On redefining the role of the immune system in psychiatric disease. Biol Psychiatry. 2006;60(8):796–8.
25. Sayuri Yamagata A, Brietzke E, Rosenblat JD, Kakar R, McIntyre RS. Medical comorbidity in bipolar disorder: the link with metabolic inflammatory systems. J Affect Disorder. 2017;211:99–106.
26. Versace A, Andreazza AC, Young LT, Fournier JC, Almeida JRC, Stiffler RS, Lockovich JC, Asiam HA, Pollock MA, Park H, Nimgaonkar VL, Kupfer DJ, Philips ML. Elevated serum measures of lipid peroxidation and abnormal prefrontal white matter in euthymic bipolar adults: toward peripheral biomarkers of bipolar disorder. Mol Psychiatry. 2014;19:200–8.
27. Müller N, Ackenheil M. Psychoneuroimmunology and the cytokine action in the CNS: implications for psychiatric disorders. Prog Neuro-Psychopharmacol Biol Psychiatry. 1998;22(1):1–33.
28. Aktas O, Ulrich O, Infante-Duarte C, Nitsch R, Zipp F. Neuronal damage in brain inflammation. Arch Neurol. 2007;64(2):785–9.
29. Maes M, Leonard BE, Myint AM, Kubera M, Verkerk R. The new '5-HT' hypothesis of depression: cell-mediated immune activation induces indoleamine 2,3- dioxygenase, which leads to lower plasma tryptophan and an increased synthesis of detrimental tryptophan catabolites (TRYCATs), both of which contribute to the onset of depression. Prog Neuro-Psychopharmacol Biol Psychiatry. 2011;35:702–21.
30. Noto C, Rizzo LB, Mansur RB, McIntyre RS, Maes M, Brietzke E. Targeting the inflammatory pathway as a therapeutic tool for major depression. Neuroimmunomodulation. 2014;21:131–9.
31. Modabbernia A, Taslimi S, Brietzke E, Ashrafi M. Cytokine alterations in bipolar disorder: a meta-analysis of 30 studies. Biol Psychiatry. 2013;74:15–25.
32. Söderlund J, Olsson SK, Samuelsson M, Walther-Jallow L, Johansson C, Erhardt S, Landén M, Engberg G. Elevation of cerebrospinal fluid interleukin-1ß in bipolar disorder. J Psychiatry Neurosci. 2011;36:114–8.
33. Rolstad S, Jakobsson J, Sellgren C, Isgren A, Ekman CJ, Bjerke M, Blennow K, Zetterberg H, Pålsson E, Landén M. CSF neuroinflammatory biomarkers in bipolar disorder are associated with cognitive impairment. Eur Neuropsychopharmacol. 2015;25:1091–8.
34. Munkholm K, Vinberg M, Vedel KL. Cytokines in bipolar disorder: a systematic review and meta-analysis. J Affect Disord. 2013;144:16–27.
35. Brietzke E, Stertz L, Fernandes BS, Kauer-Sant'Anna M, Mascarenhas M, Vargas AE, Chies JA, Kapczinski F. Comparison of cytokine levels in depressed, manic and euthymic patients with bipolar disorder. J Affect Disord. 2009;116(3):214–7.
36. Ortiz-Dominguez A, Hernandez ME, Berlanga C, Gutiérrez-Mora D, Moreno J, Hinze G, Pavòn L. Immune variations in bipolar disorder: phasic differences. Bipolar Disord. 2007;9(6):596–602.
37. Maes M, Bosman E, Calabrese J, Smith R, Meltzer HY. Interleukin-2 and interleukin-6 in schizophrenia and mania: effects of neuroleptic and mood stabilizers. J Psychiatr Res. 1995;29(2):141–52.
38. Kauer-Sant'Anna M, Kapczinski F, Andreazza AC, Bond DJ, Lam RW, Young LT, Yatham LN. Brain-derived neurotrophic factor and inflammatory markers in patients with early- vs. late-stage bipolar disorder. Int J Neuropsychopharmacol. 2009;12 (4):447–58.
39. Dickerson F, Stallings C, Origoni A, Boronow J, Yolken R. Elevated serum levels of C-reactive protein are associated with mania symptoms in outpatients with bipolar disorder. Prog Neuro-Psychopharmacol Biol Psychiatry. 2007;31:952–5.
40. Drago A, Crisafulli C, Calabro M, Serretti A. Enrichment pathway analysis. The inflammatory genetic background in bipolar disorder. J Affect Disord. 2015;179:88–94.
41. Musselman DL, Lawson DH, Gumnick JF, Manatunga AK, Penna S, Goodkin RS, Greiner K, Nemeroff CB, Miller AH. Paroxetine for the prevention of depression induced by high-dose interferon alfa. N Engl J Med. 2001;344(13):961–96.
42. Capuron L, Ravaud A, Gualde N, Bosmans E, Dantzer R, Maes M, Neveu PJ. Association between immune activation and early depressive symptoms in cancer patients treated with interleukin-2-based therapy. Psychoneuroendocrinology. 2001;26:797–808.
43. Raison CL, Rutherford RE, Woolwine BJ, Shuo C, Schettler P, Drake DF, Haroon E, Miller AH. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. JAMA Psychiat. 2013;70:31–41.
44. Leboyer M, Soreca I, Scott J, Frye M, Henry C, Tamouza R, et al. Can bipolar disorder be viewed as a multi-system inflammatory disease? J Affect Disord. 2012;141(1):1–10.

45. Berk M, Kapczinski F, Andreazza AC, Dean OM, Giorlando F, Maes M, et al. Pathways underlying neuroprogression in bipolar disorder: focus on inflammation, oxidative stress and neurotrophic factors. Neurosci Biobehav Rev. 2011;35(3):804–17.
46. Dargél AA, Godin O, Kapczinski F, Kupfer DJ, Leboyer M. C-reactive protein alterations in bipolar disorder: a meta-analysis. J Clin Psychiatry. 2015; 76:142–50.
47. Soczynska JK, Kennedy SH, Woldeyohannes HO, Liauw SS, Alsuwaidan M, Yim CY, et al. Mood disorders and obesity: understanding inflammation as a pathophysiological nexus. NeuroMolecular Med. 2011;13(2):93–116.
48. Bond DJ, Andreazza AC, Hughes J, Dhanoa T, Torres IJ, Kozicky J, et al. Association of peripheral inflammation with body mass index and depressive relapse in bipolar disorder. Psychoneuroendocrinology. 2016;65:76–83.
49. Ridker PM. High-sensitivity C-reactive protein and cardiovascular risk: rationale for screening and primary prevention. Am J Cardiol. 2003;92(4):17–22.
50. Drake C, Boutin H, Jones MS, Denes A, McColl BW, Selvarajah JR, Hulme S, Georgiou R, Hinz R, Gerhard A, Vail A, Prenant C, Julyan P, Maroy R, Brown G, Smigova A, Herholz K, Kassiou M, Crossman D, Francis S, Proctor S, Russel JC, Hookins SL, Tvrrell P, Rothweil N, Alllan S. Brain inflammation is induced by co-morbidities and risk factor for stroke. Brain Behav Immun. 2011;25:1113–22.
51. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. Circulation. 2002;105(9):1135–43.
52. Hannson GK, Libby P, Tabas I. Inflammation and plaque vulnerability. J Intern Med. 2015;278(5): 483–93.
53. Corrado E, Rizzo M, Coppola G, Fattouch K, Novo G, Marturana I, Ferrara F, Novo S, et al. An update on the role of markers of inflammation in atherosclerosis. J Atheroscler Thromb. 2010;17:1–11.
54. Greenland P, Alpert JS, Beller GA, Benjamin EJ, Budoff MJ, Fayad ZA, Foster E, Hlatky MA, Hodgson JM, Kushner FG, Lauer MS, Shaw LJ, Smith SC Jr, Taylor AJ, Weintraub WS, Wenger NK, Jacobs AK, Smith SC Jr, Anderson JL, Albert N, Buller CE, Creager MA, Ettinger SM, Guyton RA, Halperin JL, Hochman JS, Griffiths DJ. Endogenous retroviruses in the human genome sequence. Genome Biol. 2001;2(6):1017.
55. Ridker PM. Inflammatory biomarkers and risks of myocardial infarction, stroke, diabetes, and total mortality: implications for longevity. Nutr Rev. 2007;65(2):253–9.
56. Lorgis L, Amoureux S, de Maistre E, Sicard P, Bejot Y, Zeller M, Vergely C, Sequeira-Le-Grand A, Lagrost AC, Nerchoud J, Cottin Y, Rohcette L. Serum brain derived neurotrophic factor and platelet activation evaluated by soluble-P-selectin and soluble CD-40-ligand in patients with acute myocardial infarction. Fundam Clin Pharmacol. 2010;4:525–30.
57. Berk M, Kapczinski F, Andreazza AC, Dean OM, Giorlando F, Maes M, Yucel M, Gama CS, Dodd S, Dean B, Magalhaes PVS, Amminger P, McGorry P, Malhi GS. Pathways underlying neuroprogression in bipolar disorder: focus on inflammation, oxidative stress and neurotrophic factors. Neurosci Behav Rev. 2011;35:804–17.
58. Andreazza AC, Kapczinski F, Kauer-Sant'Anna M, Walz JC, Bond DJ, Goncalves CA, Young LT, Yatham LN. 3-Nitrotyrosine and glutathione antioxidant system in patients in the early and late stages of bipolar disorder. J Psychiatry Neurosci. 2009;34 (4):263–71.
59. Dalle-Donne I, Aldini G, Carini M, Colombo R, Rossi R, Milzani A. Protein carbonylation, cellular dysfunction, and disease progression. J Cell MolMed. 2006;10:389–406.
60. Hatch J, Andreazza A, Olowoyeye O, Rezin GT, Moody A, Goldstein BI. Cardiovascular and psychiatric characteristics associated with oxidative stress markers among adolescents with bipolar disorder. J Psychosom Res. 2015;79(3):222–7.
61. Maes M, Ruckoanich M, Chang YS, Mahanonda N, Berk M. Multiple aberrations in shared inflammatory and oxidative & nitrosative stress (IO&NS) pathways explain the co-association of depression and cardiovascular disorder (CVD), and the increased risk for CVD and due mortality in depressed patients. Progr Neuro-Psychopharmacol Biol Psychiatry. 2011;35(3):769–83.
62. Assies J, Mocking RJT, Lok A, Ruhé HG, Pouwer F, Schene AH. Effects of oxidative stress on fatty acid- and one-carbon- metabolism in psychiatric and cardiovascular disease comorbidity. Acta Psychiatr Scand. 2014;130:163–80.
63. Fyhrquist F, Saijonmaa O, Strandberg T. The roles of senescence and telomere shortening in cardiovascular disease. Nat Rev Cardiol. 2013;10:274–83.
64. Madamanchi NR, Vendrov A, Runge MS. Oxidative stress and vascular disease. Arterioscler Thromb Vasc Biol. 2005;25:29–38.
65. Frey BN, Andreazza AC, Houenou J, Jamain S, Goldstein BI, Frye MA, Leboyer M, Berk M, Malhi GS, Lopez-Jaramillo C, Taylor VH, Dodd S, Frangou S, Hall GB, Fernandes BS, Kauer-Sant'Anna M, Yatham LN, Kapczinski F, Young LT. Biomarkers in bipolar disorder: a positional paper from the International Society for Bipolar Disorders Biomarkers Task Force. Aust N Z J Psychiatry. 2013;47:321–32.
66. Brown NC, Andreazza AC, Young LT. An updated metaanalysis of oxidative stress markers in bipolar disorder. J Psychiatr Res. 2014;218:61–8.
67. Andreazza AC, Frey BN, Erdtmann B, Salvador M, Rombaldi F, Santin A, Gonçalves CA, Kapczinski F. DNA damage in bipolar disorder. Psychiatry Res. 2007;153:27–32.
68. Gergerlioglu HS, Savas HA, Bulbul F, Selek S, Uz E, Yumru M. Changes in nitric oxide level and superoxide dismutase activity during antimanic treatment.

Prog Neuro-Psychopharmacol Biol Psychiatry. 2007;31:697–702.
69. Andreazza AC, Kauer-Sant'anna M, Frey BN, Bond DJ, Kapczinski F, Young LT, Yatham LN. Oxidative stress markers in bipolar disorder: a meta-analysis. J Affect Disord. 2008;111:135–4.
70. Kato T, Kato N. Mitochondrial dysfunction in bipolar disorder. Bipolar Disord. 2000;2:180–90.
71. Konradi C, Eaton M, MacDonald ML, Walsh J, Benes FM, Heckers S. Molecular evidence for mitochondrial dysfunction in bipolar disorder. Arch Gen Psychiatry. 2004;61:300–8.
72. Clay HB, Sillivan S, Konradi C. Mitochondrial dysfunction and pathology in bipolar disorder and schizophrenia. Int J Dev Neurosci. 2011;29:311–24.
73. Kapczinski F, Vieta E, Andreazza AC, Frey BN, Gomes FA, Tramontina J, Kauer Sant'Anna M, Grassi-Oliveira R, Post RM. Allostatic load in bipolar disorder: implications for pathophysiology and treatment. Neurosci Biobehav Rev. 2008;32 (4):675–92.
74. Maas JW, Katz MM, Koslow SH, Swann A, Davis JM, Berman N, Bowden CL, Stokes PE, Landis H. Adrenomedullary function in depressed patients. J Psychiatr Res. 1994;28(4):357–67.
75. Gold PW, Gabry KE, Yasuda MR, Chrousos GP. Divergent endocrine abnormalities in melancholic and atypical depression: clinical and pathophysiologic implications. Endocrinol Metab Clin N Am. 2002;31(1):37–62.
76. Carney RM, Blumenthal JA, Stein PK, Watkins L, Catellier D, Berkman LF, Czajkowski SM, O'Connor C, Stone PH, Freedland KE. Depression, heart rate variability, and acute myocardial infarction. Circulation. 2001;104(17):2024–8.
77. Licht CM, de Geus EJ, Zitman FG, Hoogendijk WJ, van Dyck R, Penninx BW. Association between major depressive disorder and heart rate variability in the Netherlands Study of Depression and Anxiety (NESDA). Arch Gen Psychiatry. 2008;65:1358–67.
78. Byrne ML, Sheeber L, Simmons JG, Davis B, Shortt JW, Katz LF, Allen NB. Autonomic cardiac control in depressed adolescents. Depress Anxiety. 2010;27:1050–6.
79. Voss A, Baier V, Schulz S, Bar KJ. Linear and nonlinear methods for analyses of cardiovascular variability in bipolar disorders. Bipolar Disord. 2006;8 (1):441–52.
80. Henry BL, Minassian A, Paulus MP, Geyer MA, Perry W. Heart rate variability in bipolar mania and schizophrenia. J Psychiatr Res. 2010;44(3):168–76.
81. Quintana DS, Westlye LT, Kaufmann T, Rustan ØG, Brandt CL, Haatveit B, Steen NE, Andreassen OA. Reduced heart rate variability in schizophrenia and bipolar disorder compared to healthy controls. Acta Psychiatr Scand. 2016;133(1):44–52.
82. Buccelletti E, Gilardi E, Scaini E, Galiuto L, Persiani R, Biondi A, Basile F, Silveri NG. Heart rate variability and myocardial infarction: systematic literature review and metaanalysis. Eur Rev Med Pharmacol Sci. 2009;13(4):299–307.
83. Björkander I, Forslund L, Ericson M, Rehnqvist N, Hjemdahl P, Kahan T. Long-term stability of heart rate variability in chronic stable angina pectoris, and the impact of an acute myocardial infarction. Clin Physiol Funct Imaging. 2009;29:201–8.
84. Singh JP, Larson MG, Tsuji H, Evans JC, O'Donnell CJ, Levy D. Reduced heart rate variability and new-onset hypertension: insights into pathogenesis of hypertension: the Framingham Heart Study. Hypertension. 1998;32:293–7.
85. Liao D, Carnethon M, Evans GW, Cascio WE, Heiss G. Lower heart rate variability is associated with the development of coronary heart disease in individuals with diabetes: the Atherosclerosis Risk In Communities (ARIC) study. Diabetes. 2002; 51:3524–31.
86. Benichou T, Pereira B, Mermillod M, Tauveron I, Pfabigan D, Maqdasy S, Dutheil F. Heart rate variability in type 2 diabetes mellitus: A systematic review and metaanalysis. PLoS One. 2018;79:465–466.
87. Amare AT, Schubert KO, Klinger-Hoffmann M, Cohen-Woods S, Baune BT. The genetic overlap between mood disorders and cardiometabolic diseases: a systematic review of genome wide and candidate gene studies. Transl Psychiatry. 2017;7 (1):1007.
88. McDonald ML, MacMullen C, Liu DJ, Leal SM, Davis RL. Genetic association of cyclic AMP signaling genes with bipolar disorder. Transl Psychiatry. 2012;2:e169.
89. Locke AE, Kahali B, Berndt SI, et al. Genetic studies of body mass index yield new insights for obesity biology. Nature. 2015;518(7538):197–206.
90. Speliotes EK, Willer CJ, Berndt SI, Monda KL, Thorleifsson G, Jackson AU, Lango Allen H, et al. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. Nat Genet. 2010;42(11):937–48.
91. Ehret GB, Munroe PB, Rice KM, Bochud M, Johnson AD, et al. Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk. Nature. 2011;478:103–9.
92. Lage R, Dieguez C, Vidal-Puig A, Lopez M. AMPK: a metabolic gauge regulating whole-body energy homeostasis. Trends Mol Med. 2008;14:539–49.
93. Steinberg GR, Kemp BE. AMPK in health and disease. Physiol Rev. 2009;89:1025–78.
94. Donaldson ZR, le Francois B, Santos TL, et al. The functional serotonin 1a receptor promoter polymorphism, rs6295, is associated with psychiatric illness and differences in transcription. Transl Psychiatry. 2016;6(3):e746.
95. Ohta Y, Kosaka Y, Kishimoto N, Wang J, Smith SB, Honig G, Kim H, Gasa RM, Neubauer N, Liou A, Tecott LH, Deneris ES, German MS. Convergence of the insulin and serotonin programs in the pancreatic β-cell. Diabetes. 2011;60(12):3208–16.

96. Pruitt K, Brown G, Tatusova T, Maglott D. The reference sequence (RefSeq) database. Rockville: National Center for Biotechnology Information; 2012.
97. Cornier MA, Dabelea D, Hernandez TL, Lindstrom RC, Steig AJ, Stob NR, Van Pelt RE, Wang H, Eckel RH. The metabolic syndrome. Endocr Rev. 2008;29(7):777–822.
98. Bowden CL, Mosolov S, Hranov L, Chen E, Habil H, Kongsakon R, Manfredi R, Lin HN. Efficacy of valproate versus lithium in mania or mixed mania: a randomized, open 12-week trial. Int Clin Psychopharmacol. 2010;25(2):60–7.
99. Zuo S, Fries BE, Szafara K, Regal R. Valproic acid as a potentiator of metabolic syndrome in institutionalized residents on concomitant antipsychotics: fat chance, or slim to none? Pharm Ther. 2015;40:126–32.
100. Ackerman S, Nolan LJ. Bodyweight gain induced by psychotropic drugs. CNS Drugs. 1998;9:135–51.
101. Calabrese JR, Bowden CL, Sachs G, Yatham LN, Behnke K, Mehtonen OP, et al. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar I disorder. J Clin Psychiatry. 2003; 64:1013–24.
102. Chengappa KN, Chalasani L, Brar JS, Parepally H, Houck P, Levine J. Changes in body weight and body mass index among psychiatric patients receiving lithium, valproate, or topiramate: an open-label, nonrandomized chart review. Clin Ther. 2002;24:1576–84.
103. McIntyre RS, McElroy SL, Eudicone JM, Forbes RA, Carlson BX, Baker RA. A 52-week, double-blind evaluation of the metabolic effects of aripiprazole and lithium in bipolar I disorder. Prim Care Companion CNS Disord. 2011;13(6):PCC.11m01182.
104. Ezzaher A, Mouhamed DH, Mechri A, Neffati F, Douki W, Gaha L, et al. Thyroid function and lipid profile in bipolar I patients. Asian J Psychiatr. 2011;4:139–43.
105. Vik-Mo AO, Birkenaes AB, Ferno J, Jonsdottir H, Andreassen OA, Steen VM. Increased expression of lipid biosynthesis genes in peripheral blood cells of olanzapine-treated patients. Int J Neuropsychopharmacol. 2008;11:679–84.
106. Schwarz E, Prabakaran S, Whiteld P, Major H, Leweke FM, Koethe D, et al. High throughput lipidomic proling of schizophrenia and bipolar disorder brain tissue reveals alterations of free fatty acids, phosphatidylcholines, and ceramides. J Proteome Res. 2008;7:4266–77.
107. Verrotti A, D'Egidio C, Mohn A, Coppola G, Chiarelli F. Weight gain following treatment with valproic acid: pathogenetic mechanisms and clinical implications. Obes Rev. 2011;12(5):e32–43.
108. Rodriguezgil J, Guinovart J, Bosch F. Lithium restores glycogen synthesis from glucose in hepatocytes from diabetic rats. Arch Biochem Biophys. 1993;301:411–5.
109. Li H, Fang M, Xu M, Li S, Du J, Li W, et al. Chronic olanzapine treatment induces disorders of plasma fatty acid pro le in Balb/c mice: a potential mechanism for olanzapine-induced insulin resistance. PLoS One. 2016;11:e0167930.
110. Tabata I, Schluter J, Gulve EA, Holloszy JO. Lithium increases susceptibility of muscle glucose transport to stimulation by various agents. Diabetes. 1994;43:903–7.
111. Beach SR, Celano CM, Noseworthy PA, Januzzi JL, Huffman JC. QTc prolongation, torsades de pointes, and psychotropic medications. Psychosomatics. 2013;54(1):1–13.
112. Ray WA, Chung CP, Murray KT, Hall K, Stein CM. Atypical antipsychotic drugs and the risk of sudden cardiac death. N Engl J Med. 2009;360(3):225–35.
113. Wu CS, Tsai YT, Tsai HJ. Antipsychotic drugs and the risk of ventricular arrhythmia and/or sudden cardiac death: a nation-wide case-crossover study. J Am Heart Assoc. 2015;4(2):e001568.
114. Parsons B, Allison DB, Loebel A, Williams K, Giller E, Romano S, Siu C. Weight effects associated with antipsychotics: a comprehensive database analysis. Schizophr Res. 2009;110(1–3):103–10.
115. Rummel-Kluge C, Komossa K, Schwarz S, Hunger H, Schmid F, Lobos CA, Kissling W, Davis JM, Leucht S. Head-to-head comparisons of metabolic side effects of second generation antipsychotics in the treatment of schizophrenia: a systematic review and meta-analysis. Schizophr Res. 2010;123 (2–3):225–33.
116. Komossa K, Rummel-Kluge C, Schmid F, Hunger H, Schwarz S, El-Sayeh HG, Kissling W, Leucht S. Aripiprazole versus other atypical antipsychotics for schizophrenia. Cochrane Database Syst Rev. 2009;4: CD006569.
117. Komossa K, Rummel-Kluge C, Schmid F, Hunger H, Schwarz S, Srisurapanont M, Kissling W, Leucht S. Quetiapine versus other atypical antipsychotics for schizophrenia. Cochrane Database Syst Rev. 2010;1: CD006625.
118. Komossa K, Rummel-Kluge C, Hunger H, Schmid F, Schwarz S, Silveira da Mota Neto JI, Kissling W, Leucht S. Amisulpride versus other atypical antipsychotics for schizophrenia. Cochrane Database Syst Rev. 2010;1:CD006624.
119. Komossa K, Rummel-Kluge C, Schwarz S, Schmid F, Hunger H, Kissling W, Leucht S. Risperidone versus other atypical antipsychotics for schizophrenia. Cochrane Database Syst Rev. 2011;1:CD006626.
120. Hirsch L, Yang J, Bresee L, Jette N, Patten S, Pringsheim T. Second-generation antipsychotics and metabolic side effects: a systematic review of population-based studies. Drug Saf. 2017;40(9): 771–81.
121. Smith M, Hopkins D, Peveler RC, Holt RI, Woodward M, Ismail K. First- v. second-generation antipsychotics and risk for diabetes in schizophrenia: systematic review and meta-analysis. Br J Psychiatry. 2008;192(6):406–11.

122. Hartling L, Abou-Setta AM, Dursun S, Mousavi SS, Pasichnyk D, Newton AS. Antipsychotics in adults with schizophrenia: comparative effectiveness of first- generation versus second-generation medications: a systematic review and meta- analysis. Ann Intern Med. 2012;157(7):498–511.
123. De Hert M, Einfinger G, Scherpenberg E, Wampers M, Peuskens J. The prevention of deep venous thrombosis in physically restrained patients with schizophrenia. Int J Clin Pract. 2010;64(8):1109–15.
124. Drici MD, Priori S. Cardiovascular risks of atypical antipsychotic drug treatment. Pharmacoepidemiol Drug Saf. 2007;16(8):882–90.
125. Leung JY, Barr AM, Procyshyn RM, Honer WG, Pang CC. Cardiovascular side-effects of antipsychotic drugs: the role of the autonomic nervous system. Pharmacol Ther. 2012;135(2):113–22.
126. Gonsai NH, Amin VH, Mendpara CG, Speth R, Hale GM. Effects of dopamine receptor antagonist antipsychotic therapy on blood pressure. J Clin Pharm Ther. 2018;43(1):1–7.
127. Cassidy F, Ahearn EP, Carroll BJ. Substance abuse in bipolar disorder. Bipolar Disord. 2001;3 (4):181–8.
128. Ambrose JA, Barua RS. The pathophysiology of cigarette smoking and cardiovascular disease: an update. J Am Coll Cardiol. 2004;43(10):1731–7.
129. Diaz FJ, James D, Botts S, Maw L, Susce MT, de Leon J. Tobacco smoking behaviors in bipolar disorder: a comparison of the general population, schizophrenia, and major depression. Bipolar Disord. 2009;11(2):154–65.
130. Arias F, Arnsten JH, Cunningham CO, Coulehan K, Batchelder A, Brisbane M, Segal K, Rivera-Mindt M. Neurocognitive, psychiatric, and substance use characteristics in opioid dependent adults. Addict Behav. 2016;60:137–43.
131. Nesvåg R, Knudsen GP, Bakken IJ, Høye A, Ystrom E, Surén P, Reneflot A, Stoltenberg C, Reichborn-Kjennerud T. Substance use disorders in schizophrenia, bipolar disorder, and depressive illness: a registry-based study. Soc Psychiatry Psychiatr Epidemiol. 2015;50(8):1267–76.
132. Hidalgo-Mazzei D, Walsh E, Rosenstein L, Zimmerman M. Comorbid bipolar disorder and borderline personality disorder and substance use disorder. J Nerv Ment Dis. 2015;203(1):54–7.
133. Degenhardt L, Stockings E, Strang J, Marsden J, Hall WD. Illicit drug dependence. In: Patel V, Chisholm D, Dua T, Laxminarayan R, Medina-Mora ME, editors. Mental, neurological, and substance use disorders: disease control priorities, vol. 4. 3rd ed. Washington (DC): The International Bank for Reconstruction and Development/The World Bank; 2016. Chapter 6.
134. Comtois KA, Russo JE, Roy-Byrne P, Ries RK. Clinicians' assessments of bipolar disorder and substance abuse as predictors of suicidal behavior in acutely hospitalized psychiatric inpatients. Biol Psychiatry. 2004;56(10):757–63.
135. Lewinsohn PM, Klein DN, Seeley JR. Bipolar disorders in a community sample of older adolescents: prevalence, phenomenology, comorbidity, and course. J Am Acad Child Adolesc Psychiatry. 1995;34(4):454–63.
136. Garcia-Portilla MP, Saiz PA, Benabarre A, Florez G, Bascaran MT, Díaz EM, Bousoño M, Bobes J. Impact of substance use on the physical health of patients with bipolar disorder. Acta Psychiatr Scand. 2010;121 (6):437–45.
137. Martínez-Gómez D, Eisenmann JC, Gómez-Martínez S, Veses A, Marcos A, Veiga OL. Sedentary behavior, adiposity and cardiovascular risk factors in adolescents: the AFINOS study. Rev Esp Cardiol. 2010;63:277–85.
138. Vaccarino V, Votaw J, Faber T, Veledar E, Murrah NV, Jones LR, Zhao J, Su S, Goldberg J, Raggi JP, Quyyumi AA, Sheps DS, Bremner JD. Major depression and coronary ow reserve detected by positron emission tomography. Arch Intern Med. 2009;169: 1668–76.
139. Chuang HT, Mansell C, Patten SB. Lifestyle characteristics of psychiatric outpatients. Can J Psychiatr. 2008;53:260–6.
140. Penninx BW, Leveille S, Ferrucci L, van Eijk JT, Guralnik JM. Exploring the effect of depression on physical disability: longitudinal evidence from the established populations for epidemiologic studies of the elderly. Am J Public Health. 1999;89:1346–52.
141. Sylvia LG, Salcedo S, Bernstein EE, Baek JH, Nierenberg AA, Deckersbach T. Nutrition, exercise, and wellness treatment in bipolar disorder: proof of concept for a consolidated intervention. Int J Bipolar Disord. 2013;1(1):24.
142. Jacka FN, Pasco JA, Mykletun A, Williams LJ, Hodge AM, O'Reilly SL, Nicholson GC, Kotowicz MA, Berk M. Association of western and traditional diets with depression and anxiety in women. Am J Psychiatry. 2010;167(3):305–11.
143. Quirk SE, Williams LJ, O'Neil A, Pasco JA, Jacka FN, Housden S, Berk M, Brennan SL. The association between diet quality, dietary patterns and depression in adults: a systematic review. BMC Psychiatry. 2013;13:175.
144. Hall MH, Muldoon MF, Jennings JR, Buysse DJ, Flory JD, Manuck SB. Self-reported sleep duration is associated with the metabolic syndrome in midlife adults. Sleep. 2008;31(5):635–43.
145. Arora T, Jiang CQ, Thomas GN, Lam KB, Zhang WS, Cheng KK, Lam TH, Taheri S. Self-reported long total sleep duration is associated with metabolic syndrome: the Guangzhou Biobank Cohort Study. Diabetes Care. 2011;34(10):2317–9.
146. Gangwisch JE, Malaspina D, Babiss LA, Opler MG, Posner K, Shen S, Turner JB, Zammit GK, Ginsberg HN. Short sleep duration as a risk factor for hypercholesterolemia: analyses of the National Longitudinal Study of Adolescent. Health Sleep. 2010;33 (7):956–61.

147. Kaneita Y, Uchiyama M, Yoshiike N, Ohida T. Associations of usual sleep duration with serum lipid and lipoprotein levels. Sleep. 2008;31(5):645–52.
148. Millar A, Espie CA, Scott J. The sleep of remitted bipolar outpatients: a controlled naturalistic study using actigraphy. J Affect Disord. 2004;80(2–3): 145–53.
149. Jones SH, Hare DJ, Evershed K. Actigraphic assessment of circadian activity and sleep patterns in bipolar disorder. Bipolar Disord. 2005;7(2):176–86.
150. Harvey AG, Schmidt DA, Scarnà A, Semler CN, Goodwin GM. Sleep-related functioning in euthymic patients with bipolar disorder, patients with insomnia, and subjects without sleep problems. Am J Psychiatry. 2005;162(1):50–7.
151. Soreca I, Wallace ML, Frank E, Hasler BP, Levenson JC, Kupfer DJ. Sleep duration is associated with dyslipidemia in patients with bipolar disorder in clinical remission. J Affect Disord. 2012;141 (2–3):484–7.
152. Kwak SM, Myung SK, Lee YJ, Seo HG, Korean Meta-analysis Study Group. Efficacy of omega-3 fatty acid supplements (eicosapentaenoic acid and docosahexaenoic acid) in the secondary prevention of cardio-vascular disease: a meta-analysis of randomized, double-blind, placebo-controlled trials. Arch Intern Med. 2012;172:686–94.
153. Lin PY, Su KP. A meta-analytic review of double-blind, placebo-controlled trials of antidepressant efficacy of omega-3 fatty acids. J Clin Psychiatry. 2007;68:1056–61.
154. Sarris J, Mischoulon D, Schweitzer I. Omega-3 for bipolar disorder: meta-analyses of use in mania and bipolar depression. J Clin Psychiatry. 2012;73:81–6.
155. Carney RM, Freedland KE, Rubin EH, Rich MW, Steinmeyer BC, Harris WS. Omega-3 augmentation of sertraline in treatment of depression in patients with coronary heart disease: a randomized controlled trial. JAMA. 2009;302:1651–7.
156. Noaghiul S, Hibbeln JR. Cross-national comparisons of sea- food consumption and rates of bipolar disorders. Am J Psychiatry. 2003;160:2222–7.
157. McNamara RK, Jandacek R, Rider T, Tso P, Dwivedi Y, Pandey GN. Selective deficits in erythrocyte docosahexaenoic acid composition in adult patients with bipolar disorder and major depressive disorder. J Affect Disord. 2010;126:303–11.
158. Lin PY, Huang SY, Su KP. A meta-analytic review of polyunsaturated fatty acid compositions in patients with depression. Biol Psychiatry. 2010;68:140–7.

Borderline Personality Disorder and the Heart

18

Annalisa Boldrini

Contents

Abstract

Many researches point the existence of a rich network of direct and indirect connections between the brain and heart, resulting in a complex mix of processes involved in self-regulation and adaptability. Prefrontal cortex has a central role both in emotional, behavioral, and cognitive self-regulation and in the regulation of cardiac autonomic activity. Markers of prefrontal cortex activity could be indicators of the functional integrity of the neural networks implicated in emotion–cognition interactions. Heart rate variability (HRV) has gained increasing interest in psychiatry because of the link between autonomic dysfunction and psychiatric illness. In particular, neurobiological evidences point out Heart Rate Variability (HRV) as a transdiagnostic biomarker of psychopathology. In particular, his role as an index of vagal function, and thus of prefrontal inhibitory function, provides a useful key to understand the psychophysiological mechanisms underlying difficulties in emotion regulation and impulsivity in patients with BPD. Research findings on alterations in HRV in borderline personality disorder (BPD) individuals are thus consistent with the idea that emotion dysregulation is a key feature of BPD, related to an impairment in inhibitory control, which is the ability to inhibit and regulate prepotent emotions.

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*,
https://doi.org/10.1007/978-3-030-28008-6_25

Keywords

Borderline personality disorder · Heart rate variability · Emotion regulation · Impulsivity · Prefrontal cortex · Amygdala

Introduction

Borderline personality disorder (BPD) is a complex mental disorder described by a pervasive pattern of instability in self-image, affects, interpersonal relationships, and marked impulsivity, often resulting in self-destructive behavior. It is diagnosed by pathological personality traits in the domains of negative affectivity, emotional liability, anxiousness, separation insecurity, or depression and behavioral characteristics such as disinhibition (i.e., impulsivity and risk-taking) and antagonism (hostility) [1, 2]. BPD affects about 1–2% of the general population [3, 4] and is the most common personality disorder in clinical settings, with approximately 23% of psychiatric outpatients meeting diagnostic criteria for the disorder [5].

As underlined by Koenig et al. in a recent meta-analysis [6], many key features of BPD (i.e., emotional liability and impulsivity) are related to an impairment in inhibitory control, which is the ability to inhibit and regulate prepotent emotional responses. According to the neurovisceral integration model [7], developed from the theories enunciated by the great French Physiologist Claude Bernard over 150 years ago, neural networks implicated in emotional and cognitive self-regulation are also involved in the control of cardiac autonomic activity. The aim of this text is to describe the rich network of direct and indirect connections between the brain and heart, resulting in a complex mix of processes involved in self-regulation and adaptability. Prefrontal cortex plays a main role in these modulation processes; an alteration of its inhibitory function has been identified as a common feature of impairment in physiological, behavioral, emotional, and cognitive regulation, and it has thus been linked to many psychopathological conditions, among which borderline personality disorder. Many neurobiological evidences point out heart rate variability (HRV) as an indicator of the functional integrity of the neural networks implicated in emotion–cognition interaction. The present chapter will summarize the research findings linking alterations in HRV in BPD individuals, from psychopathology to physiology.

Neuroimaging Aspects of Borderline Personality Disorder

Although precise nature and etiopathogenesis of borderline personality disorder (BPD) continue to elude the efforts of researchers and clinicians, there is growing evidence that an interplay of altered emotion regulation, dysfunctional cognitive appraisals, maladaptive behavior patterns, and neurobiological alterations underlies BPD psychopathology [8]. Over the last decades, neuroimaging has become one of the most important methods to investigate structural and functional neurobiological alterations possibly underlying core features of BPD.

Krause-Utz et al. [9], reviewing several structural neuroimaging studies, showed reduced volume in the limbic and paralimbic brain regions, most prominently amygdala and hippocampus, as a common finding in patients with BPD compared to healthy controls [10–12]. Given the crucial role of the amygdala in emotion processing [13], this brain area is of high relevance to BPD psychopathology [2].

Interpretation of early volumetric studies is often complicated. This is particularly true for psychiatric condition with frequent comorbidity. In BPS traumatic experiences are frequent both in childhood and later in life; for this reason, it is important to control comorbidities such as post-traumatic stress disorder (PTSD), in which hippocampus and amygdala volume are also reduced. However, in a meta-analysis by Rodrigues and colleagues [14], volume reductions in the amygdala and hippocampus were found to be more pronounced in BPD patients with comorbid PTSD than in BPD patients without comorbid PTSD. A study by Niedtfeld et al. [15] found smaller volumes in BPD than in healthy controls

in the amygdala and hippocampus. Importantly, BPD symptoms' severity predicted volume loss in the amygdala regardless of PTSD comorbidity. Aside from volume reductions in limbic brain regions, structural abnormalities in various regions of the temporal and parietal lobes were reported in BPD [16]. In addition, many investigations in BPD patients revealed reduced volumes in the frontal and orbitofrontal cortex (OFC) [17–19]. These findings are particularly significant considering that OFC as well as dorsolateral prefrontal cortex (DLPFC) play a critical role in regulatory processes such as the downregulation of activation in limbic and subcortical brain areas [13] and impulse control [20]. In a study by Sala and colleagues [21], gray matter volume in the dorsolateral prefrontal cortex (DLPFC) was inversely correlated with measures of impulsivity in a group of BPD patients.

These findings were corroborated by studies investigating structural connectivity between brain regions. For example, Carrasco and colleagues [22] examined microstructural abnormalities of white matter tracts in the prefrontal cortex (PFC) in BPD, displaying a significant damage of white matter in the corpus callosum and loss of bilateral prefrontal white matter fasciculi. Interestingly, volume reductions of the OFC [23], anterior cingulated cortex (ACC) [24], DLPFC [25], and left caudal superior temporal gyrus [26] were reported in adolescents with BPD compared to controls, while volumes of the amygdala and hippocampus [23] were found to be unaffected in teenagers with BPD.

The role of amygdala and frontal cortical alterations in BPD has been confirmed by a large number of functional neuroimaging studies, investigating reactivity to standardized emotional material in patients with BPD compared to healthy controls (for an overview, see [27]). The majority of these studies observed hyper-reactivity of limbic brain areas in response to negative emotional stimuli, most prominently in the amygdala [28–36] and insula [33, 34, 36–38] in BPD patients compared to healthy controls. Recent studies also demonstrated a slower return of amygdala activation to baseline in BPD [39].

In addition to limbic hyper-reactivity, numerous functional neuroimaging studies revealed a hypo-activation of frontal brain regions in response to emotionally arousing or trauma-related stimuli. For example, in the study by Minzenberg and colleagues [35], BPD patients showed amygdala hyper-reactivity to fearful faces but also exhibited decreased activation in the ACC. Consistently, in a positron emission tomography (PET) study, New and colleagues demonstrated an altered metabolic activity in limbic and prefrontal areas as well as lower correlation between right OFC and ventral amygdala metabolism in BPD patients [40].

A possible explanation of these neuroimaging findings is that an impairment in inhibitory circuits of prefrontal cortex may contribute to hyper-reactivity of amygdala, leading to deficient emotion regulation capacities in BPD. It has been proposed that early-life maltreatments or traumas in the context of the primary attachment relationships could impair the maturative configuration of the cerebral structures implied in stress regulation and emotional regulation [41]. In this process, prefrontal cortex plays a central role.

The implications of an emotional hyper-activation in BPD subjects are clarified by the model outlined by Mayes [42], based on Arnsten's [43] dual-arousal system model. This model suggests the existence of two different but complementary arousal systems: the prefrontal cortical system and the posterior cortical and subcortical system. The prefrontal cortical system inhibits the second arousal system, which is normally active for elevated levels of emotional stress. In fact, as the level of cortical activation increases through mutually interactive norepinephrine α2 and dopamine D1 systems, prefrontal cortical function improves, including the capacity for attentional control, planning/organization, and explicit reflective functioning. However, with further increases of arousal, norepinephrine α1 and dopamine D1 inhibitory activity increases to the point that the prefrontal cortex goes "offline" and posterior cortical and subcortical functions enhance and finally take over: there is a switch from relatively flexible and slow executive functions

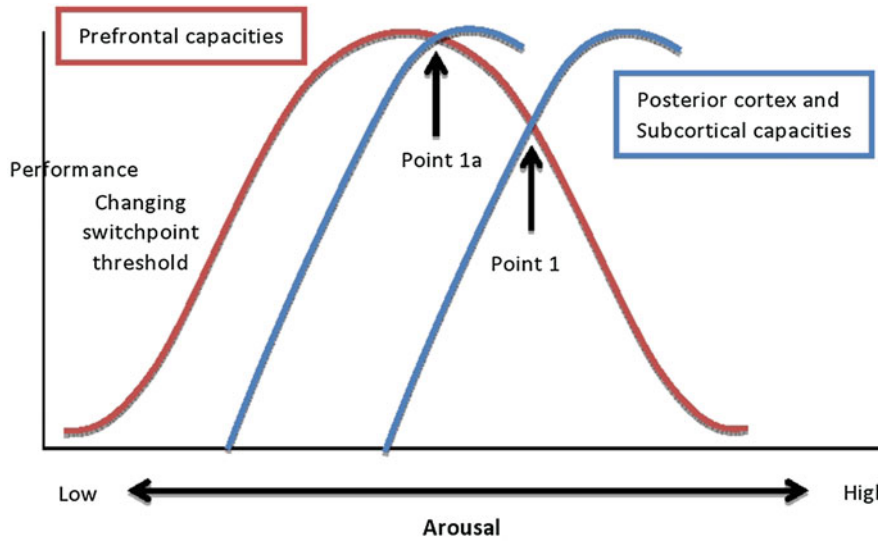

Fig. 1 Mayes' (2000) adaptation of Arnsten's dual arousal system model [42]. In borderline personality disorder, the threshold for switching from relatively flexible and slow executive functions meditated by prefrontal cortex to faster, automatic, and instinctual behaviors mediated by posterior cortical and subcortical structures (e.g., amygdala, hippocampus, and striatum) is translated from point 1 to point 1a. This switch occurs thus for lower levels of emotional arousal

mediated by the prefrontal cortex to faster habitual, automatic, and instinctual behaviors mediated by posterior cortical (e.g., parietal) and subcortical structures (e.g., amygdala, hippocampus, and striatum), known as fight–flight–freeze responses. Thus, self-protective physical reactions (fight–flight–freeze) come to dominate behavior.

According to Schore [41], Luyten, Mayes, et al. [44] assume that an impaired self-regulation ability arouses the background level of activation particularly in attachment context, reaching the point at which the switch from more prefrontal and controlled to more automatic responses occurs. In particular, in BPD the exposure to early stress and trauma could result in a lowering of the threshold for behavioral switching. If the switch point is translated from point 1 to point 1a (see Fig. 1), the subject will show a primitive and automatic response for lower levels of emotional arousal than in normal subjects.

This point is central to investigate emotional regulation in BPD, which has been shown to be altered in particular in response to relevant personal stimuli eliciting hyper-intense emotional arousal.

Prefrontal Cortex, Inhibition, and Self-Regulation

Adaptation to changing environment is a key ability for living organisms, and ultimately the species, to survive. According to neurovisceral integration model [7, 45], adaptation is mediated by influences from many sources: physiological, behavioral, affective, cognitive, social, and environmental. A hallmark of successful adaptation is flexibility in the face of changing physiological and environmental demands, providing an organism with the ability to integrate signals from inside and outside the body and adaptively regulate perception, cognition, action, and physiology. The result of this process of self-regulation is the ability to flexibly choose responses that are appropriate for different situational demands [45]. Several neural systems associated with cognitive, emotional, and autonomic self-regulation have been identified, one of which is the *central autonomic network* (CAN) [7, 45, 46]. The structures of the CAN include the anterior cingulate, the insula, the ventromedial prefrontal cortex,

the central nucleus of the amygdala, the paraventricular and related nuclei of the hypothalamus, the periaqueductal gray matter, the parabrachial nucleus, the nucleus of the solitary tract (NTS), the nucleus ambiguus, the ventrolateral and ventromedial medulla, and the medullary tegmental field, among others. These brain structures are reciprocally connected, and information can flow in both top-down and bottom-up ways, in order to elicit visceromotor, neuroendocrine, and behavioral responses that are adaptive and flexible for various environmental demands [7, 45, 47]. Interestingly, many of these structures have been identified as linked with BPD in the neuroimaging studies descripted above.

Obviously, the capacity to effectively choose behavioral responses requires a correct appraisal (whether conscious or unconscious) of situations of threat and safety. To illustrate the importance of threat appraisal, Thayer et al. [48] make the example of one of our ancestors walking in the woods and seeing something coiled on the path ahead, which could be a harmless vine or a deadly snake. If the ancestor assumes that the amorphous shape is a threat, he will change path and thus live another day and perhaps procreate, passing on his genes to future generations. If he wrongly evaluates the path is safe and proceeds ahead, he could die. So, the adaptive response is to assume that the coiled object is a threat, and such appraisal can be made rapidly and without much deliberation.

It has been suggested that, among CAN structures, the amygdala may serve as a rapid detector of potential threats and a mediator of adaptive "fear" responses [49]. Given the evolutionary advantage associated with the assumption of threat, many authors propose that the "default" response to uncertainty, novelty, and threat is the sympathoexcitatory preparation for actions commonly known as "fight-or-flight" response [7, 45, 50]. This kind of response is context-sensitive, with a major impact of negative information over positive information in guiding behavior ("negativity bias"; see [51]). From an evolutionary perspective, this system is very useful because it acts maximizing adaptive responses and survival; in other words, it is a system that "errs on the side of caution" [49].

However, in typical daily life in modern society, continual perception of threat is maladaptive, causing the prevalence of "fight-or-flight" behavioral responses, and it is associated with dysregulation in hippocampal circuits, endocrine and autonomic output, and cognitive and general health decline [52–56]. If living under a chronic state of threat is maladaptive, it becomes important for an organism to determine if threat appraisals are appropriate depending on the context. The prefrontal cortex, and the ventral medial prefrontal cortex (vmPFC) in particular, is central in this process.

In safe contexts, "fear" or threat representations in the amygdala appear to be inhibited by PFC. A variety of manipulations of vmPFC, including pharmacological and electrical stimulation, inhibit subcortical threat circuits and reduce stress responses and fear behavior [57–60]. Thus, it is possible to state that prefrontal cortex plays a central role in inhibitory processes – which are fundamental components of many executive functions including working memory, attentional set-shifting, and response inhibition but also of affective functions including emotional regulation, affective set-shifting, and extinction – to support goal-directed behavior [45, 61, 62].

According to this idea, under normal circumstances prefrontal cortex identifies safety cues from the environment and exerts its inhibitory control over sympathoexcitatory subcortical circuits, including the central nucleus of the amygdala, tonically inhibited via GABAergic-mediated projections by prefrontal cortex [63–66]. The removal of this inhibition permits (rather than causes) an increase in physiological activity, with disinhibition of sympathoexcitatory circuits that are essential for energy mobilization. However, a prolonged inhibition of prefrontal cortex under conditions of uncertainty (resulting in a disinhibition of sympathoexcitatory subcortical threat circuits) may be maladaptive, causing the prevalence of "fight-or-flight" behavioral responses. Not surprisingly, many psychopathological states including depression [67, 68], anxiety [69], schizophrenia [70, 71], and addictive behavior (for a review, see [72]) are associated with prefrontal hypoactivity and a lack of

inhibitory neural processes. This is reflected in poor habituation to novel neutral stimuli and therefore a failure to recognize neutral signals, with a sort of preattentive bias for threat information resulting in an increased negativity bias, deficit in executive functions, and poor affective information regulation [73–75].

Interestingly, however, the functional relationship between the amygdala and the vmPFC is likely to be more complicated than an automatic inhibition of the amygdala by vmPFC, for several reasons. First of all, vmPFC stimulation seems not to automatically reduce fear or potentiate fear extinction but rather to play a role in the consolidation and retrieval of safety context memories. Second, it is associated with higher-level appraisal processes that operate under the guidance of information retrieved from long-term memory. In other words, vmPFC inhibitions of threat circuits which are by default active depend on integrating external context (environmental threat) with the internal one (perceptions of control over the threat), with a more powerful protective role when cognitive appraisals are specifically engaged to regulate emotions [76–78]. For example, a research by Thayer and Siegle [79] supports the idea that the amygdala responds rapidly to biologically relevant positive or threatening stimuli but may be subsequently inhibited if the stimuli are appraised to be safe or innocuous. Thus, Thayer et al. [48] suggest a new view of the stress response: not an exaggerated reaction to threatening signals but a failure to recognize safety signals with threat responses to neutral or harmless stimuli (see also [80, 81]). According to this vision, Buchanan et al. [82] reported that patients with damage to mPFC perceived a challenging social situation as more threatening to those with damage to another brain region or non-brain damaged controls.

The researches discussed above suggest that proper functioning of prefrontal cortex, and in particular vmPFC, is vital for cognitive, affective, and physiological inhibitory processes necessary for the detection of safety and threat and thus to regulate behavior. According to this views, a predisposition to chronic threat perception and thus to amygdala hyper-activation should be associated with a vmPFC dysfunction in integrating external and internal context and thus to dysregulated brain-peripheral integration.

As a significant point, these inhibitory prefrontal processes can be indexed by measures of vagal function such as HRV. Consistent with this hypothesis, Shook et al. [75] showed that a smaller negativity bias and a greater capacity to approach positive novel objects in uncertainty situations are associated with greater resting HRV. In addition, it has been reported that greater resting HRV is associated with more rapid extinction in an interoceptive fear conditioning paradigm [83]. Thus, showing the association of HRV with the structures and functions of the descripted "brain's threat-detection system" means that HRV might be useful as an index of how this regulatory system works.

To better understand how this inhibitory circuit acts also on the cardiovascular system to influence heart rate (HR) and heart rate variability (HRV), it is useful to describe briefly the cortical control of cardiac activity.

Cortical Control of Cardiac Activity

Heart rate is determined by intrinsic cardiac mechanism and the joint activity of the autonomic nervous system (ANS) at the sinoatrial node. In normal conditions, both branches of the ANS are tonically active in the control of HR, leading to both a tonic acceleratory drive (sympathoexcitatory action) and a tonic deceleratory drive (parasympathoinhibitory action) to the heart [84, 85]. Importantly, when both cardiac parasympathetic and sympathetic inputs are blocked pharmacologically (e.g., with atropine plus propranolol, the so-called double blockade), intrinsic HR is higher than resting HR [84]. This fact supports the idea that the heart is under tonic inhibitory control by parasympathetic influences and precisely peripherally via vagus nerve [85, 86].

Many researches have been directed at identifying the pathways by which cortical activity modulates cardiovascular function. In primates and humans, there appear to be both direct and indirect pathways connecting the frontal cortex to autonomic motor circuits responsible for both the

sympathoexcitatory and parasympathoinhibitory effects on the heart (see [45, 87–98]).

In the model proposed by Thayer and Lane [7], prefrontal cortical areas including the orbitofrontal cortex (OFC) and medial prefrontal cortex (mPFC) tonically inhibit the amygdala via pathways to intercalated GABAergic neurons in the amygdala [88, 95]. The central nucleus of amygdala is the main efferent modulator of cardiovascular, autonomic, and endocrine responses; it could be activated (disinhibited) by three ways:

1. Activation (disinhibition) of tonically active sympathoexcitatory neurons in the rostral ventrolateral medulla (RVLM) by decreased inhibition from tonically active neurons in the caudal ventrolateral medulla (CVLM), resulting in an increase in sympathetic activity.
2. Inhibition of neurons in the nucleus of the solitary tract (NTS) with consequent inhibition of tonically active neurons of nucleus ambiguous (NA) and dorsal vagal motor nucleus (DVN), resulting in a decrease in sympathetic activity.
3. Direct activation of sympathoexcitatory RVLM neurons, resulting in an increase in sympathetic activity (minor pathway).

Globally, decreased activation of the prefrontal cortex would lead to disinhibition of the tonically inhibited central nucleus of amygdala. The activation of amygdala would lead to a simultaneous disinhibition of sympathoexcitatory neurons in the RVLM (pathway number 1 above) and an inhibition of parasympathoexcitatory neurons (pathway number 2 above); the result would be an increase in heart rate (HR) and a simultaneous decrease in vagally mediated heart rate variability (vmHRV) [7]. This association between prefrontal cortical activity and vmHRV has been proved in a series of studies using both pharmacological and neuroimaging approaches [99–104].

The core idea of the neurovisceral integration model is the existence of a "supersystem" able to continuously assess the environment for signs of threat and safety and then to adaptively regulate cognition, perception, action, and physiology in order to prepare the organism for the best behavioral response. In addition, this system monitors the match between external environment and internal homeostatic processes to generate adaptive physiological adjustments. This implies the existence of multiple processes influencing one another, so that the system has to oscillate spontaneously within a range of states. When these processes are balanced, the system can respond flexibly to a wide range of physical and environmental demands. When the system becomes unbalanced, a particular process can come to dominate the system's behavior, rendering it unresponsive to the normal range of inputs [48]. In the context of physiological regulation, and heart regulation specifically, a balanced system is healthy [105]; this is why the HR oscillate spontaneously (showing high HRV). Thayer and colleagues [48], thus, suggest the idea that HRV may be more than just an index of healthy heart function and may in fact provide an index of the degree to which the brain's "integrative" system for adaptive regulation provides flexible control over the periphery, leading the organism to effectively function in a complex environment.

The lack in emotion regulation in BPD has been proposed to be caused by taking "off-line" of prefrontal cortex during threat to let automatic, primitive, and prepotent processes regulate behavior [106]. In fact, the conscious experience of emotion requires the transmission of subcortical affective information to the cerebral cortex, with a top-down inhibitory and thus modulatory effect on the subcortical centers that shapes the nature of subjective experience. As seen, this top-down effect is consequently necessary to produce appropriate responses to environmental demands [63, 107, 108]. According to the idea of the existence of a unique inhibitory "supersystem" with a central integration role of PFC, whose output HRV measures, it could be hypothesized that HRV is used as a marker of emotion dysregulation in BPD.

Heart Rate Variability as a Marker of Emotional Regulation

Consistent with the theories descripted above, in the last decades, cardiac vagal (parasympathetic) tone has emerged as a psychophysiological

marker of many aspects of emotional regulation and behavioral functioning in both children, adolescents, and adults. Research efforts during these years have produced an extensive list of vagal tone indices.

As mentioned earlier, the heart is dually innervated by ANS so that relative increases in sympathetic activity are associated with HR increases, causing the time between heartbeats (interbeat interval) to become shorter, while relative increases in parasympathetic activity are associated with HR decreases, causing the time between heartbeats to become longer. When both cardiac parasympathetic and sympathetic inputs are blocked pharmacologically (e.g., with atropine plus propranolol, the so-called double blockade), intrinsic HR is higher than resting HR [84], supporting the idea that the heart is under tonic inhibitory control by parasympathetic influences: parasympathetic dominance over the sympathetic system thus favors energy conservation. In addition, the sympathetic effects are slow, on the time scale of seconds, while the parasympathetic effects are fast, on the time scale of milliseconds. Thus, vagal dominance is also implied by the beat-to-beat variability over a wide range which characterize HR time series: in fact, the sympathetic influence over the heart is too slow to produce beat-to-beat changes. So, to assess vagal tone, it becomes important to detect the variability in HR which is specifically related to parasympathetic activity having the sequence of time intervals between heartbeats as basic data for the calculation of all measured HRV.

For these reasons, many researchers tried to find HRV measures that are devoid of sympathetic influences other than beat-to-beat measures, by applying spectral analyses to the ECG recordings. Spectral analysis consists in the decomposition of HR time series into component frequencies using mathematical algorithms, such as Fourier transformations. The resulting total power can be divided into very-low-frequency variability (less than 0.04 Hz), low-frequency variability (between 0.04 and 0.15 Hz), and high-frequency variability (more than 0.15 Hz). Pharmacologic blockade studies have shown that sympathetic influences on HRV are linked to low frequencies and mid-frequencies, whereas parasympathetic influences are observed mainly in the high-frequency range [109, 110]. Therefore, high-frequency heart rate variability (HF-HRV) represents primarily parasympathetic influences over the heart.

The root mean square of the successive R-R interval differences (RMSSD) is an important time-domain beat-to-beat measure, among the large variety of measures which have been used to operationalize HRV. Another measure which has been widely used to estimate vagal tone is respiratory sinus arrhythmia (RSA) or the degree of ebbing and flowing of heart rate during the respiratory cycle [109–112]. RSA results from increases in vagal efferences during exhalation, with a deceleration of HR, and decreases in vagal efferences during inhalation, with an acceleration of HR. The high-frequency component of the power spectrum (HF power), RSA, and time-domain measures reflecting these fast changes has thus been considered as available measures of vagal activity. In particular, RMSSD showed to be highly correlated with the high-frequency component of the power spectrum (Task force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [113]), being used as measures of vagally mediated HRV in several studies [114–116].

The conclusion that HF-HRV marks PFC function is based on three considerations, according to Beauchaine and Thayer [117]. First, according to neurovisceral integration theory descripted above [65], it has been known the existence of inhibitory neural efferent pathways from medial PFC to the parasympathetic nervous system (the substrate of HF-HRV); through this network efficient PFC function is translated into high tonic and well-regulated phasic HF-HRV. Second, there are positive associations between resting HF-HRV and performance on executive function tasks, widely known to be mediated by PFC [118–120]. Third and perhaps most convincingly, there are positive correlations between HF-HRV and PFC activity as assessed by pharmacological blockade [99], lesion studies [82], cerebral blood flow using positron emission tomography (PET), and functional magnetic resonance imaging (fMRI). In particular, Thayer et al. [48] provide a meta-analysis of

neuroimaging published studies in which HRV has been related to functional brain activity using either PET or fMRI, with the goal to identify areas that were consistently associated with HRV. Studies identified three regions: the right pregenual cingulate of mPFC, the right subgenual cingulate of mPFC, and the left sublenticular extended amygdala/ventral striatum. Moreover, authors tried to identify cerebral areas in which HRV was closely associated with emotional versus cognitive/motor tasks, pointing out once specifically the role of the mPFC, and in particular of the right rostral mPFC.

Beauchaine and Thayer [117] identify HRV as a measure of emotion regulation and of prefrontal cortex activity, and thus conceptualize HF-HRV as transdiagnostic biomarker of psychopathology, in the contest of a model of vulnerability in which individual differences in approach motivation and avoidance motivation – related to activity of subcortical neural circuits – interact with effortful self-regulation, related to activity of cortical neural circuits, to affect behavior [65, 117, 121]. Abnormally low resting HF-HRV and excessive HF-HRV reactivity to different challenges – in particular emotional challenges – has displayed to be associated with symptoms of both internalizing and externalizing psychopathology and with a wide range of psychopathological syndromes, including anxiety, phobia, attention problems, conduct disorder, callousness, depression, autism, non-suicidal self-injury, trait hostility, psychopathy, and schizophrenia [109, 122, 123].

Vagal Tone in Borderline Personality Disorder

Focusing the attention on borderline personality disorder, emotion dysregulation has been widely considered as the core feature of the disorder [124] or a key facet of the disorder [125, 126]: thus, the study of HRV in BPD patients becomes very interesting. It is important to note that emotion dysregulation has been proposed to be distinguished in two components: emotional reactivity and emotion regulation [127]. Emotional reactivity refers to physiological and behavioral changes in response to an emotionally evocative stimulus, and it has been studied addressing resting state or baseline physiological level of vagal activity. Emotion regulation refers to the process by which a subject attempts to modulate the emotion-generative process, often with the goal of decreasing emotion intensity; it has been evaluated addressing the variation of vagal activity in response to emotional challenges. Researches were addressed to find out if either of these aspects were related to BPD. A majority of emotion-based research in BPD has addressed emotion reactivity, using a wide range of investigation methodologies including laboratory paradigms with negative images, scripts, and film clips. Findings from this literature are mixed, but recent evidence suggests that emotional reactivity in BPD may not be pervasive but rather specific to personally relevant negative stimuli [128, 129]. Research examining emotion regulation in BPD is smaller, showing some evidence that individuals with BPD could be able to effectively reduce their emotional reactivity using strategies of cognitive reappraisal (which means generating new appraisals of a situation to reduce its emotional impact; see [130]). However, the findings are often limited (e.g., to the examination of only one strategy of emotion regulation) and thus not generalizable.

To organize and clarify the evidence on alterations in resting state vmHRV in BPD individuals, Koenig and colleagues [6] recently meta-analyzed literature about this topic. They searched literature for empirical investigations in humans comparing any measure of recorded vmHRV in clinical samples of BPD patients (diagnosed according to clinical criteria, validated structural clinical interviews or psychometric instruments with high specificity and sensitivity) and healthy controls. A total of five studies [131–135] were considered eligible for inclusion in the meta-analysis (see Table 1).

Austin et al. [131] measured RSA during viewing of three 10 min film clips; the first and the third film clips were selected to elicit a strong emotional response, while the second film clip was a neutral scene. The clinical group was composed of 9 female BPD patients, who were off medication while participating in the study, while the control

Table 1 Studies included in Koenig et al. 2016 [6]

Authors/ year	BPD criteria	N (female)	Mean age (SD)	vmHRV indices	Condition at recording	Length of recording	BPD/HRV resting state differences
Austin et al. (2007)	Clinical, DSM-IV, SCID	BPD: 9 (9)[a] HC: 11 (11)	18–45	RSA estimates, R-R intervals	Seated in a quiet room facing a television screen	10 min, last 5 min analyzed	No baseline differences
Dixon-Gordon et al. (2011)	PAI-BOR	High BPD: 28 (28) Mid BPD: 30 (30)[b] Low BPD: 28 (28)	All: 21.59 (5.57)	RSA	True and vanilla baselines; asked to sit very still (true baseline) followed by a vanilla baseline (sitting still and counting the number of times a specific chosen color appeared on a computer screen)	5 min	No significant group x time effect on RSA
Gratz et al. (2013)	Clinical, DSM-IV, SCID-I and DIPD-IV	BPD AVPD: 13 (14) NPD NO-AVPD: 26 (26) HC: 11 (11)	BPD AVPD: 24.9 (11.3) NPD NO-AVPD: 24.6 (8.8) HC: 24.1 (11.5)	HF-HRV	Baseline, not further specified	5 min	No significant group differences in HF-HRV at baseline
Kuo and Linehan (2009)	Clinical, DSM-IV	BPD: 20 (20) SAD: 20 (20) HC: 20 (20)	BPD: 23.55 (n.r.) SAD: 23.90 (n.r.) HC: 23.30 (n.r.)	RSA	True and vanilla baselines; instructed to maintain wakefulness and sit quietly and still (true baseline); non-stressful, non-demanding cognitive task requiring to count the number of times a specific chosen color appeared on a computer screen (vanilla baseline)	30 s	BPD showed reduced basal RSA
Weinberg et al. (2009)	MSI-BPD	BP: 12 (n.r.)[c] HC: 28 (n.r.)	All: 19.9 (5.0)	RSA	Participants were asked to sit still and relax	4 min/ 4 min	BPD exhibited significantly lower parasympathetic activity overall

AVPD Avoidant personality disorder, *BP*D borderline personality disorder, *HC* healthy controls, *HRV* heart rate variability, *MSI-BPD* McLean Screening Instrument for Borderline Personality Disorder, *RSA* respiratory sinus arrhythmia, *SAD* social anxiety disorder

[a]Data from one participant was lost during baseline condition. However, it is not reported if it was a BPD or control participant. Total n before dropout reported and used for analysis

[b]Only the high and slow BPD groups were compared for analysis. Reported n differs in the manuscript. N of participants who accepted invitations to participate in the laboratory portion of the study used

[c]Of the entire sample, 29 participants were female, and 11 were male

group was composed of 11 female controls, free of psychiatric or neurological disorders. The authors reported that RSA was similar for the two groups during baseline, but over the course of experiment, it increased in HC while decreased in BPD patients.

Gratz et al. [132] measured resting baseline and phasic HF-HRV during a distress-tolerance task. The clinical group was composed of 39 female BPD patients, further divided into two subgroups: those with comorbid avoidant personality disorder (AVPD, 13 patients) and those without comorbid avoidant personality disorder (26 patients). The control group was composed of 11 healthy controls. All participants were excluded for current mood episodes (past 2 weeks), current substance dependence (past month), primary psychosis, and current use of psychotropic medications other than antidepressants, including benzodiazepines, mood stabilizers, and beta-blockers. The authors found no significant differences comparing BPD with AVPD, BPD without BPD, and controls on HF-HRV at baseline and HRV during the low-stress section of the distress tolerance task. They noted that while BPD with AVPD displayed a decrease in HF-HRV reactivity, the other two groups displayed a slight increase. They concluded that without emotional distress, BPD participants respond similarly to normal controls.

The study by Kuo and Linehan [134] investigated RSA in 20 women with BPD, 20 women with social anxiety disorder (SAD), and 20 women without a current Axis I diagnosis or BPD diagnosis. All participants were excluded for schizophrenia, schizophreniform, and schizoaffective disorders, psychosis not otherwise specified, bipolar disorder, current substance dependence, epilepsy or other seizure disorders, asthma, heart disease, current use of psychotropic medications other than selective serotonin reuptake inhibitors (SSRIs), major tranquilizers, antihistamines, and beta-blockers. The study consisted of two sessions in counterbalanced order. In one session there were baseline recordings (true and vanilla baseline, each 4 min) followed by standardized emotion induction (sad, fear, anger, and neutral). During the vanilla baseline, participants engaged in a non-stressful, nondemanding cognitive task requiring them to count the number of times a specified color appeared on a screen. The other session comprised baseline recordings followed by emotion induction using personal relevant content. The authors found that BPD patients showed reduced baseline RSA compared with controls and SAD patients. After investigating interactions between group status and phase of the study, the only significant difference was found between BPD and SAD patients during the sad emotion induction, with a significant increase in RSA from baseline to the sad film in BPD subjects; the SAD subjects displayed a non-significant decrease in RSA.

Weinberg et al. [135] investigated RSA and cardiac sympathetic index (CSI), a measure of sympathetic activity) in 12 participants with BPD and 28 controls without BPD. Participants were not excluded for medical status. CSI was evaluated using a baseline resting period, followed by a mental arithmetic task. The authors noted a gender effect on RSA and CSI, with female participants showing lower parasympathetic activity and higher sympathetic activity, respectively. Among groups, BPD participants displayed lower overall parasympathetic activity compared to controls; this effect was robust including gender as a covariate. BPD participants also displayed a higher sympathetic activity compared to controls. The authors did not find any effect of group or gender on HR.

Dixon-Gordon et al. [133] assessed BPD features in female university students, divided in three groups: low borderline personality ($n = 28$), mid-borderline personality ($n = 30$), and high borderline personality features ($n = 28$). Participants completed a true baseline and a vanilla baseline, responded to three problem-solving test procedures scenarios, completed a second vanilla baseline, underwent the negative emotion induction procedure, responded to other three scenarios, and then completed a final true baseline. HRV was measured continuously during the whole procedure. The authors found no significant group or condition effect on RSA.

Koenig and colleagues subjected to meta-analysis data from these studies to summarize

differences on resting vagal tone, indexed by vmHRV, comparing patients with BPD (n = 128) and healthy controls (n = 143); they applied transformations to the indices used and requested additional data when necessary. The study by Austin et al. [131] reported reduced RSA in BPD patients, although statistical tests did not reach the level of significance. The study by Gratz et al. [132] reported no significant differences between the three groups (BPD, BPD-AVP, HC) on baseline HF-HRV; they displayed however a trend in acclimation HF-HRV (which refers to the low-stress levels of the stress test used; see [132], Table 1), with a linear increase in HF-HRV from individuals with BPD and comorbid AVPD (lowest HF-HRV), followed by individuals with BPD without comorbid AVPD, to healthy controls (highest HF-HRV). The study published by Dixon-Gordon et al. [133] did not obtain any significant group differences, but a graphical display of baseline RSA values (see [133], Fig. 1) showed a linear trend, such that individuals high on BP features display the lowest RSA, followed by those with moderate BPD features, with participants low on BPS features displaying the greatest levels of RSA.

Globally, the meta-analysis shows that a significant reduction in vagal tone might be an important trait characteristic in BPD, providing a psychophysiological mechanism underlying difficulties in emotion regulation and impulsivity in BPD patients. Despite this, several experimental studies have failed to find a baseline difference [131–133]. A similar result was obtained by Meyer et al. [136], who compared HRV parameters of patients with PTSD, current BPD, and BPD in remission with healthy volunteers in a 5-min resting state ECG recording. Although the study displayed significant differences between the groups in both HRV time domain and frequency domain (in particular, a significant reduction of all the measures in PTSD patients), patients with current BPD did not differ significantly from those from HC in any of the analyzed HRV measures. The results of this study are thus inconsistent with the recent meta-analysis by Koenig et al. [6]. This finding could be explained referring to the experimental methodology used. Recruited subjects were asked to take part in an emotional face recognition task (requiring the classification of ambiguous angry and happy facial expressions) and, then, after a short break of about 10 min, were seated in a relaxing and comfortable situation to record a 5-min resting state ECG. This kind of task may be not able to trigger emotional reactivity in BPD, which is not pervasive, but rather specific to personally relevant negative stimuli [128, 129]. Despite this limitation, the study has the strength to address together two trauma-related diseases, such as PTSD and BPD, consistently with the idea that traumatic experiences, either early-life maltreatment or acute or chronic stress later in life, could have a severe impact on ANS [136]. The design study does not allow to clarify whether alterations in HRV are a result of the disorder or a precondition that gives trauma the foundation to lead to mental illness. However, authors underline the negative correlation of self-reported early-life maltreatments (assessed with the Childhood Trauma Questionnaire, by Bernstein and Fink [137]) and mean independent RMSSD of the diagnostic group: this finding supports the idea of an interaction between early-life maltreatments, altered ANS regulatory capacities, and increased vulnerability to adverse life events.

Future studies are needed to investigate younger sample of BPD patients to explore if decreased vagal tone represents an endophenotype preceding the development of BPD or instead, whether it is a consequence of the disorder's psychopathogenesis. There is in fact some evidence supporting that lower vmHRV might precede the development of BPD. Research on the genetic and environmental influences on human HRV has shown that genetic actors account for between 13% and 57% [138, 139] of the variation among HRV measures in adults and there is good evidence for genetic contribution to HRV in children [140]. Moreover, important heritable trait such as affective instability is related to HRV [141], so that individuals with lower parasympathetic tone are emotionally less stable.

On the other side, research has shown that a persistent emotional stress influences vagal

modulation of the heart, regardless of the trait anxiety [142], which is consistent with recent findings on how the early caregiving environment shapes the stress response system reactivity in humans [143]. Childhood abuse and neglect might overstrain early adaptive emotion regulation capacities, during the sensitive period of infancy, and finally might constitute a developmental pathway to BPD. Reduced adaptive capacities – indexed by lower resting vmHRV – might represent a predisposition (trans-generational perspective) that is further burdened by early-life experience within the child environment [144]. Two studies by Koenig et al. [145, 146] explored resting cardiac function in adolescents engaging in non-suicidal self-injury (NSSI). They found that vmHRV was inversely correlated to global functioning and directly correlated with the number of BPD symptoms. These findings remained after controlling with a stepwise regression analysis for a series of variables, which have been previously discussed to potentially underlie altered ANS function in BPD (e.g., BMI, smoking, alcohol intake, medications, among others): a decrease in vmHRV showed to be related to greater symptom severity in BPD, so that authors hypothesize that cardiac function in adolescent engaging non-suicidal self-injury could be less indicative of current behavioral symptoms of affective states but of phenotypic traits and level of functioning. Subsequently, Koenig et al. [146] investigated longitudinal covariance of cardiac function and BPD symptoms in adolescents NSSI, completing a baseline and 1-year follow-up assessment of physiological data, clinical interviews, and self-reports. In this research, changes in BPD symptomatology were associated with changes in HR and vmHRV, suggesting the utility of cardiac markers to track treatment outcome in BPD.

The possible reversibility of vagal dysfunction in BPD patients by effective psychotherapeutic treatment is thus another important research task, as pointed by Koenig and colleagues [6]. It has been displayed in depressed patients that sertraline treatment led to significant increase in the covariation of synchronized neural activity (measured with fMRI) and vagal control (HRV measured with ECG recordings) for patients compared to controls [147]. In BPD, psychotherapy is the primary treatment option. Exploring the impact of available treatment options on resting state vmHRV, as well as the potential to monitor therapeutic outcome through the assessment of vmHRV, is an interesting field for future research. On the other hand, authors suggest it would be interesting to explore if potential treatment options designed to increase cardiac vagal tone during the resting state (e.g., physical activity; see [148, 149]) might lead to improved emotion regulation capacities in individuals with BPD.

Conclusion/Summary

In conclusion, HRV has been widely identified as a transdiagnostic biomarker of psychopathology. In particular, his role as an index of vagal function, and thus of prefrontal inhibitory function, provides a useful key to understand the psychophysiological mechanisms underlying difficulties in emotion regulation and impulsivity in patients with BPD. Research on this topic is still at the beginning: despite some studies in this direction, it is necessary to further investigate adolescents with BPD to point out if decreased vagal tone represents an endophenotype preceding the development of disorder, or whether it is a consequence of the disorder. Future studies need also to improve by addressing larger standardized samples and carefully controlling for the effect of psychotropic medications and comorbid psychopathology, often present in those with BPD, but also by using reliable standardized vagal tone measures. To this purpose, Quintana et al. [150] provided recommendations to improve HRV research in psychiatry, introducing Guidelines for Reporting Articles on Psychiatry and Heart rate variability (GRAPH) checklist for good practice; these guidelines consist of four main areas: selection of participants, interbeat interval collection, data analysis and cleaning, and HRV calculation. Carr et al. [151] referred to this checklist to

identify studies following the GRAPH checklist relatively well.

Moreover, comorbid physical pathology has to be controlled too: altered HF-HRV also marks several adverse health outcomes, including cardiovascular disease [152] and diabetes [153], and is more strongly related to self-rated health than other common biomarkers [154]. In a population-based observational study among Quebec residents aged 14 years and older, cluster B PD diagnosis is associated with a loss of 9–13 years of life expectancy at age 20 years, explained by both suicide rate and medical comorbidities: interestingly, the three most important causes of death were suicide (20.4%), cardiovascular diseases (19.1%), and cancers (18.6%) [155]. Similar findings emerged in a study on life expectancy at birth and all-cause mortality among people with personality disorder [156]. Some studies tried to test the hypothesis that BPD may have a higher risk of developing cardiovascular disease caused by altered endocrine, metabolic, and inflammatory parameter. Greggersen et al. measured intima-media thickness (IMT, considered an early marker of atherosclerosis and associated with most cardiovascular risk factors) in BPD women: BPD women had a significantly higher IMT than healthy women with increased risk of developing subsequent cardiovascular disease [157]. This underlines once more the existence of an integrated psychophysiological system of regulation in human beings. Efferent outflows from the heart affect the brain and vice versa, with vagus acting as an integral part of this heart-brain system and vagally mediated HRV appearing to be capable of providing valuable information about the functioning of this system. This regulation network has shown to involve not only an interplay between brain areas, cardiovascular system, and ANS but also neuroendocrine system (including in particular the hypothalamic-pituitary-adrenal axis) as well as immune alterations with a role of proinflammatory cytokines. For example, a recent exploratory study addresses the association between variability in subjective mood and variability in measures of diurnal physiology (the circadian or clock system, which activity has a complex neuroendocrine regulation; see [158]). Future directions of research have to clarify this complexity to better understand mental disorders.

References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington: American Psychiatric Association; 2013.
2. Leichsenring F, Leibing E, Kruse J, New AS, Leweke F. Borderline personality disorder. Lancet. 2011;377:74–84.
3. Coid J, Yang M, Tyrer P, Roberts A, Ullrich S. Prevalence and correlates of personality disorder in Great Britain. Br J Psychiatry. 2006;188:423–31.
4. Trull TJ, Jahng S, Tomko RL, Wood PK, Sher KJ. Revised NESARC personality disorder diagnoses: gender, prevalence, and comorbidity with substance dependence disorders. J Personal Disord. 2010;24:412–26.
5. Korzekwa MI, Dell PF, Links PS, Thabane L, Webb SP. Estimating the prevalence of borderline personality disorder in psychiatric outpatients using a two-phase procedure. Compr Psychiatry. 2008;49:380–6.
6. Koenig J, Kemp AH, Feeling NR, Thayer JF, Kaess M. Resting state vagal tone in borderline personality disorder: a meta-analysis. Prog Neuro-Psychopharmacol Biol Psychiatry. 2016;64:18–26.
7. Thayer JF, Lane RD. Claude-Bernard and the heart-brain connection: further elaboration of a model of neurovisceral integration. Neurosci Biobehav Rev. 2009;33:81–8.
8. Fonagy P, Luyten P. A developmental, mentalization-based approach to the understanding and treatment of borderline personality disorder. Dev Psychopathol. 2009;21:1355–81.
9. Krause-Utz A, Winter D, Niedtfeld I, Schmahl C. The latest neuroimaging findings in borderline personality disorder. Curr Psychiatry Rep. 2014;16(438):1–13.
10. Nunes PM, Wenzel A, Borges KT, Porto CR, Caminha RM, de Oliveira IR. Volumes of the hippocampus and amygdala in patients with borderline personality disorder: a meta-analysis. J Personal Disord. 2009;23(4):333–45.
11. O'Neill A, D'Souza A, Carballedo A, Joseph S, Kerskens C, Frodl T. Magnetic resonance imaging in patients with borderline personality disorder: a study of volumetric abnormalities. Psychiatry Res. 2013;213(1):1–10.
12. Rossi R, Lanfredi M, Pievani M, Boccardi M, Beneduce R, Rillosi L, et al. Volumetric and topographic differences in hippocampal subdivisions in borderline personality and bipolar disorders. Psychiatry Res. 2012;203(2–3):132–8.
13. Ochsner KN, Gross JJ. The neural architecture of emotion regulation. In: Gross JJ, editor. Handbook

of emotion regulation. New York: Guilford Press; 2007. p. 87–109.
14. Rodrigues E, Wenzel A, Ribeiro MP, Quarantini LC, Miranda-Scippa A, de Sena EP, et al. Hippocampal volume in borderline personality disorder with and without comorbid posttraumatic stress disorder: a meta-analysis. Eur Psychiatry. 2012;26(7):452–6.
15. Niedtfeld I, Schulze L, Krause-Utz A, Demirakca T, Bohus M, Schmahl C. Voxel-based morphometry in women with borderline personality disorder with and without comorbid posttraumatic stress disorder. PLoS One. 2013;8(6):e65824.
16. Soloff P, Nutche J, Goradia D, Diwadkar V. Structural brain abnormalities in borderline personality disorder: a voxel-based morphometry study. Psychiatry Res. 2008;164(3):223–36.
17. Soloff P, Pruitt P, Sharma M, Radwan J, White R, Diwadkar VA. Structural brain abnormalities and suicidal behavior in borderline personality disorder. J Psychiatr Res. 2012;46(4):516–25.
18. Lyoo IK, Han MH, Cho DY. A brain MRI study in subjects with borderline personality disorder. J Affect Disord. 1998;50:235–43.
19. Van Elst TL, Hesslinger B, Thiel T, et al. Frontolimbic brain abnormalities in patients with borderline personality disorder: a volumetric magnetic resonance imaging study. Biol Psychiatry. 2003;54:163–71.
20. Pessoa L, Padmala S, Kenzer A, Bauer A. Interactions between cognition and emotion during response inhibition. Emotion. 2012;12(1):192–7.
21. Sala M, Caverzasi E, Lazzaretti M, Morandotti N, DeVidovich G, Marraffini E, et al. Dorsolateral prefrontal cortex and hippocampus sustain impulsivity and aggressiveness in borderline personality disorder. J Affect Disord. 2011;131(1–3):417–21.
22. Carrasco JL, Tajima-Pozo K, Diaz-Marsa M, Casado A, LopezIbor JJ, Arrazola J, et al. Microstructural white matter damage at orbitofrontal areas in borderline personality disorder. J Affect Disord. 2012;139 (2):149–53.
23. Chanen AM, Velakoulis D, Carison K, Gaunson K, Wood SJ, Yuen HP, et al. Orbitofrontal, amygdala and hippocampal volumes in teenagers with first-presentation borderline personality disorder. Psychiatry Res. 2008;163(2):116–25.
24. Whittle S, Chanen AM, Fornito A, McGorry PD, Pantelis C, Yucel M. Anterior cingulate volume in adolescents with first presentation borderline personality disorder. Psychiatry Res. 2009;172(2):155–60.
25. Brunner R, Henze R, Parzer P, Kramer J, Feigl N, Lutz K, et al. Reduced prefrontal and orbitofrontal gray matter in female adolescents with borderline personality disorder: is it disorder specific? NeuroImage. 2010;49(1):114–20.
26. Takahashi T, Chanen AM, Wood SJ, Yucel M, Kawasaki Y, McGorry PD, et al. Superior temporal gyrus volume in teenagers with first-presentation borderline personality disorder. Psychiatry Res. 2010;182(1): 73–6.
27. Mauchnik J, Schmahl C. The latest neuroimaging findings in borderline personality disorder. Curr Psychiatry Rep. 2010;12(1):46–55.
28. Schore AN. Affect regulation and the repair of the self. New York: Norton; 2003.
29. Donegan NH, Sanislow CA, Blumberg HP, Fulbright RK, Lacadie C, Skudlarski P, Gore JC, Olson IR, McGlashan TH, Wexler BE. Amygdala hyperreactivity in borderline personality disorder: implications for emotional dysregulation. Biol Psychiatry. 2003;54(11):1284–93.
30. Herpertz SC, Dietrich TM, Wenning B, Krings T, Erberich SG, Willmes K, et al. Evidence of abnormal amygdala functioning in borderline personality disorder: a functional MRI study. Biol Psychiatry. 2001;50(4):292–8.
31. Wagner AW, Linehan MM. Facial expression recognition ability among women with borderline personality disorder: implications for emotion regulation? J Personal Disord. 1999;13(4):329–44.
32. Koenigsberg HW, Fan J, Ochsner KN, Liu X, Guise KG, Pizzarello S, et al. Neural correlates of the use of psychological distancing to regulate responses to negative social cues: a study of patients with borderline personality disorder. Biol Psychiatry. 2009;66(9):854–63.
33. Krause-Utz A, Oei NY, Niedtfeld I, Bohus M, Spinhoven P, Schmahl C, et al. Influence of emotional distraction on working memory performance in borderline personality disorder. Psychol Med. 2012;42(10):2181–92.
34. Niedtfeld I, Schulze L, Kirsch P, Herpertz SC, Bohus M, Schmahl C. Affect regulation and pain in borderline personality disorder: a possible link to the understanding of self-injury. Biol Psychiatry. 2010;68(4):383–91.
35. Minzenberg MJ, Fan J, New AS, Tang CY, Siever LJ. Fronto-limbic dysfunction in response to facial emotion in borderline personality disorder: an event-related fMRI study. PsychiatryRes. 2007;155(3):231–43.
36. Schulze L, Domes G, Kruger A, Berger C, Fleischer M, Prehn K, et al. Neuronal correlates of cognitive reappraisal in borderline patients with affective instability. Biol Psychiatry. 2011;69(6):564–73.
37. Beblo T, Driessen M, Mertens M, Wingenfeld K, Piefke M, Rullkoetter N, et al. Functional MRI correlates of the recall of unresolved life events in borderline personality disorder. Psychol Med. 2006;36(6): 845–56.
38. Ruocco AC, Amirthavasagam S, Choi-Kain LW, McMain SF. Neural correlates of negative emotionality in borderline personality disorder: an activation-likelihood-estimation meta-analysis. Biol Psychiatry. 2013;73(2):153–60.
39. Kamphausen S, Schroder P, Maier S, Bader K, Feige B, Kaller CP, et al. Medial prefrontal dysfunction and prolonged amygdala response during instructed fear processing in borderline personality disorder. World J Biol Psychiatry. 2013;14(4):307–18, S1-4

40. New AS, Hazlett EA, Buchsbaum MS, Goodman M, Mitelman SA, Newmark R, et al. Amygdala-prefrontal disconnection in borderline personality disorder. Neuropsychopharmacology. 2007;32(7):1629–40.
41. Schore AN. Effects of a secure attachment relationship on right brain development, affect regulation, and infant mental health. Infant Ment Health J. 2001;22:7–66.
42. Mayes LC. A developmental perspective on the regulation of arousal states. Semin Perinatol. 2000;24:267–79.
43. Arnsten AF. The biology of being frazzled. Science. 1998;280:1711–2.
44. Luyten P, Mayes L, Fonagy P, Van Houdenhove B. The interpersonal regulation of stress. 2009. Unpublished manuscript.
45. Thayer JF, Lane RD. A model of neurovisceral integration in emotion regulation and dysregulation. J Affect Disord. 2000;61:201–16.
46. Benarroch E. The central autonomic network: functional organization, dysfunction, and perspective. Mayo Clin Proc. 1993;68:988–1001.
47. Park G, Vasey M, Van Bavel JJ, Thayer JF. Cardiac vagal tone is correlated with selective attention to neutral distractors under load. Psychophysiology. 2013;50:398–406.
48. Thayer JF, Ahs F, Fredrikson M, Sollers JJ III, Wager TD. A meta-analysis of heart rate variability and neuroimaging studies: implications for heart rate variability as a marker of stress and health. Neurosci Biobehav Rev. 2012;36:747–56.
49. LeDoux J. Emotional networks and motor control: a fearful view. Prog Brain Res. 1996;107:437–46.
50. Herry C, Bach DR, Esposito F, Di Salle F, Perrig WJ, Scheffler K, Luthi A, Seifritz E. Processing of temporal unpredictability in human and animal amygdala. J Neurosci. 2007;27:5958–66.
51. Cunningham WA, van Bavel JJ, Johnsen IR. Affective flexibility: evaluative processing goals shape amygdala activity. Psychol Sci. 2008;19:153–60.
52. Chrousos GP, Kino T. Interactive functional specificity of the stress and immune responses: the ying, the yang, and the defense against 2 major classes of bacteria. J Infect Dis. 2005;192:551–5.
53. McEwen BS. From molecules to mind. Stress, individual differences, and the social environment. Ann N Y Acad Sci. 2001;935:42–9.
54. McEwen BS, Sapolsky RM. Stress and cognitive function. Curr Opin Neurobiol. 1995;5:205–16.
55. Sapolsky RM. Why stress is bad for your brain. Science. 1996;273:749–50.
56. Seeman TE, McEwen BS, Rowe JW, Singer BH. Allostatic load as a marker of cumulative biological risk: MacArthur studies of successful aging. Proc Natl Acad Sci USA. 2001;98:4770–5.
57. Amat J, Paul E, Watkins LR, Maier SF. Activation of the ventral medial prefrontal cortex during an uncontrollable stressor reproduces both the immediate and long-term protective effects of behavioral control. Neuroscience. 2008;154:1178–86.
58. Milad MR, Quirk GJ. Neurons in medial prefrontal cortex signal memory for fear extinction. Nature. 2002;420:70–4.
59. Milad MR, Vidal-Gonzalez I, Quirk GJ. Electrical stimulation of medial prefrontal cortex reduces conditioned fear in a temporally specific manner. Behav Neurosci. 2004;118:389–94.
60. Quirk GJ, Beer JS. Prefrontal involvement in the regulation of emotion: convergence of rat and human studies. Curr Opin Neurobiol. 2006;16:723–7.
61. Aron AR, Robbins TW, Poldrack RA. Inhibition and the right inferior frontal cortex. Trends Cogn Sci. 2004;8:170–7.
62. Chikazoe J, Konishi S, Asari T, Jimura K, Miyashita Y. Activation of right inferior frontal gyrus during response inhibition across response modalities. J Cogn Neurosci. 2007;19:69–80.
63. Thayer JF. On the importance of inhibition: central and peripheral manifestations of nonlinear inhibitory processes in neural systems. Dose-Response (formerly Nonlinearity in Biology, Toxicology and Medicine). 2006;4:2–21.
64. Davidson RJ. The functional neuroanatomy of affective style. In: Lane RD, Nadel L, editors. Cognitive neuroscience of emotion. New York: Oxford University Press; 2000. p. 106–28.
65. Thayer JF, Hansen AL, Saus-Rose E, Johnsen BH. Heart rate variability, prefrontal neural function and cognitive performance: the neurovisceral integration perspective on self-regulation, adaptation, and health. Ann Behav Med. 2009;37:141–53.
66. Heatherton TF, Wagner DD. Cognitive neuroscience of self-regulation failure. Trends Cogn Sci. 2011;15:132–9.
67. Davidson RJ, Pizzagalli D, Nitschke JB, Putnam K. Depression: perspectives from affective neuroscience. Annu Rev Psychol. 2002;53:545–74.
68. Johnstone T, van Reekum CM, Urry HL, Kalin NH, Davidson RJ. Failure to regulate: counterproductive recruitment of top-down prefrontal-subcortical circuitry in major depression. J Neurosci. 2007;27:8877–84.
69. Kim MJ, Whalen PJ. The structural integrity of an amygdala–prefrontal pathway predicts trait anxiety. J Neurosci. 2009;29:11614–8.
70. Callicott JH, Mattay VS, Verchinski BA, Marenco S, Egan MF, Weinberger DR. Complexity of prefrontal cortical dysfunction in schizophrenia: more than up or down. Am J Psychiatry. 2003;160:2209–15.
71. Lewis DA, Hashimoto T, Volk DW. Cortical inhibitory neurons and schizophrenia. Nat Rev Neurosci. 2005;6:312–24.
72. Li CSR, Sinha R. Inhibitory control and emotional stress regulation: neuroimaging evidence for frontal–limbic dysfunction in psycho-stimulant addiction. Neurosci Biobehav Rev. 2008;32:581–97.
73. Thayer JF, Friedman BH. A neurovisceral integration model of health disparities in aging. In:

Anderson NB, Bulato RA, Cohen B, editors. Critical perspective on racial and ethnic differences in health in late life. Washington, DC: The National Academy Press; 2004. p. 567–603.
74. Shook NJ, Fazio RH, Vasey MW. Negativity bias in attitude learning: a possible indicator of vulnerability to emotional disorders? J Behav Ther Exp Psychiatry. 2007;38:144–55.
75. Shook NJ, Pena P, Fazio RH, Sollers JJ, Thayer JF. Friend or foe: heart rate variability and the negativity bias in learning about novel objects. Psychophysiology. 2007;44:539.
76. Eippert F, Veit R, Weiskopf N, Erb M, Birbaumer N, Anders S. Regulation of emotional responses elicited by threat-related stimuli. Hum Brain Mapp. 2007;28:409–23.
77. Urry HL, van Reekum CM, Johnstone T, Kalin NH, Thurow ME, Schaefer HS, Jackson CA, Frye CJ, Greischar LL, Alexander AL, Davidson RJ. Amygdala and ventromedial prefrontal cortex are inversely coupled during regulation of negative affect and predict the diurnal pattern of cortisol secretion among older adults. J Neurosci. 2006;26:4415–25.
78. Wager TD, Hughes B, Davidson M, Lindquist ML, Ochsner KN. Prefrontal–subcortical pathways mediating successful emotion regulation. Neuron. 2008;59:1037–50.
79. Thayer JF, Siegle GJ. Neurovisceral integration in cardiac and emotional regulation. IEEE Eng Med Biol Mag. 2002;21:24–9.
80. Ruiz-Padial E, Sollers JJ, Vila J, Thayer JF. The rhythm of the heart in the blink of an eye: emotion-modulated startle magnitude covaries with heart rate variability. Psychophysiology. 2003;40:306–13.
81. Thayer JF, Friedman BH. Stop that! Inhibition, sensitization, and their neurovisceral concomitants. Scand J Psychol. 2002;43:123–30.
82. Buchanan TW, Driscoll D, Mowrer SM, Sollers JJ 3rd, Thayer JF, Kirschbaum C, Tranel D. Medial prefrontal cortex damage affects physiological and psychological stress responses differently in men and women. Psychoneuroendocrinology. 2010;35(1):56–66.
83. Smets E, Pappens M, Thayer JF, van den Bergh O, van Diest I. Interindividual differences in inhibitory control predict extinction of interoceptive fear. Psychophysiology. 2011;4:8.
84. Jose AD, Collison D. The normal range and determinants of the intrinsic heart rate in man. Cardiovasc Res. 1970;4:160–7.
85. Levy MN. Autonomic interactions in cardiac control. Ann N Y Acad Sci. 1990;601:209–21.
86. Uijtdehagge SBH, Thayer JF. Accentuated antagonism in the control of human heart rate. Clin Auton Res. 2000;10:107–10.
87. Balaban CD, Thayer JF. Neurobiological bases for balance-anxiety links. J Anxiety Disord. 2001;15:53–79.
88. Barbas H, Saha S, Rempel-Clower N, Ghashghael T. Serial pathways from primate prefrontal cortex to autonomic areas may influence emotional expression. BMC Neurosci. 2003;4:25.
89. Barbas H, Zikopoulos B. The prefrontal cortex and flexible behavior. Neuroscientist. 2007;13:532–45.
90. Grace AA, Rosenkranz JA. Regulation of conditioned responses of basolateral amygdala neurons. Physiol Behav. 2002;77:489–93.
91. Rempel-Clower NL. Role of orbitofrontal cortex connections in emotion. Ann N Y Acad Sci. 2007;1121:72–86.
92. Resstel LBM, Correa FMA. Involvement of the medial prefrontal cortex in central cardiovascular modulation in the rat. Auton Neurosci. 2006;126–127:130–8.
93. Saha S. Role of the central nucleus of the amygdala in the control of blood pressure: descending pathways to medullary cardiovascular nuclei. Clin Exp Pharmacol Physiol. 2005;32:450–6.
94. Saha S, Batten TFC, Henderson ZA. GABAergic projections from the central nucleus of the amygdala to the nucleus of the solitary tract: a combined anterograde tracing and electron microscopic immunohistochemical study. Neuroscience. 2000;99:613–26.
95. Shekhar A, Sajdyk TJ, Gehlert DR, Rainnie DG. The amygdala, panic disorder, and cardiovascular responses. Ann N Y Acad Sci. 2003;985:308–25.
96. Spyer KM. Central nervous mechanisms contributing to cardiovascular control. J Physiol. 1994;474:1–19.
97. Ter Horst GJ, Postema F. Forebrain parasympathetic control of heart activity: retrograde transneuronal viral labeling in rats. Am J Physiol. 1997;273:H2926–30.
98. Wong SW, Masse N, Kimmerly DS, Menon RS, Shoemaker JK. Ventral medial prefrontal cortex and cardiovagal control in conscious humans. NeuroImage. 2007;35:698–708.
99. Ahern GI, Sollers JJ, Lane RD, Labiner DM, Herring AM, Weinand ME, Hutzler R, Thayer JF. Heart rate and heart rate variability changes in the intracarotid sodium amobarbital (ISA) test. Epilepsia. 2001;42:912–21.
100. Lane RD, Reiman EM, Ahern GL, Thayer JF.Activity in medial prefrontal cortex correlates with vagal component of heart rate variability during emotion. Brain Cogn. 2001;47:97–100.
101. Lane RD, McRae K, Reiman EM, Ahern GL, Thayer JF. Neural correlates of vagal tone during emotion. Psychosom Med. 2007;69:A-8.
102. Lane RD, Weidenbacher H, Fort CL, Thayer JF, Allen JJB. Subgenual anterior cingulate (BA25) activity covaries with changes in cardiac vagal tone during affective set shifting in healthy adults. Psychosom Med. 2008;70:A-42.
103. Nugent AC, Bain EE, Thayer JF, Drevets WC. Anatomical correlates of autonomic control during a motor task. Psychosom Med. 2007;69:A-74.
104. Nugent AC, Bain EE, Sollers JJ, Thayer JF, Drevets WC. Alteration in neural correlates of

autonomic control in female with major depressive disorder. Psychosomatic Medicine. 2008;70:A-99.
105. Thayer JF, Sternberg E. Beyond heart rate variability: vagal regulation of allostatic systems. Ann N Y Acad Sci. 2006;1088:361–72.
106. Arnsten AF, Goldman-Rakic PS. Noise stress impairs prefrontal cortical cognitive function in monkeys: evidence for a hyperdopaminergic mechanism. Arch Gen Psychiatry. 1998;55:362–9.
107. Knight R, Staines W, Swick D, Chao L. Prefrontal cortex regulates inhibition and excitation in distributed neural networks. Acta Psychol. 1999;101:159–8.
108. Thayer JF, Lane RD. The importance of inhibition in dynamical systems models of emotion and neurobiology. Brain Behav Sci. 2005;28:218–9.
109. Beauchaine TP. Vagal tone, development, and gray's motivational theory: toward an integrated model of autonomic nervous system functioning in psychopathology. Dev Psychopathol. 2001;13:183–214.
110. Berntson GG, Bigger JT Jr, Eckberg DL, Grossman P, Kaufmann PG, Malik M, Nagaraja HN, Porges SW, Saul JP, Stone PH, van der Molen MW. Heart rate variability: origins, methods, and interpretive caveats. Psychophysiology. 1997;34(6):623–48.
111. Hayano J, Sakakibara Y, Yamada A, Yamada M, Mukai S, Fujinami T, Yokoyama K, Watanabe Y, Takata K. Accuracy of assessment of cardiac vagal tone by heart rate variability in normal subjects. Am J Cardiol. 1991;67(2):199–204.
112. Katona PG, Jih F. Respiratory sinus arrhythmia: noninvasive measure of parasympathetic cardiac control. J Appl Physiol. 1975;39(5):801–5.
113. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation, and clinical use. Eur Heart J. 1996;17:354–81.
114. DeGiorgio CM, Miller P, Meymandi S, Chin A, Epps J, Gordon S, Gornbein J, Harper RM. RMSSD, a measure of vagus-mediated heart rate variability, is associated with risk factors for SUDEP: the SUDEP-7 inventory. Epilepsy Behav. 2010;19:78–81.
115. Koenig J, Jarczok MN, Ellis RJ, Warth M, Hillecke TK, Thayer JF. Lowered parasympathetic activity in apparently healthy subjects with self-reported symptoms of pain: preliminary results from a pilot study. Pain Pract. 2015;15:314–8.
116. Koenig J, Williams DP, Kemp AH, Thayer JF. Vagally mediated heart rate variability in headache patients – a systematic review and meta-analysis. Cephalalgia. 2016;36:265–78.
117. Beauchaine TP, Thayer JF. Heart rate variability as a transdiagnostic biomarker of psychopathology. Int J Psychophysiol. 2015;98:338–50.
118. Hansen AL, Johnsen BH, Thayer JF. Vagal influence on working memory and attention. Int J Psychophysiol. 2003;48:263–74.
119. Hovland A, Pallesen S, Hammar Å, Hansen AL, Thayer JF, Tarvainen MP, Nordhus IH. The relationships among heart rate variability, executive functions, and clinical variables in patients with panic disorder. Int J Psychophysiol. 2012;86:269–75.
120. Gillie BL, Vasey MW, Thayer JF. Heart rate variability predicts control over memory retrieval. Psychol Sci. 2014;25:458–65.
121. Park G, Thayer JF. From the heart to the mind: cardiac vagal tone modulates topdown and bottom-up visual perception and attention to emotional stimuli. Front Psychol. 2014;5:278.
122. Beauchaine TP. Respiratory sinus arrhythmia: a transdiagnostic biomarker of emotion dysregulation and psychopathology. Curr Opin Psychol. 2015;3:43–7.
123. Beauchaine TP. Future directions in emotion dysregulation and youth psychopathology. J Clin Child Adolesc Psychol. 2015;44(5):875–96.
124. Linehan MM. Cognitive-behavioral treatment of borderline personality disorder. New York: Guilford Press; 1993.
125. Fonagy P, Bateman A. The development of borderline personality disorder – a mentalizing model. J Personal Disord. 2008;22:4–21.
126. Selby EA, Joiner TE Jr. Cascades of emotion: the emergence of borderline personality disorder from emotional and behavioral dysregulation. Rev Gen Psychol. 2009;13:219–29.
127. Gross JJ, Thompson RA. Emotion regulation: conceptual foundations. New York: Guilford Press; 2007.
128. Kuo JR, Neacsiu AD, Fitzpatrick S, MacDonald DE. A methodological examination of emotion inductions in borderline personality disorder: a comparison of standardized versus idiographic stimuli. J Psychopathol Behav Assess. 2014;36:155-164. https://doi.org/10.1007/s10862-013-9378-x
129. Limberg A, Barnow S, Freyberger HJ, Hamm AO. Emotional vulnerability in borderline personality disorder is cue specific and modulated by traumatization. Biol Psychiatry. 2011;69:574–82.
130. Gross JJ, John OP. Individual differences in two emotion regulation processes: implications for affect, relationships, and Well-being. J Pers Soc Psychol. 2003;85:348–62.
131. Austin MA, Riniolo TC, Porges SW. Borderline personality disorder and emotion regulation: insights from the polyvagal theory. Brain Cogn. 2007;6:69–76.
132. Gratz KL, Tull MT, Matusiewicz AM, Breetz AA, Lejuez CW. Multimodal examination of emotion regulation difficulties as a function of co-occurring avoidant personality disorder among women with borderline personality disorder. Personal Disord. 2013;4(4):304–14.
133. Dixon-Gordon KL, Chapman AL, Lovasz N, Walters K. Too upset to think: the interplay of borderline personality features, negative emotions, and social problem solving in the laboratory. Personal Disord. 2011;2:243–60.
134. Kuo JR, Linehan MM. Disentangling emotion processes in borderline personality disorder: physiological and self-reported assessment of biological vulnerability, baseline intensity, and reactivity to

emotionally evocative stimuli. J Abnorm Psychol. 2009;118(3):531–44.
135. Weinberg A, Klonsky ED, Hajcak G. Autonomic impairment in borderline personality disorder: a laboratory investigation. Brain Cogn. 2009;71(3):279–86.
136. Meyer PW, Müller LE, Zastrow A, Schmidinger I, Bohus M, Herpertz SC, Bertsch K. Heart rate variability in patients with post-traumatic stress disorder or borderline personality disorder: relationship to early life maltreatment. J Neural Transm (Vienna). 2016;123(9):1107–18.
137. Bernstein DP, Fink L. Childhood trauma questionnaire: a retrospective self-report manual. San Antonio: The Psychological Corporation; 2009.
138. Singh JP, Larson MG, O'Donnell CJ, Tsuji H, Evans JC, Levy D. May heritability of heart rate variability: the Framingham heart study. Circulation. 1999;4(17): 2251–4.
139. Uusitalo AL, Vanninen E, Levälahti E, Battié MC, Videman T, Kaprio J. Role of genetic and environmental influences on heart rate variability in middle-aged men. Am J Physiol Heart Circ Physiol. 2007;293(2):1013–22.
140. Mueller A, Strahler J, Armbruster D, Lesch KP, Brocke B, Kirschbaum C. Genetic contributions to acute autonomic stress responsiveness in children. Int J Psychophysiol. 2012;83(3):302–8.
141. Koval P, Ogrinz B, Kuppens P, Van den Bergh O, Tuerlinckx F, Sütterlin S. Affective instability in daily life is predicted by resting heart rate variability. PLoS One. 2013;8(11):e81536.
142. Dishman RK, Nakamura Y, Garcia ME, Thompson RW, Dunn AL, Blair SN. Heart rate variability, trait anxiety, and perceived stress among physically fit men and women. Int J Psychophysiol. 2000;37(2): 121–33.
143. McLaughlin KA, Sheridan MA, Tibu F, Fox NA, Zeanah CH, Nelson CA 3rd. Causal effects of the early caregiving environment on development of stress response systems in children. Proc Natl Acad Sci USA. 2015;112(18):5637–42.
144. Braeken MA, Kemp AH, Outhred T, Otte RA, Monsieur GJ, Jones A, Van den Bergh BR. Pregnant mothers with resolved anxiety disorders and their offspring have reduced heart rate variability: implications for the health of children. PLoS One. 2013;10: e83186.
145. Koenig J, Rinnewitz L, Parzer P, Resch F, Thayer JF, Kaess M. Resting cardiac function in adolescent non-suicidal self-injury: the impact of borderline personality disorder symptoms and psychosocial functioning. Psychiatry Res. 2017;248:117–20.
146. Koenig J, Weise S, Rinnewitz L, Parzer P, Resch F, Kaess M. Longitudinal covariance of resting-state cardiac function and borderline personality disorder symptoms in adolescent non suicidal self-injury. World J Biol Psychiatry. 2018;19(2):152–7.
147. Schafer SM, Wager TD, Mercado RA Jr, Thayer JF, Allen JJB, Lane RD. Partial amelioration of medial visceromotor network dysfunction in major depression by sertraline. Psychosom Med. 2015;77(7):752–61.
148. Buchheit M, Platat C, Oujaa M, Simon C. Habitual physical activity, physical fitness and heart rate variability in preadolescents. Int J Sports Med. 2007;28 (3):204–10. Epub 2006 Nov 16
149. Rennie KL, Hemingway H, Kumari M, Brunner E, Malik M, Marmot M. Effects of moderate and vigorous physical activity on heart rate variability in a British study of civil servants. Am J Epidemiol. 2003;158(2):135–43.
150. Quintana DS, Alvares GA, Heathers JA. Guidelines for reporting articles on psychiatry and heart rate variability (GRAPH): recommendations to advance research communication. Transl Psychiatry. 2016; 6:803–10.
151. Carr O, de Vos M, Saunders KEA. Heart rate variability in bipolar disorder and borderline personality disorder: a clinical review. Evid Based Ment Health. 2018;21:23–30.
152. Thayer JF, Lane RD. The role of vagal function in the risk of cardiovascular disease and mortality. Biol Psychol. 2007;74:224–42.
153. Masi CM, Hawkley LC, Rickett EM, Cacioppo JT. Respiratory sinus arrhythmia and diseases of aging: obesity, diabetes mellitus, and hypertension. Biol Psychol. 2007;74:212–23.
154. Jarczok MN, Kleber ME, Koenig J, Loerbroks A, Herr RM, Hoffmann K, Fischer JE, Benyamini Y, Thayer JF. Investigating the associations of self-rated health: heart rate variability is more strongly associated than inflammatory and other frequently used biomarkers in a cross sectional occupational sample. PLoS One. 2015;10:e0117196.
155. Cailhol L, Pelletier È, Rochette L, Laporte L, David P, Villenueve È, Paris J, Lesage A. Prevalence, mortality, and health care use among patients with cluster B personality disorders clinically diagnosed in Quebec: a provincial cohort study, 2001–2012. Can J Psychiatr. 2017;62(5):336–42.
156. Fok ML, Hayes RD, Chang CK, et al. Life expectancy at birth and all-cause mortality among people with personality disorder. J Psychosom Res. 2012;73(2): 104–7.
157. Greggersen W, Rudolf S, Brandt PW, Schulz E, Fassbinder E, Willenborg B, Kahl KG, Bergmann-Koester C, Stoeckelhuber BM, Hohagen F, Schweiger U. Intima-media thickness in women with borderline personality disorder. Psychosom Med. 2011;73(7): 627–32. https://doi.org/10.1097/PSY.0b013e3182231fe2. Epub 2011 Aug 1
158. Carr O, Saunders KEA, Tsanas A, Bilderbeck AC, Palmius N, Geddes JR, Foster R, Goodwin GM, De Vos M. Variability in phase and amplitude of diurnal rhythms is related to variation of mood in bipolar and borderline personality disorder. Sci Rep. 2018;8(1649):1–11.

Cardiovascular Manifestations in Schizophrenia

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Federica Calorio, Cristina Grazia Catania, and Matteo Rocchetti

Contents

Abstract

Many studies demonstrate the high association between cardiovascular diseases and psychotic disorders such as schizophrenia. People suffering of schizophrenia presented an up to triple the risk of attaining cardiovascular disease than the general population with higher cardiac mortality rates (approximately an expectancy of life 20% shorter). Several factors contribute to the increased cardiovascular risk in these types of patients. First of all unhealthy lifestyle factors, such as poor diet, low physical activity, high rate of cigarette smoking, and alcohol/substance abuse associated with socioeconomic difficulties, have an important role in predisposing the genesis of cardiovascular diseases (CVD). Reinforcing the hypothesis of the presence of a psycho-neuro-endocrine-cardiovascular axis, studies have shown a hormone imbalance conditioning an increase of metabolic abnormalities. Moreover the exposure to antipsychotic medications with consequent cardiometabolic collateral effect and a suspected genetic predisposition with a probable overlap between schizophrenia spectrum

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*, https://doi.org/10.1007/978-3-030-28008-6_24

disorders and cardiometabolic phenotypes studied in drug-naive patients increase the risk. Genetic and iatrogenic effects are linked in pharmacogenomic studies that demonstrate a different susceptibility to antipsychotic in relationship to specific gene polymorphisms. Another major contributing factor associated with increased cardiovascular mortality in schizophrenic patients is a dysfunction of the autonomic system that implicates several abnormalities, for example, a decreased heart rate variability (HRV). To improve the expectancy and the quality of life of schizophrenic patients, a strict monitoring of metabolic risk is important, as well as promoting behavioral interventions and information and trying to focus the attention on an intervention in the first years of the psychiatric disease.

Keywords

Schizophrenia · Psychosis · Cardiovascular · Antipsychotic drugs · Genetic · Inflammation · Autonomic dysfunction · Lifestyle · Metabolic syndrome · Smoking

Introduction

Schizophrenia is associated with higher cardiac mortality rates, an approximately 15–20 years of shorter life expectancy for these patients, and up to triple the risk of attaining cardiovascular disease compared with the general population [1]. A 24% of deaths worldwide is determined by cardiovascular disease (CVD), being the leading cause of overall mortality. Severe mental illnesses (SMI) (schizophrenia, bipolar disorder, schizoaffective disorder, and major depressive disorder) have an important impact on global mortality [2]. The mortality and the cardiovascular risk (CVR) are higher two or three times than in general population [1, 3, 4]. It is not yet clear if there is a difference between schizophrenia and other SMI. The study made by Bioque recruited a majority of patients diagnosed of "non-affective psychosis" but also a percentage of patients affected by "affective psychosis" (unipolar depression or bipolar disorder with psychotic features and schizoaffective disorder). They found no significant interaction between diagnosis and any of the CVR factor measures, suggesting similar evolution both in affective and non-affective psychoses [5], except for metabolic syndrome. A meta-analysis, conducted by Bartoli, compared rates of metabolic syndrome in schizophrenia with those in schizoaffective disorder [5]. People with schizoaffective disorders might be more prone to develop metabolic syndrome because affective symptoms may determine a greater vulnerability to sedentary and unhealthy lifestyles [6]. Furthermore, patients with schizoaffective disorder are more often treated with antidepressants and mood stabilizers, along with antipsychotics [7, 8], with additional burden for several metabolic abnormalities, including weight gain and diabetes [9, 10]. A recent meta-analysis has carried out an analysis of the subgroups of severe mental illness and find out a higher global CVR associated with schizophrenia spectrum disorders (according to the definition of DSM-V, they are characterized by abnormalities in one or more of the following five domains: delusions, hallucinations, disorganized thinking (speech), grossly disorganized or abnormal motor behavior (including catatonia), and negative symptoms [11]) than with other severe psychiatric illness like depressive disorders or bipolar disorders [2]. Several studies have underlined that there are abnormalities also in drug-naive patients and in their healthy first-degree relatives [12, 13]. These findings suggested that the etiology of cardiovascular risk in schizophrenia is multifactorial. In fact it has been demonstrated that it includes genetic factors, cardiac autonomic dysfunction and altered brain-heart interaction, dysregulation of hypothalamus-pituitary-adrenal axis, unhealthy lifestyle, inflammation, and antipsychotic treatment effects. In the present chapter, we will discuss the factors implicated in the genesis of the cardiovascular disease in patients affected by schizophrenia.

An easily resolvable problem is that this kind of patients often do not receive adequate monitoring of cardiovascular health and deal with inequalities in the availability of healthcare provision [14, 15]. For these reasons strict

monitoring of metabolic risk is essential. Some studies suggest that the first year of treatment represents a critical period for the cardiovascular risk. Early intervention such as the challenging task of engaging young patients with psychotic disorders is an opportunity to reduce premature cardiovascular mortality, applying different preventive strategies [16]. Existing clinical guidelines recommend scheduled monitoring for metabolic risk factors (smoking status, body mass index, dietary content, participation in physical activity, levels of blood pressure, blood glucose, and total cholesterol) [17] in patients prescribed with antipsychotic medication and switching antipsychotic therapy if a patient experiences weight gain of more than 5% of the initial weight [18, 19]. Moreover, the patients should be informed of the necessity of a balanced diet and regular physical activity, trying to avoid an unhealthy lifestyle (smoke, alcohol). The choice of a specific antipsychotic should be done on drug efficacy and on assessment of risk factors (propensity to gain weight, family or personal history of diabetes or hyperlipidemia, elevated fasting glucose, lipid or insulin levels) [20].

Risk Factors in the Early Phase of Psychosis

In the last years, many studies on drug-naive patients with a first episode of psychosis (FEP) have been conducted. Studies on this population are of great interest because they avoided the effect of confounding variables, such as somatic comorbidities, prolonged antipsychotic treatment, and chronicity [21], and underlined that there are abnormalities not just in drug-naive patients, but also in their healthy first-degree relatives [12, 13]. It was demonstrated that patients with FEP present a wide array of metabolic disturbances, which might predict the development of medical conditions, such as metabolic syndrome or CVD.

A cohort study of patients with FEP, evaluating the metabolic profile, highlights that the first 2-year period can be characterized by an extremely high risk of developing CVR factors and a rapid worsening of the metabolic profile. At the baseline, the FEP group showed differences in metabolic parameters compared to the control group. After 2 years of follow-up, FEP patients presented a worsening of almost all the metabolic measures with higher rates of metabolic syndrome and overweight/obesity. This study through the baseline findings supports the existence of a predisposition of FEP patients to present alterations, such as statistically significant higher total and LDL cholesterol and lower HDL cholesterol mean levels, from the beginning of the disorder or even before starting the psychopharmacological treatment [22]. Other studies performed on drug-naive first-episode psychosis patients indicate abnormal glycemic control [23] and increased levels of C-reactive protein and pro-inflammatory cytokines [24, 25]. The data collected indicate the predisposition of FEP patients to develop metabolic abnormalities even though in the European first-episode schizophrenia trial (EUFEST), an open-label, randomized trial of five commonly-used antipsychotics (amisulpride, haloperidol, olanzapine, quetiapine and ziprasidone) the subjects with metabolic syndrome was 5.9% of patients in treatment, 5.6% in antipsychotic-naive and 6.1% in patients with a brief exposure of antipsychotics, suggesting that the baseline prevalence rate of metabolic syndrome in this group of patients is similar to the prevalence in general population of same age [26]. Further evidence, supporting a baseline predisposition, suggests that individuals at ultrahigh risk for (UHR) psychosis have unhealthy lifestyle factors and poor physical health, prior to the onset of a first episode [27]. Criteria of UHR have been developed to identify individuals vulnerable to developing a psychotic disorder [28], and they also have an implication for an early intervention and for the monitoring of physical health. A patient in UHR status must exhibit one or more of the following characteristics: presence of attenuated psychotic symptoms, brief limited intermittent psychotic symptoms that spontaneously resolve, or a genetic risk combined with a significant recent decline in functioning [29]. Approximately one-third of the UHR individuals make the transition to psychotic disorders within 3 years [30]. Carney conducted a retrospective

analysis on the case notes of individuals accepted into a specialized early detection service for young people at ultrahigh risk for psychosis. The metabolic abnormalities (higher rates of metabolic syndrome and reduced high-density lipoproteins (HDL) levels, higher levels of fasting blood glucose and blood pressure [31]) might be in part attributed to unhealthy lifestyle factors (low levels of physical activity and high rates of cigarette smoking or alcohol abuse) [32]. This underlined the importance of clear monitoring guidelines for the assessment of metabolic risk factors, so appropriate interventions can then be targeted to prevent future development of organic diseases [27, 33].

Genetic Factors

Metabolic dysregulation observed in drug-naive patients with FEP suggests that schizophrenia spectrum disorders might share overlapping genetic background with cardiometabolic phenotypes [34]. It is proved by several studies that polymorphisms in genes, such as apolipoprotein C-III (ApoC3), apolipoprotein A-V gene (ApoA5), and lipoprotein lipase (LPL) genes, implicated in the lipid metabolism, influence cholesterol and other lipid parameters [35, 36, 37]. These variations could provide additional markers for differential gene effects of antipsychotic tendencies to produce an elevation in lipid blood levels as well as polymorphisms, which determine a different response to statin therapy [38, 39].

Furthermore, other genes such as the ApoE, ApoA1, ApoB, hepatic lipase, and PPAR genes have been associated, in general population, with changes in lipid levels and/or cardiovascular disease outcomes [35, 38, 40]. A study made by Smith associates allelic variations in the ApoC3 and ApoA5 with modification induced by antipsychotics on lipid levels, considering a monotherapy to assess in a clearer way the phenotype.

In some single-nucleotide polymorphisms (SNP), the minor allele was associated with lower serum lipid levels in patients with olanzapine or clozapine and increased levels in patients treated with first-generation antipsychotics. For example, an ApoA5CG haplotype had a similar effect, and the W (minor) allele of the ApoA5_S19W SNP was associated with increased serum cholesterol in patients treated with risperidone. It seems that genes that may influence weight gain are correlated with differential drug gene effect on serum lipids such as the polymorphisms in the 5-HT2C receptor (759T/C), polymorphisms of the leptin gene, and polymorphisms in the a2A receptor (1291C/G) [41].

It was demonstrated that for most regions that have been reported to be linked to schizophrenia, overlapping regions of linkage have been obtained in type 2 diabetes. One of the most promising regions of interest in both schizophrenia and type 2 diabetes is chromosome 1q21–25, in particular, the CAPON gene recently identified, whose protein primarily functions as an adapter protein targeting neuronal nitric oxide synthase [42]. The regulator of G protein signalling 4 (RGS4) gene, a negative regulator of G protein-coupled receptors, is another good positional candidate in this region for schizophrenia [43]. It may modulate activity at certain serotonergic and metabotropic glutamatergic receptors [44, 45]. It has been hypothesized that interactions of atypical antipsychotic agents with several neurotransmitter receptors, including serotonin (5-HT) receptors, may play an important role in weight gain in patients with schizophrenia. There are currently 14 known 5-HT receptors; 2 of these are of particular interest. First, the 5-HT5A receptor may be involved in higher cortical and limbic functions. Its gene maps to chromosome 7q36, and a number of researchers have examined common polymorphisms within the gene and reported an association with schizophrenia [46]. Second is the 5-HT2C receptor gene on the X chromosome. 5-HT2C knockout mice develop increased feeding and obesity. A number of antipsychotic agents are 5-HT2C antagonists and induce high expression of HTR2CmRNAA–759C/T polymorphism in the promoter region of this gene that influences transcriptional activity [47] previously reported to be associated with type 2 diabetes and obesity. Different studies [48, 49] now support the view that antipsychotic-induced weight gain is associated with the low-expressing C allele of this polymorphism. These genetic studies are beginning to

identify susceptibility genes conferring risk through allelic variants at a high frequency in the general population.

Cardiac Autonomic Dysfunction and Altered Brain-Heart Interaction

There is a relationship between cardiac autonomic dysfunction (CADF), reported in acute and chronic patients with schizophrenia irrespective of the received treatment [12, 50], and the development of cardiovascular diseases [51]. Reduced vagal activity might be one crucial mechanism inducing CADF, with the physiological consequences of increased resting heart rates, decreased heart rate variability (HRV) and complexity, reduced baroreceptor sensitivity, and reduced vagal thresholds during exercise, all factors that indicate a decreased physical fitness [13]. Moreover, distinct changes occur in heart rate and respiratory regulation and to a far lesser extent in blood pressure regulation [52]. A study conducted by Herbsleb describes different findings. First, the reduced physical fitness in patients with schizophrenia at submaximal and maximal levels, in accordance with previous studies, as suggestion of relation between cardio-respiratory regulation and reduced physical fitness in this patients [53, 54]. Second, this study shows an occurrence rate of chronotropic incompetence (CI) of 45% in patients with schizophrenia. A strong correlation exists between CI and physical incapacity. CI is a significant contributor to exercise intolerance and has been shown to be associated with reduced quality of life, major cardiovascular events, and premature death [55]. One of the possible complicating factors related to an increased mortality rate in schizophrenia is the imbalanced autonomic nervous system (ANS). In schizophrenia patients, severe CADF is not initially caused by major structural or functional alterations of the heart, like other patient populations suffering from primary cardiac conditions (e.g., myocardial infarction, cardiomyopathy) and which present signs of CADF. It seems to be associated with an altered brain-heart interaction influenced by a lack of cortical inhibitory control over sympathoexcitatory subcortical regions [13, 56]. Moreover, patients with schizophrenia benefit of relative longevity, when compared with more frequent shorter survival rates of cardiac patients. It was stated by William that paranoid schizophrenia is characterized by a disjunction of arousal and amygdala-prefrontal circuits that leads to impaired processing of, particularly threat-related, signals. This excessive arousal with reduced amygdala activity or a lack of "with-arousal" medial prefrontal engagement points to a dysregulation in the normal cycle of mutual feedback between amygdala function and somatic state (autonomic activity), leading to a perseveration and exacerbation of arousal responses. The precise mechanism of ANS dysregulation in schizophrenia still remains unclear, complicated by the large number of cortical, subcortical, and brainstem structures that coordinate autonomic function [56]. Like seen in previous studies, people with lower heart rate variability (HRV), as seen in the case of schizophrenia, exhibit effective behavioral responses (e.g., faster response times and higher accuracy rates) on executive cognitive tasks as well as exhibit flexible and adaptive emotions [57, 58]. Thayer and Lane proposed the "neurovisceral integration model" to explain that ANS dysregulation is driven by the failure of the prefrontal cortex to inhibit the amygdala-mediating cardiovascular and autonomic responses to stress. They showed that resting HRV is tied to the functioning of frontal-subcortical circuits and, in particular, that a higher resting HRV is associated with the effective functioning of the frontal top-down control over subcortical brain regions that support flexible and adaptive responses to environmental demands [59, 60]. Considering the hypothesis that frontal, cingulated, and subcortical brain regions play a critical role in such self-regulatory functions involved in reward and emotion, such as the amygdala, it is not difficult to understand why the disruption of frontal-subcortical circuits has been associated with a wide range of psychopathologies, including schizophrenia [61, 62]. Moreover, it was shown that the prefrontal cortex could play a critical role in ANS dysregulation and that schizophrenia

patients are characterized by a decrease in their prefrontal cortex activity and concomitant deficits in executive function and inhibition that can explain the reduced HRV in these subjects [63, 64]. They further emphasized the importance of the medial prefrontal cortex as the "core integration" system owing to its assumed critical role in the representation of internally and externally generated information, as well as its integrative function to regulate behavior and to adapt peripheral physiology. Especially noteworthy is the proof that the left and right central hemispheres are specialized for parasympathetic and sympathetic control of cardiovascular functioning and the changes in functional central system activation are related with changes in heart rate and blood pressure [60, 65]. Tanida et al. showed, during mental arithmetic (MA) task, that the right prefrontal cortex activity has a greater role in the central regulation of heart rate owing to the virtue of decreasing parasympathetic effects or increasing sympathetic effects [66]. The relationship between autonomic regulatory capacity and neuropsychological performance in patients with schizophrenia was also demonstrated by Mathewson et al. [67]. In particular, susceptibility to perseveration in patients was associated with faster heart rates at rest and reduced vagal modulation. The assumption is that an abnormal interplay between frontocingulate and subcortical brain can lead to abnormal autonomic arousal [56]. It is presumed that lesions within the central nervous system (CNS) associated to greater levels of cerebral dysfunction may result in an increasing severity of cardiovascular dysfunction, bringing to the overall changes in heart rate and blood pressure in schizophrenic patients, thus posing an increased risk of sudden cardiac death for these patients [65]. It has been assumed that an abnormal interplay between frontocingulate and subcortical brain can lead to abnormal autonomic arousal, being expressed as a functional disconnection in autonomic and central systems when patients with paranoid schizophrenia process threat-related signals. Thus, paranoid cognition may reflect an internally generated cycle of misattribution regarding incoming fear signal sowing to a breakdown in the regulation of these systems resulting in an altered brain-heart interaction, influenced by a lack of cortical inhibitory control over sympathoexcitatory subcortical regions [56]. Two further medullary areas contain preganglionic parasympathetic neurons: these are the nucleus ambiguous and the dorsal motor nucleus of the vagus nerve. Both mediate the efferent parasympathetic components of blood pressure and heart rate, showing either cardiac- or respiration-related activity [68]. Brainstem nuclei and pathways receive modulatory inputs from supramedullary centers such as the insula, thalamus, hypothalamus, amygdala, parietal and cingulated regions or from the medial prefrontal region. Studies have shown the involvement of these brain areas in the autonomic regulation at rest and during cognitive or emotional strains by means of functional brain imaging [69, 70]. Psychopathological states such as anxiety, depression, post-traumatic stress disorder, and schizophrenia are associated with prefrontal hypoactivity. This lack of inhibitory neural processes manifests itself in a poor habituation to novel neutral stimuli, a pre-attentive bias for threat information, deficits in working memory and executive function, and poor affective information processing and regulation [71]. For healthy adults, Beissner et al. suggested that a symmetric frontal electroencephalogram (EEG) response to emotional arousal in the form of positive and negative emotions may elicit different patterns of cardiovascular reactivity [72]. In schizophrenia, the results of central activity (via EEG frequency analyses) showed a highly significantly reduced EEG activation (power) in all frequency bands from the frontal lobe, being much more pronounced in the right frontal hemisphere, when compared with healthy subjects. In particular, γ and β activity is most augmented over frontal and temporal brain regions, reflecting a genetic liability for schizophrenia [73]. This impaired neural oscillation (e.g., a reduction in amplitude and altered phase synchronization in all frequency bands with emphasis on the β and γ band activity) can be considered a marker for a functional disconnectivity between different brain areas and for dysfunctional cortical networks [74]. In summary, the activity of the prefrontal cortex is

associated with vagal-mediated HRV [75], and, moreover, the differences in central activity in schizophrenia between the two hemispheres would determine the overall changes in heart rate and blood pressure [65]. Steffen Schulz et al. [76] have clarified different aspects due to a study that enrolled 17 patients with paranoid schizophrenia (SZ) and 17 healthy subjects (CO), who were matched according to age and gender. This investigation has revealed highly significant increased heart rates, reduced HRV, decreased spontaneous baroreflex sensitivity (BRS), a reduced EEG activity (power) independent from frequency range and frontal area or left hemisphere area, as well as altered central-autonomic couplings (CAC) in patients with schizophrenia, when compared with healthy subjects. In particular, considering BRS, they found significantly reduced tachycardic and bradycardic slopes in accordance with other studies investigating unmedicated patients [77, 78]. The decrease of efferent vagal activity and the inhibition of baroreflex vagal bradycardia in schizophrenia might be caused by stress owing to psychotic experiences or to the psychosis itself, a process that allows the organism under physiological conditions to adjust to demanding environmental stress [12]. It can be assumed that the primary BRS changes in schizophrenia were a result of impaired heart rate regulation. It was shown that during stressful conditions such as mental stress (supposedly present in these patients), the arterial baroreflex was generally inhibited. From the point of view that central mechanisms are involved in BRS regulation, central sites proven to elicit the facilitation are the medial prefrontal cortex, the preoptic/anterior hypothalamus, the ventrolateral part of the periaqueductal gray matter, and the nucleus raphe magnus [79]. Central-vascular coupling analyses demonstrated that the coupling strength was highly significantly reduced in schizophrenia for the direction SYS (systogram) toward the central activity (SYS→PEEG, power EEG). For the opposite direction from the central activity toward SYS, the coupling strength (PEEG→SYS) was highly significantly increased in SZ when compared with CO. Central-vascular coupling in SZ pointed to a bidirectional one with the central driver (PEEG→SYS), whereas the direction for CO was equal in both directions (PEEG↔SYS). This suggests that the closed-loop regulation process of central-vascular regulation in SZ is more strongly focused on maintaining/regulating the blood pressure than this regulation process for CO. In the case of SZ, the central part of this closed loop seems to more strongly influence the autonomic system (SYS). This closed loop in CO indicates a balanced condition. Central-vascular coupling in SZ was dominated mainly by highly variable SYS patterns in combination with all other eight central pattern families. This was demonstrated by highly significantly decreased SYS-E1 and highly significantly increased SYS-E0, SYS-E2, SYSLU1, SYS-LD1, SYS-LA1, SYS-P, and SYS-V. It seems to be that the blood pressure regulation is more complex and mainly influences the central-vascular coupling pattern in SZ. Furthermore, it could be shown that central-vascular coupling is strongly affected by reduced BPV (SYSE1) and short-term strong/weak, increasing/decreasing, alternating, and fluctuating vascular family patterns (SYS-E0, SYS-E2, SYS-LU1, SYS-LD1, SYS-LA1, SYS-P, SYS-V), in combination with central activity. We could also found that the complexity of the central-vascular coupling is significantly increased in SZ when compared with CO. This was demonstrated by the highly significantly decreased SYS-E1 and highly significantly increase of other family patterns. The results indicated that, for SZ, this closed-loop interaction does not work well owing to the known significant heart rate changes for those patients [76, 80]. Returning to central spectral power bands (via EEG frequency analyses) with respect to central-cardiac coupling and central-vascular coupling, the strongest influence of cerebral γ activity was found for both SZ and healthy subjects, independent of the brain hemisphere, but is reduced in SZ, and this highlights the role of γ activity in people affected by SZ. The connection between central-cardiac and central-vascular coupling and central spectral power bands was characterized as bidirectional acting driver in each frequency band [80].

Dysregulation of Hypothalamus-Pituitary-Adrenal Axis

Stress is an important factor in the development of physical and mental illness. The response to stress is mediated by hypothalamus-pituitary-adrenal (HPA) axis through the secretion of glucocorticoid hormones. Despite a variety of results showing some patients affected by schizophrenia with low level of cortisol, generally have been discovered phase of hypercortisolism that can be explained by symptoms of illness as well as by a dysregulation of the HPA axis [81]. Studies have been conducted on symptomatic patients, and this made it difficult to understand whether the higher cortisol levels are due to the stress of the acute disease or to a basal dysregulation of HPA axis. Other confounding factor is antipsychotic treatment: second-generation antipsychotics (such as olanzapine, quetiapine, and clozapine) are known to reduce ACTH and cortisol level [82]. Other studies are needed to understand the presence of a baseline HPA dysregulation, but considering the important consequences in general population of prolonged exposure to hyper/hypocortisolism, it is reasonable to suppose that over many years the pattern of HPA function in schizophrenia patients probably contributes to the increased levels of central obesity, insulin resistance, lipid disturbance, and premature mortality (due to CVD) found in this group of patients.

Unhealthy Lifestyle

People affected by severe mental illness (SMI) generally conduct an unhealthy lifestyle (smoking, irregular diet, and rare physical exercise) [83, 84]. Male patients are more likely to have unhealthy dietary habits. In particular the intake of fruit, vegetables, and fibers is less than in general population, and they exceed in the consumption of calories and saturated fats [85]. For example, in a study conducted on 146 subjects affected by schizophrenia with mean body mass index (BMI) of 32.8 (condition of obesity), it was shown that they consumed more calories with a similar diet than general population [86]. The factors that interfere with achieving a weight loss in patients with schizophrenia are various: metabolic effects of psychoactive medications, impact of symptoms on motivation, sedentary, loneliness (only 3% results to be married), and chronic poverty that can have a great impact also in the ability to pursue activities such as exercise [85].

Moreover, in patients with schizophrenia, negative symptoms, which are relatively common and account for poor functional outcome, interfere with the ability to cope with daily activities [87, 88]. It determines low physical activity in these patients assessed with new validated tool such as the International Physical Activity Questionnaire [IPAQ] short form [89]. In a study made by Sicras-Mainar, it demonstrated the association between negative symptoms and the development of metabolic syndrome [90]. Another environmental factor that increases cardiovascular risk is the high prevalence of smoking in patients with schizophrenia (about 70% currently smoke). The reasons of the increased level of smoking can be self-medication of negative/cognitive symptoms and neurophysiological abnormalities [91], depressive symptoms [92], or a means of activity or staving off boredom [93] or to decrease the extrapyramidal side effects of antipsychotics [94], but there also theories about a relationship between nicotine dependence and possibly dysregulation in nicotinic receptors or other neurotransmitter systems [95]. Patients with schizophrenia are majority heavy smokers, for example, in a study made by Wehring [96], 43% of the sample were found to be heavy smokers, as confirmed in other studies where the percentage was similar [97] and exceed the rate in general population that counts 11% of heavy smokers [85]. Furthermore heavy smokers were more likely to have used substances (more likely amphetamines, cocaine, cannabis, and hallucinogens but less likely to use sedatives and opiates) [98] and alcohol, increasing the risk for morbidities and mortality [96]. In a study made in Kentucky on patients with SMI, a lifetime prevalence of alcohol abuse or dependence of 64% was found [86]. A higher than expected prevalence of hepatitis C and HIV was also found in this study.

Reviews and meta-analysis have demonstrated potential effectiveness of lifestyle interventions, even of short duration (≤6 months), for achieving weight loss in these patients [99]. It has been shown that behavioral approaches (with diet and increased physical activity) are preferred than pharmacological therapy to lose weight in psychiatric population [100]. A systematic review published in 2003 evaluated the effectiveness of any intervention to reduce weight gain in schizophrenia. Only five out of the eight pharmacological interventions reported any degree of weight loss, whereas all the behavioral interventions reported at least small reductions, or maintenance, of weight [101]. Another meta-analysis made by Naslunda [102] considered trials of lifestyle interventions targeting weight loss in people with SMI. These studies included behavioral interventions (self-monitoring, dietary changes, nutrition education, fitness, exercise or physical activity) and excluded pharmacological treatments, nutritional supplements, or surgical procedures. These studies underlined the importance of weight loss; in fact a modest ≥5% weight loss is associated with reduction in cardiovascular risk [103]. To date, there is limited evidence to support the long-term sustainability of lifestyle interventions for patients with severe mental illness [102]. Hassapidou [104] found a significant weight loss and reduction of adiposity parameters in a follow-up of 3 and 6 months, but the evidence about the reduction of adiposity parameters at long term were poor. At 9 months weight loss was significant and progressive [105]; also in the dropouts there is a continual and significant weight loss which probably indicates a general efficacy of this nutritional intervention. There was also a significant decrease in body fat mass (kg) and percent of body fat (%) in patients. This reduction contributes to an improvement in the risk factors associated with cardiovascular disease [104]. Moreover weight gain, which can be associated also with antipsychotic treatment, may affect the compliance of patients toward the pharmacological therapy. Controlling and decreasing the weight gain of psychiatric patients should be a priority within their treatment program [106].

Inflammation

Inflammation is one of the biological mechanisms that take part to an increase of CVR mainly through the development of metabolic abnormalities. Chronic inflammation is associated with metabolic-related conditions such as obesity, type 2 diabetes, and insulin resistance. This link proves the interdependence between metabolism and immune systems [107]. Recent studies have reported the onset of an inflammatory process in both chronic and first-episode psychosis patients (FEP) [108]. As regards this last group of patients, we report some evidence, but the relationship between inflammation and metabolic outcomes has to be investigated further. For example, one previous study found that elevated baseline interleukin 1β(IL-1β) levels predicted a major risk of an increase of body weight after 6 months of treatment with risperidone [109]. Furthermore, in a cross-sectional study of patients with psychosis, hs-CRP (high-sensitivity C-reactive protein, a highly sensitive quantification of C-reactive protein, an acute-phase protein released during inflammation) predicted independently the development of metabolic syndrome, an increase of waist circumference, and an elevation of triglycerides in blood [110]. A longitudinal study made by Russel [111] showed that FEP patients who experience greater increase in inflammation index early on in their illness course have a poorer metabolic prognosis in the short term. In particular the risk of dyslipidemia, a risk factor for cardiovascular disease, is higher. The mechanisms linking dyslipidemia with inflammation and higher hs-CRP are still unclear, but studies have highlighted that the acute-phase response causes lipid disturbances [112]. During an inflammatory process, the immune system redistributes essential nutrients to the cells involved in the host defense; for example, HDL cholesterol decreases as a result of a reduction of the uptake of cholesterol by cells, as well as an increase in their catabolism. Some investigations on CVR focus on markers of inflammation such as ICAM1, VCAM1, and E-selectin. There are evidence that chronic inflammation in atherosclerotic disease includes components of vascular tissues [110,

111]. Cytokines change the levels of VCAM1 and ICAM1 during the early phase of inflammation. Evidence have demonstrated that in patients with a first episode of psychosis, levels of cellular adhesion molecules aren't different from controls, except for ICAM1. Furthermore, antipsychotics increased ICAM1 and decreased VCAM1 [113]. Another way to study the inflammatory state in psychosis is to measure cytokines. Cytokines are small secreted proteins involved in the inflammatory response in physiologic and pathologic conditions through a complex network of interactions. They are also mediators between the immune system and the central nervous system, which might have implications for psychiatry [114, 115]. For our purpose is important to know that cytokines receptors exists in soluble form that can inhibit or enhance the biological activity (soluble interleukin 2R-sIL-2R; soluble IL6 receptor-SIL-6R respectively). There are also endogenous cytokine receptor antagonists (IL-1 receptor antagonist, IL-1RA). It is relevant that there is an increased prevalence of aberrant cytokine levels in patients and their first-degree relatives [116], suggesting that immune system abnormalities may be an endophenotype of the disorder.

Some evidence have associated an imbalance in Th1/Th2 cytokines, with a shift toward Th2 system in schizophrenia [117, 118]. A large number of studies have measured cytokines IL-2 and IL-6. About this topic the results are contradictory; there is evidence of decreased IL-2 levels in schizophrenia [119], not confirmed in another study [120]. In another case it has shown the reverse relationship [121]. IL-6 appears to be increased in schizophrenia; in this case the results are more consistent, but some groups haven't replicated this observation [122]. A recent meta-analysis shows that in schizophrenia, there is an in vivo increase of IL-1RA, sIL-2R, and IL-6 and a decrease in vitro of IL-2. Other important cytokines reported in schizophrenia are TNFα and IL-1β. They promote dopaminergic neural differentiation of neural stem cells and regulate the development of dopamine neurons [123]. TNFα and IL-1β participate in the selective vulnerability of the nigrostriatal pathway related with dopaminergic neurotoxicity [115]. These two cytokines appear to be responsible for an imbalance of Th1/Th2 in schizophrenia, elevating the immune response of other cytokines. A study made by Zhu [124] searched how the serum TNFα and IL1β levels changed in the first-episode psychosis and chronic psychosis patients. Data showed that TNFα and IL-1β levels were decreased in first-episode drug-naive patients, but elevated in chronic psychosis. This suggests a role of psychotropic drugs and of the progression of the disease itself. The study showed a moderate correlation between the increase of TNFα and IL-1β and the negative symptoms in chronic psychosis, so it has been supposed a contribution of the immune abnormality to the progression of the disease and that immune-modulating treatments may become a new strategy of therapy in these patients. Some trials of nonsteroidal anti-inflammatory agents in acutely relapsed patients with schizophrenia showed significant improvements in symptoms [116, 125]. It has been shown that responders to celecoxib have significantly decreased soluble tumor necrosis factor receptor levels [126] and aspirin was more efficacious in patients with a lower baseline in vitro IFNγ/IL-4 ratio [125]. Some cytokines such as IL-1β, IL-6, and TGFβ appeared to be markers of the clinical phase of the disease. They increase during exacerbation and normalize with antipsychotic treatment. There is also a positive correlation between IL-6 levels and psychopathology scores [127, 128]. In contrast, IL-12, IFNγ, TNFα, and sIL-2R levels remain elevated both in acute exacerbation and during antipsychotic treatment. Furthermore sIL-2R appears to be a marker for patients with treatment-resistant psychosis [129]. The relation between antipsychotic and serum cytokine levels has been controversial [130, 131]. First of all, the immune alteration in drug-naive patients suggests that there is an association between cytokines and clinical phase of the disease independent from antipsychotic medications. There aren't clear evidence about a direct relation between TNFα/IL-1β and antipsychotics. Some reviews suggest an anti-inflammatory effect in

schizophrenia of psychotropic drugs [132]. As previously observed [130], a meta-analysis made by Tourjman [131] confirms the increase of sIl-2R levels in schizophrenia during antipsychotic treatment. Data demonstrate that IL-2, Il-4, IL-10, Il-1RA, sIL-6R, TGFβ, and TNFα are unchanged. IL-6, a cytokine generally unaffected by antipsychotic treatment, increases during therapy with clozapine [133]. IL-1β and IFNγ levels in schizophrenia spectrum disorders appear to decrease, and IL-12 seems to increase during antipsychotic treatment.

Antipsychotic Treatment

More solid evidence demonstrate that antipsychotic treatment can induce cardiovascular and metabolic alterations that increase CVR [53, 134]. The molecular mechanisms with whom antipsychotics cause abnormalities in glucose and lipid metabolism are both obesity-related and obesity-unrelated [135]. The increased CVR is due in part to insulin resistance and weight gain caused by medications [136]. Drugs differ in effect on body weight; the mechanisms are not fully understood, but it seems that actions at receptors associated with hypothalamic control of food intake are implicated. Evidence supports 5-hydroxytryptamine receptor 2C and dopamine 2D receptor antagonism as well as antagonism at histamine H1 and muscarinic M3 receptors (they may be implicated in glucose regulation alterations provoked by antipsychotics). There are important differences in the propensity to cause weight gain between drugs. For example, aripiprazole has protective pharmacological mechanisms rather than just the absence of a hyperphagic effect. It is important to focus on the fact that there is a significant individual variation in antipsychotic drug-induced weight gain. This reflects genetic variations in several drug targets, including the 5-hydroxytryptamine receptor 2C, as well as genes involved in obesity and metabolic disturbances [137]. Antipsychotic drugs may affect the actions of hormones implicated in the hypothalamic control of food intake and body weight. A study made by Zhang [135] reported that, in people with an antipsychotic treatment, there is an increase in blood concentrations of leptin (a hormone secreted by adipose cells to inhibit hunger), but in people gaining weight during antipsychotic treatment, the anorexigenic effect of leptin is lost through the block of hypothalamic receptors implicated in control of food intake made by the drugs. This suggests that a mechanism contributing to antipsychotic weight gain is the interference with hormone control of food intake and body weight [138]. To support this hypothesis, a meta-analysis made by Bartoli [139] showed that olanzapine and clozapine are associated with a decrease in adiponectin (an orexigenic hormone secreted by adipose tissue with opposite effects to leptin on feeding behavior), a decrease in adiposity, and diabetes insulin resistance [140]. Decreased adiponectin was associated with increased insulin resistance, increased inflammation as determined by CRP, and elevated serum leptin in patients treated with second-generation antipsychotics [141]. Weight gain can be related to the interaction with the brain monoaminergic and cholinergic systems and also to the metabolic/endocrine effects of hyperprolactinemia. Evidence agrees on the hierarchy in the magnitude of body weight gain induced by diverse drugs [136, 142], being very high for clozapine and olanzapine; high for quetiapine, zotepine, chlorpromazine, and thioridazine; moderate for risperidone and sertindole; and low for ziprasidone, amisulpride, haloperidol, fluphenazine, pimozide, molindone, and aripiprazole. Furthermore, clozapine and olanzapine seem to induce glucose dysregulation and dyslipidemia despite patients with schizophrenia having a significant high prevalence of diabetes before the introduction of treatment. Both typical (first-generation) antipsychotics and atypical (second-generation) antipsychotics cause weight gain [136]. Evidence suggested that atypical antipsychotics may have lower discontinuation rates due to any cause as well as greater weight gain and diabetes, but more work is needed to clarify this [143, 144]. A meta-analysis made by Burghardt [145] highlighted that atypical antipsychotics, from the

results of trials in healthy volunteers, cause insulin resistance and weight gain directly, independent of psychiatric disease and may be associated with length of treatment. Moreover a continuous and significant weight gain due to second-generation antipsychotics is more pronounced in younger and female patients with schizophrenia [144]. Schizophrenia itself is a risk factor suggesting that illness severity and negative symptoms could contribute in weight gain. Interestingly differences in effect between second-generation and first-generation antipsychotics as regards weight and lipid outcomes declined with longer follow-up. This highlights the role of other non-iatrogenic factors (unhealthy lifestyle, environment, and genetics) [144]. Besides causing weight gain and dyslipidemia and indirectly diabetes and higher CVR, antipsychotics have a direct effect on the vascular system. They can modify blood pressure and cause endothelial alterations leading to higher risk of thrombosis and bleedings [146]. In general atypical antipsychotics are associated with lower risk of all-cause mortality and extrapyramidal symptoms, but higher risk of stroke [147], metabolic syndrome [148], dyslipidemia (in particular clozapine and olanzapine, quetiapine and risperidone confer an intermediate risk), and diabetes mellitus (risk 1.3-fold higher with second-generation antipsychotics) compared to typical antipsychotics [143]. All the types of antipsychotics are associated with QTc prolongation and/or torsades de pointes and sudden death due to cardiac arrhythmia [149]. It is relevant to know that the risk for QTc prolongation is dose-dependent, so adding a second antipsychotic may increase the risk [150]. Antipsychotics elevate the risk of cortical venous thrombosis or pulmonary embolism [151]. These effects can be caused by enhanced aggregation of platelets, raised concentration of anticardiolipin antibodies, and exacerbation of venous stasis [152]. Parker, in a case-control study based on the primary care clinical record of 115.000 people in the UK, highlights a 32% higher hazard ratio of venous thromboembolism for patients in treatment with antipsychotics in the past 24 months [153]. Liperoti conducted a retrospective cohort study of nonusers and new users of antipsychotics and calculated the rate of hospitalization for thromboembolism (higher for quetiapine, risperidone, olanzapine, and clozapine) [151]. Another risk factor for cardiovascular disease and strokes is variation of blood pressure (it's recognized that an increase of 2–3 mmHg can increase the risk). One out of three patients using antipsychotics has elevated blood pressure that seems to be due to drugs [154]. Antipsychotics can also cause orthostatic hypotension through weight gain and the intrinsic antagonistic action on adrenergic receptors [155]. Despite the few data, antipsychotics with low potency at the dopamine D2 receptor (phenothiazine, chlorpromazine, and thioridazine) are considered the most likely to cause orthostatic hypotension [137].

Conclusions

Based on the large number of factors implicated in the increased CVR of schizophrenic patients, a strict monitoring of the metabolic risk is essential, in particular, as stated before in the text, in the early phase of the disease (after 2–5 years after illness onset). First of all, a behavioral intervention is necessary, applying measures to reduce obesity and smoking. Moreover clinicians should prescribe regular blood test and monitor body weight/waist circumference to control collateral effects of antipsychotic drugs. An accurate family medical history and a coordinated action of several specialists are essential.

Cross-References

- ▶ Borderline Personality Disorder and the Heart
- ▶ Brain-Heart Communication
- ▶ Cardiovascular Adverse Effects of Psychotropic Drugs
- ▶ Cardiovascular Manifestations of Panic and Anxiety
- ▶ Depression and Cardiovascular Diseases
- ▶ Emotional Processing and Heart Activity

References

1. Laursen TM, Munk-Olsen T, Nordentoft M, Mortensen PB. Increased mortality among patients admitted with major psychiatric disorders: a register-based study comparing mortality in unipolar depressive disorder, bipolar affective disorder, schizoaffective disorder, and schizophrenia. J Clin Psychiatry. 2007;68(6):899–907.
2. Foguet-Boreu Q, Fernandez San Martin MI, Flores Mateo G, Zabaleta Del Olmo E, Ayerbe Garcia-Morzon L, Perez-Pinar Lòpez M, Martin-Lòpez LM, Montes Hidalgo J, Viòlan C. Cardiovascular risk assessment in patients with a severe mental illness; a systematic review and meta-analysis. BMC Psychiatry. 2016;16:141.
3. De Hert M, Correll CU, Bobes J, Cetkovich-Bakmas M, Cohen D, Asai I, et al. Physical illness in patients with severe mental disorders. I. Prevalence, impact of medications and disparities in health care. World Psychiatry. 2011;10:52–77.
4. De Hert M, Dekker JM, Wood D. Cardiovascular disease and diabetes in people with severe mental illness. Position statement from the European Psychiatric Association (EPA), supported by the European Association for the Study of Diabetes (EASD) and the European Society of Cardiology (ESC). Eur Psychiatry. 2009;24:412–24.
5. Bartoli F, Crocamo C, Caslini M, Clerici M, Carra G. Schizoaffective disorder and metabolic syndrome: a meta-analytic comparison with schizophrenia and other non-affective psychoses. J Psychiatr Res. 2015;66-67:127e134.
6. Kilbourne AM, Brar JS, Drayer RA, Xu X, Post EP. Cardiovascular disease and metabolic risk factors in male patients with schizophrenia, schizoaffective disorder, and bipolar disorder. Psychosomatics. 2007;48:412e7.
7. Bioque M, Llerena A, Cabrera B, Mezquida G, Lobo A, Gonzalez-Pinto A, Diaz-Caneja CM, Corripio I, Aguilar EJ, Bulbena A, Castro-Fornieles J, Vieta E, Lafuente A, Mas S, Parellada M, Saiz-Ruiz J, Cuesta MJ, Bernardo M. A pharmacovigilance study in first episode of psychosis: psychopharmacological interventions and safety profiles in the PEPs project. Int J Neuropsychopharmacol. 2016;19(4):1–10.
8. Kantrowitz JT, Citrome L. Schizoaffective disorder: a review of current research themes and pharmacological management. CNS Drugs. 2011;25:317e31.
9. Bhattacharjee S, Bhattacharya R, Kelley GA, Sambamoorthi U. Antidepressant use and new-onset diabetes: a systematic review and meta-analysis. Diabetes Metab Res Rev. 2013;29:273e84.
10. McKnight RF, Adida M, Budge K, Stockton S, Goodwin GM, Geddes JR. Lithium toxicity profile: a systematic review and meta-analysis. Lancet. 2012;379:721e8.
11. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington: American Psychiatric Publishing; 2013.
12. Bär KJ. Cardiac autonomic dysfunction in patients with schizophrenia and their healthy relative – a small review. Front Neurol. 2015;6:139.50.
13. Bär KJ, Boettger MK, Berger S, Baier V, Sauer H, Yeragani VK, Voss A. Decreased baroreflex sensitivity in acute schizophrenia. J Appl Physiol. 2007;102(3):1051–6.
14. Baller JB, McGinty EE, Azrin ST, Juliano-Bult D, Daumit GL. Screening for cardiovascular risk factors in adults with serious mental illness: a review of the evidence. BMC Psychiatry. 2015;15:55.
15. Lawrence D, Kisely S. Inequalities in healthcare provision for people with severe mental illness. J Psychopharmacol. 2010;24(4 Suppl):61–8.
16. Srihari VH, Phutane VH, Ozkan B, Chwastiak L, Ratliff JC, Woods SC, Tek C. Cardiovascular mortality in Schizophrenia: defining a critical period for prevention. Schizophr Res. 2013;146(0):64–8.
17. Yang Q, Cogswell ME, Flanders WD, Hong Y, Zhang Z, Loustalot F, Gillespie C, Merritt R, Hu FB. Trends in cardiovascular health metrics and associations with all-cause and CVD mortality among us adults. JAMA. 2012;307(12):1273–83.
18. Center for Quality Assessment and Improvement in Mental Health. Metabolic monitoring. Cambridge, MA: Center for Quality Assessment and Improvement in Mental Health; 2007.
19. Ritchie S, Muldoon L. Cardiovascular preventive care for patients with serious mental illness. Can Fam Physician. 2017;63(11):e483–7.
20. Baptista T, Kin NM, Beaulieu S, de Baptista EA. Obesity and related metabolic abnormalities during antipsychotic drug administration: mechanisms, management and research perspectives. Pharmacopsychiatry. 2002;35(6):205–19.
21. Bernardo M, Bioque M, Parellada M, Saiz Ruiz J, Cuesta MJ, Llerena A, Sanjuan J, Castro-Fornieles J, Arango C, Cabrera B. Assessing clinical and functional outcomes in a gene-environment interaction study in first episode of psychosis (PEPs). Rev Psiquiatr Salud Ment. 2013;6(1):4–16.
22. Fernandez-Egea E, Bernardo M, Donner T, Conget I, Parellada E, Justicia A, Esmatjes E, Garcia-Rizo C, Kirkpatrick B. Metabolic profile of antipsychotic-naive individuals with non-affective psychosis. Br J Psychiatry. 2009;194(5):434–8.
23. Greenhalgh AM, Gonzalez-Blanco L, Garcia-Rizo C, Fernandez-Egea E, Miller B, Arroyo MB, Kirkpatrick B. Meta-analysis of glucose tolerance, insulin, and insulin resistance in antipsychotic-naive patients with non affective psychosis. Schizophr Res. 2017;179:57–63.
24. Fernandes BS, Steiner J, Bernstein HG, Dodd S, Pasco JA, Dean OM, Nardin P, Goncalves CA, Berk M. C-reactive protein is increased in schizophrenia but is not altered by antipsychotics: meta-analysis and implications. Mol Psychiatry. 2016;21(4):554–64.

25. Upthegrove R, Manzanares-Teson N, Barnes NM. Cytokine function in medication-naive first episode psychosis: a systematic review and meta-analysis. Schizophr Res. 2014;155(1–3):101–8.
26. Fleischhacker WW, Siu CO, Boden R, Pappadopulos E, Karayal ON, Kahn RS. Metabolic risk factors in first-episode schizophrenia: baseline prevalence and course analysed from the European first-episode schizophrenia trial. Int J Neuropsychopharmacol. 2013;16(5):987–95.
27. Carney R, Bradshaw T, Yung AR. Monitoring of physical health in services for young people at ultra-high risk of psychosis. Early Interv Psychiatry. 2018;12:153–9.
28. Fusar-Poli P, Borgwardt S, Bechdolf A, et al. The psychosis high-risk state: a comprehensive state-of-the-art review. JAMA Psychiat. 2013;70:107–20.
29. Yung AR, Phillips LJ, Yuen HP, McGorry PD. Risk factors for psychosis in an ultra high-risk group: psychopathology and clinical features. Schizophr Res. 2004;67:131–42.
30. Armando M, Nelson B, Yung AR, et al. Psychotic-like experiences and correlation with distress and depressive symptoms in a community sample of adolescents and young adults. Schizophr Res. 2010;119:258–65.
31. Cordes J, Bechdolf A, Engelke C, Kahl KG, Balijepalli C, Losch C, Klosterkotter J, Wagner M, Maier W, Heinz A, de Millas W, Gaebel W, Winterer G, Janssen B, Schmidt-Kraepelin C, Schneider F, Lambert M, Juckel G, Wobrock T, Riedel M, Moebus S. Prevalence of metabolic syndrome in female and male patients at risk of psychosis. Schizophr Res. 2017;181:38–42.
32. Carney R, Cotter J, Bradshaw T, Firth J, Yung AR. Cardiometabolic risk factors in young people at ultra-high risk for psychosis: a systematic review and meta-analysis. Schizophr Res. 2016;170(2–3):290–300.
33. Barcones MF, MacDowell KS, Garcìa-Bueno B, Biogue M, Gutierrez-Galve L, Gonzàlez-Pinto A, Parellada MJ, Bobes J, Bernardo M, Lobo A, Leza JC. Cardiovascular risk in early psychosis: relationship with inflammation and clinical features 6 months after diagnosis. Int J Neuropsychopharmacol. 2018;21(5):410–22.
34. Misiak B, Stańczykiewicz B, Łaczmański L, Frydecka D. Lipid profile disturbances in antipsychotic-naive patients with first-episode non-affective psychosis: a systematic review and meta-analysis. Schizophr Res. 2017;190:18–27.
35. Busch C, Hegele R. Variation of candidate genes in triglycerid metabolism. J Cardiovasc Risk. 2000;7:309–315.5.
36. Waterworth D, Talmud P, Bujac S, Fisher R, Miller G, Humpries S. Contributions of apolipoprotein C-III gene variation to determination of triglyceride levels and interaction with smoking in middle-aged men. Aterioscler Thromb Vasc Biol. 2000;20:2663–9.
36. Chao-Qiang L, Serkalem D, Cupples L, Zhu Y, Adiconis S, Parnell L, et al. Influence of the APOA5 locus on plasma triglyceride lipoprotein subclasses and CVD risk in the Framingham Heart Study. J Lipid Res. 2004;45:2096–105.
37. Hokanson J. Functional variants in the lipoprotein lipase gene and risk of cardiovascular disease. Curr Opin Lipidol. 1999;10:393–9.
38. Knoblauch H, Bauerfeind A, Krahenbuhl C, Daury A, Rohde K, Bejanin S, et al. Common haplotypes in five genes influence genetic variance of LDL and HDL cholesterol in the general population. Hum Mol Genet. 2002;11:1477–85.
39. Schmitz G, Langmann T. Pharmacogenetics of cholesterol-lowering therapy. Vasc Pharmacol. 2006;44:75–89.
40. Baroni M, Berni A, Romeo S, Marcello A, Tesorio T, Sorropago G, et al. Genetic study of common variants at the Apo E Apo A1, Apo CIII, Apo B, lipoprotein lipase(LPL) and hepatic lipase (LIPC) genes and the coronary artery disease (CAD): variation in LIPC gene associates with clinical outcomes in patients with established CAD. MBC Med Genet. 2003;10:4–8.
41. Smith RC, Segman RH, Golcer-Dubner T, Pavlov V, Lerer B. Allelic variation in ApoC3, ApoA5 and LPL genes and first and second generation antipsychotic effects on serum lipids in patients with schizophrenia. Pharm J. 2008;8:228–36.
42. Brzustowicz LM, Simone J, Mohseni P. Linkage disequilibrium mapping of schizophrenia susceptibility to the CAPON region of chromosome 1q22. Am J Hum Genet. 2004;74:1057–63.
43. Chowdari KV, Mirnics K, Semwal P. Association and linkage analyses of RGS4 polymorphisms in schizophrenia. Hum Mol Genet. 2002;11:1373–80.
44. De Blasi A, Conn PJ, Pin J. Molecular determinants of metabotropic glutamate receptor signaling. Trends Pharmacol Sci. 2001;22:114–20.
45. Beyer CE, Ghavami A, Lin Q. Regulators of G-protein signaling 4: modulation of 5-HT(1A)-mediated neurotransmitter release in vivo. Brain Res. 2004;1022:214–20.
46. Dubertret C, Hanoun N, Ades J. Family-based association studies between 5-HT5A receptor gene and schizophrenia. J Psychiatr Res. 2004;38:371–6.
47. Buckland PR, Hoogendoorn B, Guy CA. Low gene expression conferred by association of an allele of the 5-HT2C receptor gene with antipsychotic-induced weight gain. Am J Psychiatry. 2005;162:613–5.
48. Reynolds GP, Zhang ZJ, Zhang XB. Association of antipsychotic drug-induced weight gain with a 5-HT2C receptor gene polymorphism. Lancet. 2002;359:2086–7.
49. Miller DD, Ellingrod VL, Holman TL. Clozapine-induced weight gain associated with the 5HT2C receptor –759C/T polymorphism. Am J Med Genet B Neuropsychiatr Genet. 2005;133:97–100.
50. Toichi M, Kubota Y, Murai T, Kamio Y, Sakihama M, Toriuchi T, Inakuma T, Sengoku A, Miyoshi K.

The influence of psychotic states on the autonomic nervous system in schizophrenia. Int J Psychophysiol. 1999;31(2):147–54.
51. Jensen MT, Suadicani P, Hein HO, Gyntelberg F. Elevated resting heart rate, physical fitness and all-cause mortality: a 16-year follow-up in the Copenhagen Male Study. Heart. 2013;99(12):882–7.
52. Rachow T, Berger S, Boettger MK, Schulz S, Guinjoan S, Yeragani VK, Voss A, Bär KJ. Nonlinear relationship between electrodermal activity and heart rate variability in patients with acute schizophrenia. Psychophysiology. 2010;48(10):1323–32.
53. Vancampfort D, Stubbs B, Mitchell AJ, De Hert M, Wampers M, Ward PB, Rosenbaum S, Correll CU. Risk of metabolic syndrome and its components in people with schizophrenia and related psychotic disorders, bipolar disorder and major depressive disorder: a systematic review and meta-analysis. World Psychiatry. 2015;14(3):339–47.
54. Vancampfort D, Firth J, Schuch FB, Rosenbaum S, Mugisha J, Hallgren M, Probst M, Ward PB, Gaughran F, De Hert M, Carvalho AF, Stubbs B. Sedentary behavior and physical activity levels in people with schizophrenia, bipolar disorder and major depressive disorder: a global systematic review and meta-analysis. World Psychiatry. 2017;16(3):308–15.
54. Vancampfort D, Rosenbaum S, Schuch F, Ward PB, Richards J, Mugisha J, Probst M, Stubbs B. Cardiorespiratory fitness in severe mental illness: a systematic re-view and meta-analysis. Sports Med. 2017;47(2):343–52.
55. Herbsleb M, Schumann A, Malchow B, Puta C, Schulze PC, Gabriel HW, Bär KJ. Chronotropic incompetence of the heart is associated with exercise intolerance in patients with schizophrenia. Schizophr Res. 2018;197:162–169.
56. Williams LM, et al. Dysregulation of arousal and amygdala-prefrontal systems in paranoid schizophrenia. Am J Psychiatry. 2004;161:480–9.
57. Ruiz-Padial E, Sollers JJ, Vila J, Thayer JF. The rhythm of the heart in the blink of an eye: emotion-modulated startle magnitude covaries with heart rate variability. Psychophysiology. 2003;40:306–13.
58. Hansen AL, Johnsen BH, Thayer JF. Vagal influence on working memory and attention. Int J Psychophysiol. 2003;48:263–74.
59. Thayer JF, Lane RD. A model of neurovisceral integration in emotion regulation and dysregulation. J Affect Disord. 2000;61:201–16.
60. Thayer JF, Åhs F, Fredrikson M, Sollers JJ, Wager TD. A meta-analysis of heart rate variability and neuroimaging studies: implications for heart rate variability as a marker of stress and health. Neurosci Biobehav Rev. 2012;36:747–56.
61. Heatherton TF, Wagner DD. Cognitive neuroscience of self-regulation failure. Trends Cogn Sci. 2011;15:132–9.
62. Callicott JH, Mattay VS, Verchinski BA, Marenco S, Egan MF, Weinberger DR. Complexity of prefrontal cortical dysfunction in schizophrenia: more than up or down. Am J Psychiatry. 2003;160:2209–15.
63. Thayer JF, Lane RD. Claude Bernard and the heart-brain connection: further elaboration of a model of neurovisceral integration. Neurosci Biobehav Rev. 2009;33:81–8.
64. Henry BL, Minassian A, Paulus MP, Geyer MA, Perry W. Heart rate variability in bipolar mania and schizophrenia. J Psychiatr Res. 2010;44:168–76.
65. Foster PS, Harrison DW. The covariation of cortical electrical activity and cardiovascular responding. Int J Psychophysiol. 2004;52:239–55.
66. Tanida M, Sakatani K, Takano R, Tagai K. Relation between asymmetry of prefrontal cortex activities and the autonomic nervous system during a mental arithmetic task: near infrared spectroscopy study. Neurosci Lett. 2004;369:69–74.
67. Mathewson KJ, Jetha MK, Goldberg JO, Schmidt LA. Autonomic regulation predicts performance on Wisconsin cards or ting test (WCST) in adults with schizophrenia. Biol Psychol. 2012;91:389–99.
68. McAllen RM. Inhibition of the baroreceptor input to the medulla by stimulation of the hypothalamic defence area. J Physiol. 1976;257:45–6.
69. Shoemaker JK, Norton KN, Baker J, Luchyshyn T. Fore brain organization for autonomic cardiovascular control. Auton Neurosci. 2015;188:5–9.
70. Ziegler G, Dahnke R, Yeragani VK, Bär KJ. The relation of ventromedial prefrontal cortex activity and heart rate fluctuations at rest. Eur J Neurosci. 2009;30:2205–10.
71. Thayer JF, Friedman BH. A neurovisceral integration model of health disparities in aging. In: Anderson NB, Bulato RA, Cohen B, editors. Critical perspectives on racial and ethnic differences in health in late life. Washington, DC: The National Academies Press; 2004. p. 567–603.
72. Waldstein SR, Kop WJ, Schmidt LA, Haufler AJ, Krantz DS, Fox NA. Frontal electrocortical and cardiovascular reactivity during happiness and anger. Biol Psychol. 2000;55:3–23.
73. Venables NC, Bernat EM, Sponheim SR. Genetic and disorder-specific aspects of resting state EEG abnormalities in schizophrenia. Schizophr Bull. 2009;35:826–39.
74. Uhlhaas PJ, Singer W. Abnormal neural oscillations and synchrony in schizophrenia. Nat Rev Neurosci. 2010;11:100–13.
75. Thayer JF. What the heart says to the brain (and vice versa) and why we should listen. Psychol Top. 2007;16:241–50.
76. Schulz S, Bolz M, Bär KJ, Voss A. Central and autonomic nervous system coupling in schizophrenia. Philos Trans R Soc. 2016;374:20150178.
77. Schulz S, Tupaika N, Berger S, Haueisen J, Bär KJ, Voss A. Cardiovascular coupling analysis with high-

resolution joint symbolic dynamics in patients suffering from acute schizophrenia. Physiol Meas. 2013;34:883–901.
78. Bär K, Letzsch A, Jochum T, Wagner G, Greiner W, Sauer H. Loss of efferent vagal activity in acute schizophrenia. J Psychiatr Res. 2005;39:519–27.
79. Nosaka S. Modifications of arterial baroreflexes: obligatory roles in cardiovascular regulation in stress and post stress recovery. Jpn J Physiol. 1996;46:271–88.
80. Schulz S, Bär KJ, Voss A. Analyses of heart rate, respiration and cardiorespiratory coupling in patients with schizophrenia. Entropy. 2015;17:483–501.
81. Bradley AJ, Dinan TG. A systematic review of hypothalamic-pituitary-adrenal axis function in schizophrenia: implications for mortality. J Psychopharmacol. 2010;24(Supplement 4):91–118.
82. Cohrs S, Roher C, Jordan W, Meier A, Huether G, Wuttke W, et al. The atypical antipsychotics olanzapine and quetiapine, but not haloperidol, reduce ACTH and cortisol secretion in healthy subjects. Psychopharmacology. 2006;185:11–8.
83. Peet M. Diet, diabetes and schizophrenia: review and hypothesis. Br J Psychiatry Suppl. 2004;47:S102–5.
84. De Leon J, Diaz FJ. A meta-analysis of worldwide studies demonstrates an association between schizophrenia and tobacco smoking behaviors. Schizophr Res. 2005;76:135–57.
85. McCreadie RG, Scottish Schizophrenia Lifestyle Group. Diet, smoking and cardiovascular risk in people with schizophrenia: descriptive study. Br J Psychiatry. 2003;183:534–9.
86. Susce MT, Villanueva N, Diaz FJ, de Leon J. Obesity and associated complications in patients with severe mental illnesses: a cross-sectional survey. J Clin Psychiatry. 2005;66:167–73.
87. Fervaha G, Foussias G, Remington G. Impact of primary negative symptoms on functional outcomes in schizophrenia. Eur Psychiatry. 2014;29:449–55.
88. Rabinowitz J, Levine SZ, Garibaldi G, Bugarski-Kirola D, Berardo CG, Kapur S. Negative symptoms have greater impact on functioning than positive symptoms in schizophrenia: analysis of CATIE data. Schizophr Res. 2012;137:147–50.
89. Faulkner G, Cohn T, Remington G. Validation of a physical activity assessment tool for individuals with schizophrenia. Schizophr Bull. 2005;21:S523.
90. Sicras-Mainar A, Maurino J, Ruiz-Beato E, Navarro-Artieda R. Prevalence of metabolic syndrome according to the presence of negative symptoms in patients with schizophrenia. Neuropsychiatr Dis Treat. 2015;11:51–7.
91. Winterer G. Why do patients with schizophrenia smoke? Curr Opin Psychiatry. 2010;23:112–9.
92. Lising-Enriquez K, George TP. Treatment of comorbid tobacco use in people with serious mental illness. J Psychiatry Neurosci. 2009;34(3):E1–2.
93. Roick C, Fritz-Wieacker A, Matschinger H, Heider D, Schindler J, Riedel-Heller S, Angermeyer MC. Health habits of patients with schizophrenia. Soc Psychiatry Psychiatr Epidemiol. 2007;42:268–76.
94. Madden PA, Bucholz KK, Dinwiddie SH, Slutske WS, Bierut LJ, Statham DJ, Dunne MP, Martin NG, Heath AC. Nicotine withdrawal in women. Addiction. 1997;92(7):889–902.
95. Wing VC, Wass CE, Soh DW, George TP. A review of neurobiological vulnerability factors and treatment implications for comorbid tobacco dependence in schizophrenia. Ann N Y Acad Sci. 2012;1248:89–106.
96. Wehring HJ, Liu F, McMahon RP, Mackowick KM, Love RC, Dixon L, Kelly DL. Clinical characteristics of heavy and non-heavy smokers with schizophrenia. Schizophr Res. 2012;138:285–9.
97. Lasser K, Boyd JW, Woolhandler S, Himmelstein DU, McCormick D, Bor DH. Smoking and mental illness: a population-based prevalence study. JAMA. 2000;284(20):2606–10.
98. Schneier FR, Siris SG. A review of psychoactive substance use and abuse in schizophrenia: patterns of drug choice. J Nerv Ment Dis. 1987;175:641–52.
99. Fernández-San-Martín MI, Martín-López LM, Masa-Font R, Olona-Tabueña N, Roman Y, Martin-Royo J, et al. The effectiveness of lifestyle interventions to reduce cardiovascular risk in patients with severe mental disorders: meta-analysis of intervention studies. Community Ment Health J. 2014;50(1):81–95.
99. Bruins J, Jörg F, Bruggeman R, Slooff C, Corpeleijn E, Pijnenborg M. The effects of lifestyle interventions on (long-term) weight management, cardiometabolic risk and depressive symptoms in people with psychotic disorders: a meta-analysis. PLoS One. 2014;9(12):e112276.
100. Werneke U, Taylor D, Sanders TA. Options for pharmacological management of obesity in patients treated with atypical antipsychotics. Int J Clin Psychopharmacol. 2002;17:145–60.
101. Faulkner G, Soundy AA, Lloyd K. Schizophrenia and weight management: a systematic review of interventions to control weight. Acta Psychiatr Scand. 2003;108:324–32.
102. Naslunda JA, Whitemanb KL, McHugoc GJ, Aschbrennerb KA, Marschc LA, Bartelsa SJ. Lifestyle interventions for weight loss among overweight and obese adults with serious mental illness: a systematic review and meta-analysis. Gen Hosp Psychiatry. 2017;47:83–102.
103. Wing RR, Lang W, Wadden TA, Safford M, Knowler WC, Bertoni AG, et al. Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. Diabetes Care. 2011;34(7):1481–6.
104. Hassapidou M, Papadimitriou K, Athanasiadou N, Tokmakidou V, Pagkalos I, Vlahavas G, Tsofliou F. Changes in bodyweight, body composition and cardiovascular risk factors after long-term nutritional

intervention in patients with severe mental illness: an observational study. BMC Psychiatry. 2011;11:31.
105. Poulin MJ, Chaput JP, Simard V, Vincent P, Bernier J, Gauthier Y, Lanctôt G, Saindon J, Vincent A, Gagnon S, Tremblay A. Management of antipsychotic-induced weight gain: prospective naturalistic study of the effectiveness of a supervised exercise programme. Aust N Z J Psychiatry. 2007;41:980–9.
106. Khazaal Y, Fresard E, Rabia S, Chatton A, Rothen S, Pomini V, Grasset F, Borgeat F, Zullino D. Cognitive behavioural therapy for weight gain associated with antipsychotic drugs. Schizophr Res. 2007;91:169–77.
107. Lindenmayer JP, Khan A, Wance D, Maccabee N, Kaushik S. Outcome evaluation of a structured educational wellness program in patients with severe mental illness. J Clin Psychiatry. 2009;70:1385–96.
107. Hotamisligil GS. Inflammation and metabolic disorders. Nature. 2006;444:860–7.
108. Di Nicola M, Cattaneo A, Hepgul N, Di Forti M, Aitchison KJ, Janiri L, Murray RM, Dazzan P, Pariante CM, Mondelli V. Serum and gene expression profile of cytokines in first-episode psychosis. Brain Behav Immun. 2013;31:90–5.
109. Potvin S, Stip E, Sepehry AA, Gendron A, Bah R, Kouassi E. Inflammatory cytokine alterations in schizophrenia: a systematic quantitative review. Biol Psychiatry. 2008;63(8):801–8.
109. Song X, Fan X, Li X, Zhang W, Gao J, Zhao J, Harrington A, Ziedonis D, Lv L. Changes in pro-inflammatory cytokines and body weight during 6-month risperidone treatment in drug naive, first-episode schizophrenia. Psychopharmacology. 2014;231(2):319–25.
110. Miller BJ, Mellor A, Buckley P. Total and differential white blood cell counts, high-sensitivity C-reactive protein, and the metabolic syndrome in non-affective psychoses. Brain Behav Immun. 2013;31:82–9.
111. Russel A, Ciufolini S, Gardner-Sood P, Bonaccorso S, Gaughran F, Dazzan P, Pariante CM, Mondelli V. Inflammation and metabolic changes in first episode psychosis: preliminary results from a longitudinal study. Brain Behav Immun. 2015;49:25–9.
112. Khovidhunkit W, Memon RA, Feingold KR, Grunfeld C. Infection and inflammation-induced proatherogenic changes of lipoproteins. J Infect Dis. 2000;181(Suppl(Vldl)):S462–72.
113. Kavzoglu SO, Hariri AG. Intracellular Adhesion Molecule (ICAM-1), Vascular Cell Adhesion Molecule (VCAM-1) and E-Selectin Levels in First Episode Schizophrenic Patients. Bull Clin Psychopharmacol. 2013;23(3):205–14.
114. Kronfol Z, Remick DG. Cytokines and the brain: implications for clinical psychiatry. Am J Psychiatry. 2000;157:683–94.
115. Raison CL, Miller AH. Brain-immune system interaction: relevance to the pathophysiology and treatment of neuropsychiatric disorders. In: Schatzberg AF, Nemeroff CB, editors. The American psychiatric publishing textbook of psychopharmacology. 3rd ed. Washington, DC: American Psychiatric Press; 2004. p. 147–62.
116. Akhondzadeh S, Tabatabaee M, Amini H, et al. Celecoxib as adjunctive therapy in schizophrenia: a double-blind, randomized and placebo-controlled trial. Schizophr Res. 2007;90:179–85.
117. Muller N, Riedel M, Gruber R, Ackenheil M, Schwarz MJ. The immune system and schizophrenia. An integrative view. Ann N Y Acad Sci. 2000;917:456–67.
118. Schwarz MJ, Muller N, Riedel M, Ackenheil M. The Th2-hypothesis of schizophrenia: a strategy to identify a subgroup of schizophrenia caused by immune mechanisms. Med Hypotheses. 2001;56:483–6.
119. Arolt V, Rothermundt M, Wandinger KP, Kirchner H. Decreased in vitro production of interferon-gamma and interleukin-2 in whole blood of patients with schizophrenia during treatment. Mol Psychiatry. 2000;5:150–8.
120. Kaminska T, Wysocka A, Marmurowska-Michalowska H, Dubas-Slemp H, Kandefer-Szerszen M. Investigation of serum cytokine levels and cytokine production in whole blood cultures of paranoid schizophrenic patients. Arch Immunol Ther Exp. 2001;49:439–45.
121. Ebrinc S, Top C, Oncul O, Basoglu C, Cavuslu S, Cetin M. Serum interleukin1 alpha and interleukin 2 levels in patients with schizophrenia. J Int Med Res. 2002;30:314–7.
122. Akiyama K. Serum levels of soluble IL-2 receptor alpha, IL-6 and IL-1 receptor antagonist in schizophrenia before and during neuroleptic administration. Schizophr Res. 1999;37:97–106.
123. Rodriguez-Pallares J, Guerra MJ, Labandeira-Garcia JL. Angiotensin II and interleukin-1 interact to increase generation of dopaminergic neurons from neurospheres of mesencephalic precursors. Brain Res Dev Brain Res. 2005;158:120–2.
124. Zhu F, Zhang L, Liu F, Wu R, Guo W, Ou J, Zhang X, Zhao J. Altered serum tumor necrosis factor and interleukin-1β in first-episode drug-naïve and chronic schizophrenia. Front Neurosci. 2018;12:296.
125. Laan W, Grobbee DE, Selten JP, Heijnen CJ, Kahn RS, Burger H. Adjuvant aspirin therapy reduces symptoms of schizophrenia spectrum disorders: results from a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry. 2010;71:520–7.
126. Müller N, Ulmschneider M, Scheppach C, Schwarz MJ, Ackenheil M, Möller HJ, et al. COX-2 inhibition as a treatment approach in schizophrenia: immunological considerations and clinical effects of celecoxib add-on therapy. Eur Arch Psychiatry Clin Neurosci. 2004;254:14–22.
127. Frommberger UH, Bauer J, Haselbauer P, Fräulin A, Riemann D, Berger M. Interleukin-6 (IL-6) plasma levels in depression and schizophrenia: comparison between the acute state and after remission. Eur Arch Psychiatry Clin Neurosci. 1997;247:228–33.

128. Pae CU, Yoon CH, Kim TS, Kim JJ, Park SH, Lee CU, et al. Antipsychotic treatment may alter T-helper (TH) 2 arm cytokines. Int Immunopharmacol. 2006;6:666–71.
129. Bresee C, Rapaport MH. Persistently increased serum soluble interleukin-2 receptors in continuously ill patients with schizophrenia. Int J Neuropsychopharmacol. 2009;12:861–5.
130. Miller BJ, Buckley P, Seabolt W, Mellor A, Kirkpatrick B. Meta-analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effects. Biol Psychiatry. 2011;70:663–71.
131. Tourjman V, Kouassi É, Koué MÈ, Rocchetti M, Fortin-Fournier S, Fusar-Poli P, et al. Antipsychotics' effects on blood levels of cytokines in schizophrenia: a meta-analysis. Schizophr Res. 2013;151:43–7.
132. Kato AT, Monji A, Mizoguchi Y, Hashioka S, Horikawa H, Seki Y, Kasai M, Utsumi H, Kanba S. Anti-inflammatory properties of antipsychotics via microglia modulations. Are antipsychotics a "Fire Extinguisher" in the Brain of Schizophrenia? Mini-Rev Med Chem. 2011;11(7):565–574(10).
133. Maes M, Bosmans E, Kenis G, De Jong R, Smith RS, Meltzer HY. In vivo immunomodulatory effects of clozapine in schizophrenia. Schizophr Res. 1997;26 (2–3):221–5.
134. Silva A, Ribeiro M, Sousa-Rodrigues CF, Barbosa FT. Association between antipsychotics and cardiovascular adverse events: a systematic review. Rev Assoc Med Bras (1992). 2017;63(3):261–7.
135. Zhang ZJ, Yao ZJ, Liu W, et al. Effects of antipsychotics on fat deposition and changes in leptin and insulin levels. Magnetic resonance imaging study of previously untreated people with schizophrenia. Br J Psychiatry. 2004;184:58–62.
136. Bak M, Fransen A, Janssen J, van Os J, Drukker M. Almost all antipsychotics result in weight gain: a meta-analysis. PLoS One. 2014;9(4):e94112.
137. Reynolds GP, McGowan O. Mechanisms underlying metabolic disturbances associated with psychosis and antipsychotic drug treatment. J Psychopharmacol. 2017;31(11):1430–6.
138. Reynolds GP, Kirk SL. Metabolic side effects of antipsychotic drug treatment: pharmacological mechanisms. Pharmacol Ther. 2010;125:169–79.
139. Bartoli F, Crocamo C, Clerici M, et al. Second-generation antipsychotics and adiponectin levels in schizophrenia: a comparative meta-analysis. Eur Neuropsychopharmacol. 2015;25:1767–74.
140. Li S, Shin H, Ding E, et al. Adiponectin levels and risk of type2 diabetes: a systematic review and meta-analysis. JAMA. 2009;302:179–88.
141. Sapra M, Lawson D, Iranmanesh A, et al. Adiposity-independent hypoadiponectinemia as a potential marker of insulin resistance and inflammation in schizophrenia patients treated with second generation antipsychotics. Schizophr Res. 2016;174:132–6.
142. Rummel-Kluge C, Komossa K, Schwarz S, Hunger H, Schmid F, Lobos CA, Kissling W, Davis JM, Leucht S. Head-to-head comparisons of metabolic side effects of second generation antipsychotics in the treatment of schizophrenia: a systematic review and meta-analysis. Schizophr Res. 2010;123(2–3):225–33.
143. Smith M, Hopkins D, Peveler RC, Holt RI, Woodward M, Ismail K. First- versus Second-generation antipsychotics and risk for diabetes in schizophrenia: systematic review and meta-analysis. Br J Psychiatry J Ment Sci. 2008;192(6):406–11.
144. Zhang JP, Gallego JA, Robinson DG, Malhotra AK, Kane JM, Correll CU. Efficacy and safety of individual second-generation vs. first-generation antipsychotics in first-episode psychosis: a systematic review and meta-analysis. Int J Neuropsychopharmacol. 2013;16(6):1205–18.
145. Burghardt KJ, Seyoum B, Mallisho A, Burghardt PR, Kowluru RA, Yi Z. Atypical antipsychotics, insulin resistance and weight; a meta-analysis of healthy volunteer studies. Prog Neuro-Psychopharmacol Biol Psychiatry. 2018;83:55–63.
146. Axelsson S, Hagg S, Eriksson AC, Lindahl TL, Whiss PA. In vitro effects of antipsychotics on human platelet adhesion and aggregation and plasmacoagulation. Clin Exp Pharmacol Physiol. 2007;34(8):775–80.
147. Farlow MR, Shamliyan TA. Benefits and harms of atypical antipsychotics for agitation in adults with dementia. Eur Neuropsychopharmacol. 2017;27(3):217–31.
148. DeHert M, Detraux J, VanWinkel R, Correll CU. Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. Nat Rev Endocrinol. 2011;8(2):114–26.
149. Wu CS, Tsai YT, Tsai HJ. Antipsychotic drugs and the risk of ventricular arrhythmia and/or sudden cardiac death: a nation-wide case-cross over study. J Am Heart Assoc. 2015;4(2):e001568.
150. Barbui C, Bighelli I, Carra G, Castellazzi M, Lucii C, Martinotti G, Nose M, Ostuzzi G, Star Network Investigators. Antipsychotic dose mediates the association between polypharmacy and corrected QT interval. PLoS One. 2016;11(2):e0148212.
151. Liperoti R, Pedone C, Lapane KL, Mor V, Bernabei R, Gambassi G. Venous thromboembolism among elderly patients treated with atypical and conventional antipsychotic agents. Arch Intern Med. 2005;165(22):2677–82.
152. Hagg S, Spigset O. Antipsychotic-induced venous thromboembolism: are view of the evidence. CNS Drugs. 2002;16(11):765–76.
153. Parker C, Coupland C, Hippisley-Cox J. Antipsychotic drugs and risk of venous thromboembolism: nested case-control study. BMJ. 2010;341: c4245.

154. Lewington R, Clarke N, Qizilbash R, Peto R, Collins C. Prospective Studies, Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002;360(9349):1903–13.
155. Gugger JJ. Antipsychotic pharmacotherapy and orthostatic hypotension: identification and management. CNS Drugs. 2011;25(8):659–71.
156. Bioque M, García-Portilla MP, García-Rizo C, Cabrera B, Lobo A, González-Pinto A, Díaz-Caneja CM, Corripio I, Vieta E, Castro-Fornieles J, Bobes J, Gutiérrez-Fraile M, Rodriguez-Jimenez R, Mezquida G, Llerena A, Saiz-Ruiz J, Bernardo M. Evolution of metabolic risk factors over a two-year period in a cohort of first episodes of psychosis. Schizophr Res. 2018;193:188–196.

PTSD and Cardiovascular Disease

20

A Bidirectional Relationship

Claudia Carmassi, Annalisa Cordone, Virginia Pedrinelli, and Liliana Dell'Osso

Contents

Abstract

In recent years, epidemiologic research has increasingly documented significant correlations between medical and psychiatric conditions. In most cases, this comorbidity has been shown to enhance morbidity, loss of quality of life, and mortality, implementing maladaptive behaviors and unhealthy lifestyles that inevitably affect physical health, but also to induce or worsen the course and outcomes of mental disorders. The relationship between cardiovascular diseases (CVDs) and post-traumatic stress disorder (PTSD) is one that gained growing interest in the last decades. In many instances, compared to other mental disorders, PTSD has the peculiarity of having a bidirectionality toward cardiovascular diseases: on one hand, exposure to traumatic events and consequent development of PTSD is now recognized to take an additional toll on physical health, contributing to increased risk for early incident CVDs; on the other hand, having CVDs can represent a severe stress for vulnerable individuals, leading to the onset of a PTSD symptomatology. From this perspective, the present chapter aims to reviewing and

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*,
https://doi.org/10.1007/978-3-030-28008-6_20

summarizing recent knowledge on the relationship among PTSD and CVDs, devoting special attention to factors that may contribute to bidirectionality toward both diseases.

Keywords

Post-traumatic Stress Disorder (PTSD) · Cardiovascular diseases · Acute coronary syndrome · Cardiovascular-disease-induced post-traumatic stress disorder (CDI-PTSD) · Risk factors · Maladaptive behaviors

Introduction

Post-traumatic Stress disorder (PTSD) typically arises following exposure, both direct and indirect, to a traumatic event, and is characterized by the onset and persistence of a series of clinical symptoms that can often be profoundly incapacitating and tendentially chronic [1]. There is evidence that PTSD is a chronic, drug-resistant disorder, associated with high suicidal risk (about 25% of patients have attempted suicide), substance abuse, and maladaptive behaviors, which can also be insidious beginning even after years of silence [2]. The lifetime prevalence of PTSD can vary considerably depending on the populations considered and the year in which the study was carried out, for the diagnostic criteria adopted. Nowadays, the prevalence in the general population corresponds to about 8%.

In recent years, several studies have examined and confirmed the strict relationship between mental disorders and physical health, with particular attention to the implications that the former have on the latter. Having a mental disorder often involves implementing maladaptive behaviors and unhealthy lifestyles that inevitably affect physical health, but also because mental disorders may determine biochemical and hormonal alterations in our body that can lead to various physical illnesses. In this case, PTSD has been closely correlated to various physical disorders, among which cardiovascular diseases stand out [3].

Compared to other mental disorders, PTSD has the particularity of having a bidirectionality toward cardiovascular diseases. While on one hand, exposure to traumatic events and consequent development of PTSD has a wide-ranging impact on quality of life across several domains, including occupational, family, and social and interpersonal functioning, it is now recognized to take an additional toll on physical health, contributing to increased risk for early incident cardiovascular disease (CVD) and cardiovascular (CV) mortality. On the other hand, having a cardiovascular disease can put the person under severe stress which can determine the onset of a PTSD symptomatology in predisposed individuals. In this respect, a long debate has been developed in the last decades whether which kind of physical illnesses may be defined as traumatic, focusing on the issues of severity, acuteness, chronicity, and potential lethality [4–7]. In the present chapter we'll examine most recent finding on both these aspects.

Cardiovascular Diseases (CVD) Induced by PTSD

Epidemiology

The impact of PTSD in terms of mental health and social functioning is well-recognized: it has been widely shown that it has, in itself, a wide-ranging impact on quality of life across several domains and is often associated with high suicidality and substance abuse. Nonetheless, the awareness of its impact on physical health is more recent [8]. In the last years, an increasing number of empirical researches have enlightened the existence of a relationship between PTSD and a wide range of diseases including cancer, metabolic diseases (such as diabetes mellitus), immunological disorders, hypertension, stroke, and heart diseases [9, 10]. In this sense, the PTSD-linked risk of unfavorable outcomes, in terms of physical health, is one of the reasons why PTSD diagnosis might be considered, according to some authors, as a life sentence [11].

With respect to the aforementioned pathological conditions, one of the strongest epidemiological associations has been shown to be that

between PTSD and cardiovascular or cardiometabolic diseases [12]. Not by chance, this association has been made object of growing interest [8]. More specifically, even if investigation focused on the association between PTSD and development and prognosis of CVD became widespread more than 20 years ago [13], the increase of attention paid to this aspect is related to two concurrent streams of studies: on one hand, the production of evidence about multiple effects of stress on CVD [14]; on the other, a copious production of studies relating CVD to other mental diseases, especially mood disorders [15]. This notwithstanding, PTSD is not yet listed among risk factors in the fields of endocrinological and cardiovascular medicine: as to the former field, for instance, PTSD is at most mentioned as a condition potentially leading to poor management of diabetes. This has quite a strong impact on clinical practice: individuals affected by PTSD are not provided with systematic surveillance in order to reduce this risk and are likely not to be promptly treated [11]. Accordingly, it is important to strengthen existing evidence and provide new data and more definitive answers to the issue of causality as to the association between PTSD and CVD [3].

It is well-known that PTSD is strongly associated with a large number of traditional CVD risk factors, such as maladaptive behaviors [5, 16, 17], high rate of smoking, alcohol abuse, nonadherence to therapy, hypertension, but also dyslipidemia, diabetes, endothelial dysfunction, and chronic low-grade inflammation [18–20]. However, it still stands in need of clarification, whether any association between PTSD and CVD exists independently from the aforementioned factors [8]. In this perspective, several studies have demonstrated that PTSD diagnosis is associated to a wide range of cardiovascular diseases including angina, heart failure, and coronary heart disease, even after controlling for traditional risk factors [2, 21, 22]. In order to better clarify this scenario, in what follows we shall briefly refer to some relevant epidemiological studies focusing on this issue.

The majority of epidemiological studies have focused on risk for acute cardiac events, and most of them have estimated the association in samples of male US veterans [14]. This is a group with unique epidemiological features, since the lifetime prevalence of PTSD is estimated to be 20% with an additional 10% with subthreshold PTSD symptoms [23]. Among the most representative studies belonging to this stream of research, Kubzansky [24] and Boscarino [25, 26] found a relative risk (RR) for early cardiovascular and all causes mortality ranging from 1,26 to 2,55. Consistently a recent large study on a sample of 138.000 veterans over 55 years old found a significant increase in cardiovascular risk among veterans with PTSD (3% of the sample); the estimated risk gap was of 49% after adjustment for confounding factors [27]. Even if civilian population has been historically less represented in PTSD literature, several studies have focused on nonmilitary samples, including both male and female subjects. These studies substantially confirm the aforementioned veterans studies. Edmonson et al. [8], in a meta-analysis including a cumulative sample of 402.000 participants, both civilians and veterans, and in the general population exposed to a wide range of traumatic experiences, enrolled from 1984 to 2000 with a follow-up ranging from 2,9 to 15 years, reported PTSD to be associated with a 53% increased risk for incident cardiac events or cardiac-specific mortality. Data were confirmed after adjustment for confounding factors, such as demographic, clinical, and psychosocial ones. When the authors considered also depression, as a confounding factor, this percentage decreased to 27%, which is still highly relevant.

Another important aspect to take into account is related to gender issues: while it is noteworthy that women have a higher risk in the prevalence of PTSD, female gender is less represented in the epidemiological studies with an overwhelming predominance of male samples (such as veterans). This aspect is even more significant if one considers that both PTSD and CVD show some gender-specific features in the clinical presentation. In this framework, a recent study conducted by Summer [28] is of particular importance. By taking into account a sample of 50.000 women, this study confirmed the epidemiological association

between PTSD and CVD on an exclusively female sample, namely, by reporting a HR 1,6 of developing CVD. This general point given, two further aspects are worth mentioning: on one hand, more than a half of this risk increase was not explained by other traditional risk factors or behavioral factors; on the other, women with a PTSD diagnosis showed higher rates of new-onset venous thromboembolism, a finding that was not explained by other risk factors or medical comorbidities.

A different approach consists in taking into account specific cases of traumatic history in patients developing CVD. In this respect, a study conducted by Sachs-Ericsson [29] analyzed a cohort of 17.000 adults from the general population highlighting a relationship between a history of childhood traumatic experience and ischemic heart disease. In this case, the RR resulted of 3,5, leaving aside traditional risk factors such as smoking, poor diet, and physical inactivity [29]. Even if this study did not consider whether involved subjects had developed PTSD, but only the presence of traumatic history in childhood, we can infer there could be a significant overlap between childhood abuse and the development of PTSD symptoms.

Even though evidence suggests PTSD has an independent detrimental effect on CV functioning, in order to estimate the physical health burden, it is important to take into account the association with pathological conditions tightly bound to CVD, namely, hypertension and atherosclerotic disease (ATS). The association between PTSD and hypertension may be an important mechanism by which PTSD could increase CVD risk. However, even if the existence of this association is widely acknowledged, its strength is still debated. The national comorbidity survey found a twofold greater prevalence of hypertension among people with PTSD if compared with healthy controls. This result confirms the findings of a large prospective study on a sample of 300.000 veterans: veterans with PTSD resulted to have a double prevalence of hypertension [18]. These results are further confirmed by another prospective study involving 200.000 veterans: the PTSD-associated HR was 1,3 for hypertension diagnosis or prescription for hypertension medicaments [3]. Although these studies have produced massive evidence, if considered altogether they do not seem to lead to definitive conclusions [14].

For what concerns the atherosclerotic disease, probably the main proxy of CVD disease, a study conducted on 600 veterans identified PTSD as an independent predictor of the presence and extension of atherosclerotic lesions and as a predictor of mortality to each increasing level of ATS burden [30]. In this framework, taking into account the overlap between the risk factors and pathogenesis of cardiovascular and cerebrovascular event, it is not surprising that PTSD seems to be associated to a higher risk of stroke. Indeed, a recent meta-analysis founded a PTSD-associated relative risk of stroke of 2,3 [8, 14], and according to a study based on the Danish National Patient Registry, this association was stronger in male population [31].

This survey should have shown that epidemiological data, gathered in a huge range of studies, clearly indicated a correlation between PTSD and CVD. However, demonstrating the casual nature of this link is much more controversial. Several factors contribute to this complexity. First of all, one could object that it is possible to hypothesize at least two forms of bidirectionality [11]: PTSD could lead to CVD and the development of a serious disease could worsen PTSD symptoms. In other words, these pathological conditions may mutually influence each other, no causal relationship being at stake in this case. Another issue concerns the role of confounding factors, such as maladaptive behaviors [3] (e.g., smoking, alcohol and drug abuse, poor compliance to therapy) and psychiatric comorbidity [3], that are highly prevalent among people suffering from PTSD. Furthermore, the majority of the aforementioned epidemiological studies have some methodological shortcomings: for instance, they tend to measure PTSD and CVD symptoms only once at the beginning of the study, but then typically rely on lengthy follow-up periods during which the confounding factors may vary over time [11, 14]. However, other important studies shed light on this issue approaching the open

question about causality from different perspectives. Some significant suggestions came from the study of Vaccarino and colleagues, who carefully examined a sample of twins from the Vietnam Era Twin Registry in order to estimate the role of common genetic background and familiar confounders in determining PTSD and CVD risk. The results of this study have shown that the association between PTSD and CVD was not significantly confounded by genetic or other environmental factors suggesting that PTSD is a causal risk factor for CVD. In addition, the recent studies of Koenen [11], Dennis [32], and Scherrer [33] have further strengthened the case in favor of the existence of a causal relation between PTSD and CVD. In the first [11], the authors inquired the development of changing in the CVD biomarkers in women with new-onset PTSD without previous CVD. In the study of Dennis and colleagues, the focus was on the extent to which modifications in PTSD symptoms affect autonomic dysregulation, inflammation, and endothelial dysfunction [32]. Finally, Scherrer and colleagues have been examining if PTSD treatment can reduce CVD risk [33].

In light of these data, there is enough evidence to suggest the existence of a causal relationship between PTSD and CVD: available data clearly emphasize an epidemiological association between PTSD and risk of CVD and suggest that PTSD can be considered, in a multifactorial pathogenetic model, an independent risk factor. To put it with Boscarino's words "The question now is not if there is a link between PTSD and CVD, but why this association exists and can this outcome be prevented?" [34]. In this regard, more studies are needed from non-US population and nonveterans, and research should provide more precise estimates by rigorously adjusting for depression and lifestyles as well as established CVD risk factors.

Risk Factors

The pathogenetic model which best accounts for the association that has been detected between PTSD and the aforementioned pathological conditions and, more specifically, CVD is multifactorial: both biological and behavioral factors contribute, to different extents, in determining a higher risk of CVD in PTSD patients [11]. It is currently acknowledged that people with PTSD are prone to develop a pattern of maladaptive behaviors, such as smoking, substance and alcohol abuse, and poor adherence to medical treatment. This clearly constitutes in itself a source of additional risk in terms of general health outcome. However, as emerged from the previously quoted epidemiological studies, the contribution of PTSD to the increased risk of CVD and related conditions, such as cerebrovascular disease, hypertension, atherosclerotic disease, and venous thromboembolism, seems to be independent from these factors. Accordingly, a growing amount of literature has been analyzing the physiopathological pathways underlying this association. In what follows we will provide a discussion of the principal mechanisms which are potentially involved in determining this association, such as autonomic and neuroendocrinological dysregulation, pro-phlogistic diathesis, genetic factors, and behavioral factors. Each of these pathways may influence the cardiovascular function; it follows that related pathological modifications – being acute, chronic, or both – can contribute to CVD risk, and this can happen either directly or through an increase of the risk to develop strictly related pathological conditions, such as hypertension [35].

Physiopathological Factors

The majority of theories formulated with the aim of detecting a causal path leading from PTSD to physical diseases have been focused on autonomic imbalance and on dysregulation in the hypothalamus-pituitary-adrenal axis (HPA) [3]. An ongoing dysregulation in these pathways may have pleiotropic effects, for instance, on blood pressure regulation and on inflammatory response, and can contribute to a cardiovascular system damage [36–38]. This depends on the fact that, in the immediate aftermath of a stressful or traumatic event, there is a sudden, massive activation of the autonomic system and of the HPA axis. This activation

represents the physiological substrate of "flight or fight" response, an adaptive reaction that leads to an increase in catecholamines and cortisol levels. This reaction gives rise to a complex series of behavioral and physiologic modifications, aimed to deal with the newly occurred condition, and usually extinguishes itself in a short timespan thanks to the activation of negative feedback homeostatic mechanisms [39]. By contrast, among people who develop PTSD, several abnormalities have been documented, namely, an abnormal persistence of psychological, behavioral, and physiological stress response [38] and neuroendocrinological and autonomic alterations. More specifically, among PTSD sufferers, an imbalance of autonomic activity has been detected, leading to a sympathetic predominance with pervasive effects on cardiovascular functioning. It is noteworthy that this response, which is detectable by measuring urinary catecholamine level, is combined with lower cortisol levels and daily cortisol output [40, 41]. All this leads to outline a complex scenario, in which two particular conditions occur: on one hand, there is a lowering of the threshold for a sympathetic response, meaning that a lot of stimuli potentially activate a flight or fight response with a massive catecholamines release; on the other hand, the baseline functioning of the HPA axis is impaired with chronically lower cortisol levels [42, 43].

In consequence to the autonomic imbalance, patients with PTSD show an exaggerated and poorly modulated sympathetic response with higher catecholamine levels. At the same time, there is a downregulation of parasympathetic activity with a decreased vagal control of hemodynamic homeostasis and of inflammatory response. In this respect, among PTSD sufferers a lower heart rate variability (HRV) has been detected: this is a reliable indicator of parasympathetic nervous system activity, along with subtle baroreflex abnormalities [19, 44–46]. These results outlined a lack of autonomic modulation, with a consequent autonomic inflexibility, which in turn constitutes an acknowledged risk factor for unfavorable CV outcomes [47, 48]. These abnormalities showed a strong association with current PTSD, independently of other genetic, familial, and sociodemographic factors. Furthermore, there was a linear relationship between PTSD symptom burden and decrease in HRV, and this alteration resulted to be at least partially reversible [44].

Among the several physiopathological consequences of the aforementioned imbalance, there is also a sustained higher heart rate, with frequent peaks after exposure to reminders of the traumatic experiences [49]. A chronically high heart rate is an acknowledged major risk factor for acute cardiac events and mortality in CVD patients [48]. Moreover, in the short term, the iterated heart-rate peaks cause sudden increase of the shear stress on the endothelium, potentially leading to an acute injuring of atheromatous plaque, and this in turn triggers an atherothrombotic mechanism. In a longer perspective, a sympathetic tone higher than normal is linked to a sustained increase in vascular resistance: in this way, by eliciting iterated autonomic response, PTSD can exert a deep influence on arterial blood pressure [8, 35, 50].

For what concerns the HPA, during the last three decades, a growing literature has been enlightening to what extent there is an impairment of this axis in stress-related psychiatric disorder, leading to an insufficient glucocorticoid signaling with a lower daily cortisol output [37, 40, 51]. This is a somewhat counterintuitive finding, since it is widely acknowledged that the HPA axis represents one of the principal stress response mechanisms. Several hypotheses have been formulated in order to explain this evidence, mainly about the role of an increased negative feedback sensitivity [52] that could represent the mediator between the initial stress-related hypercortisolism and the subsequent development of hypocortisolism [53]. Noteworthy, peripheral tissues show a heterogeneous pattern of glucocorticoid responsiveness with an overall hyperreactivity of some target tissues such as adrenal gland and hypothalamus [37]. This finding has several pathophysiological implications. An absolute or relative hypocortisolism, in fact, may play a permissive role for the autonomic imbalance, reducing the capacity to modulate the sympathetic response [37] or constitute a contributory cause to the pro-

phlogistic diathesis commonly associated to stress-related disorder [54]. Moreover, a recent study pointed out the existence of an association between HPA hypofunctioning and metabolic and cardiovascular risk factors. However, it is still unclear whether it is rather the case that this association is ascribed to the previous state of hypercortisolism that can be detected in the aftermath of traumatic event and may persist for a variable timespan [55].

Several studies have provided solid grounds to the hypothesis of the existence of an inflammatory diathesis among PTSD sufferers. A large number of studies, whose results have been gathered in a recent meta-analysis [56], have pointed out the existence of an association between PTSD symptoms and blood level of inflammatory biomarkers, such as IL-1, IL-6, and IFN [56–58]. Moreover, it has been found that blood level of phlogistic markers show a linear association with PTSD symptom burden [20]. This is a noteworthy point, since the phlogistic state can be considered one of the main determiners of the association between PTSD and CVD, since it may lead to endothelial dysfunction, hypertension, earlier development, and accelerated progression of atherosclerosis disease [14]. Indeed, one of the mechanisms through which inflammation plays a pathogenetic role in mediating the detrimental effects of PTSD on CV functioning is its contribution to atherosclerosis, which is the main proxy of CVD. It is widely recognized that atherosclerotic disease is sustained by an inflammatory process from the initiation, through the progression of the atheroma, until the acute plaque events that constitute the substrate of catastrophic cardiovascular events, such as acute myocardial infarction (AMI) [20, 59]. Both autonomic and neuroendocrine mechanisms, already discussed in the previous paragraph, are involved in determining this inflammatory state. On one hand, chronically elevated catecholamine levels act on B-adrenergic receptors of immune cells and induce transcription of nuclear factor kappa B (NFkB); NFkB exerts a critical control on synthesis of a large number of cytokines; consequently an increase in NFkB expression leads to the activation of the inflammatory response. High levels of NFkB were found among a sample of women with PTSD who had a history of childhood abuse [60]. In this framework, NFkB can be considered an important mediator for the translation of social stress into inflammation [61]. It is worth mentioning that NFkB transcription is regulated both by glucocorticoid hormones and by catecholamines with an effect respectively inhibiting and inducing. Indeed, NFkB DNA expression in immune cells shows an inverse correlation with glucocorticoid sensitivity of GC. In this finding it is not unexpected considering that glucocorticoid signaling exerts a pervasive modulation of the inflammatory and immune response. Glucocorticoid generally restricts the inflammatory process by inhibiting immune cell proliferation, regulating pro-inflammatory cytokine production such as tumor necrosis factors (TNF-α) or interleukin 6 (IL-6), and stimulating apoptosis [20, 62, 63].

The endothelium is the innermost stratum of vascular wall and is constituted by a single layer of cells. It has a critical role in determining the vascular permeability and mediates the vasomotor response to hemodynamic factors and circulating mediators even by synthesizing in its turn a wide series of vasoactive substances. In addition, it has a role also in the regulation of coagulation cascade and platelet activation and, under normal circumstances, exerts an anti-aggregatory effect. Overall, the endothelium plays a crucial role in keeping vascular homeostasis: endothelial dysfunction has been proved to exert a systemic detrimental effect on CV function, it is detectable in early stages of CVD, and it is nowadays recognized as an independent and highly predictive index of CVD [64, 65]. Moreover, endothelial dysfunction, just as an abnormal endothelial response to vasoactive mediators, has been detected during and after a period of stress [19, 66]. Consequently, the endothelial function has been object of growing interest in researches focused on the pathways binding PTSD and CVD risk. As previously demonstrated by studies conducted on samples of people undergoing stressful circumstances, experiencing of anger and negative moods is associated to an acute worsening of endothelial function that lasts 1 h or more. If we consider that re-experience of traumatic events and hyperarousal

constitute two of the main features of PTSD, this finding can be easily generalized to PTSD sufferers. The result of a study conducted by von Kanel adds evidence to this claim: the author measured three markers of endothelial function, namely, von Willebrand factors (vWF), soluble tissue factor (sTF), and soluble intercellular adhesion molecule-1 (sICAM-1), and found a correlation between sTF and vWF and PTSD symptoms that was only partly affected by psychological distress. It is worth mentioning that this association was also observed among people whose symptoms did not reach the threshold for a categorical PTSD diagnosis; this finding suggests the existence of a continued relationship between the severity of PTSD and the endothelial impairment [20]. Both autonomic imbalance and chronic low-grade inflammation may be implicated in determining endothelial damage. First, the chronic exposition to high blood level of norepinephrine and epinephrine causes vasoconstriction both directly, acting on beta-1 and alpha-1 adrenergic receptors, and indirectly, through the mobilization of endothelin-1 (ET-1) from plaque resident macrophages. In this framework, norepinephrine and ET-1, which are synergistically involved in stress-related vasoconstriction, may play a key role in emotion-triggered cardiac events. Moreover the iterated catecholaminergic peaks induce a rapid release of vWF from endothelial storage sites via stimulation of endothelial B2 adrenergic receptor causing an imbalance in coagulation homeostasis [3, 20]. In addition, the inflammatory state described above constitutes a well-known endothelial injuring in as much as it causes an increase in oxidative stress and a hypercoagulable state.

Several studies have demonstrated the existence of an association between PTSD and hypertension. This evidence is of particular significance, in as much as hypertension is a traditional risk factor for CVD and cerebrovascular disease. Among these researches, it is worth mentioning a recent prospective study conducted by Burg on a sample of 195,000 veterans [35] of both genders, in which a PTSD diagnosis was shown to be associated with a 25–46% increased risk to develop hypertension. Moreover, the hypertension occurred much earlier than in the general population, and this age gap was wider among female patients [35]. This finding confirms what was previously reported in other studies conducted on veterans: the National Comorbidity Study [67, 68] found a twofold greater prevalence of hypertension among people with PTSD; similar data had come from a large study conducted on a sample of over 300,000 subjects [18], while two prospective studies reported an increased risk (33–38%) of receiving a subsequent hypertension diagnosis [69, 70]. The PTSD-related physiopathological alterations described above account for this increased risk in as much as the autonomic, neuroendocrinological, and inflammatory correlates of PTSD act on arterial capacity, peripheral vascular resistances, endothelial functioning, and heart rate, which are altogether among the main determinants of arterial blood pressure [14].

Behavioral and Environmental Factors

Among diagnostic criteria for PTSD, the DSM-5 recently introduced the emergence of reckless or self-destructive behavior, such as dangerous driving, excessive alcohol or drug abuse, or self-injurious or suicidal behavior (criterion E2), in the context of marked alterations in arousal and reactivity associated with the traumatic event beginning or worsening after the traumatic event (criterion E) [1]. This is consistent with several studies, conducted on heterogeneous epidemiological samples, showing a significant association between PTSD diagnosis and a wide range of maladaptive behaviors, that is, volitional behavior whose outcome is uncertain and which negatively affects everyday life functioning. In a wider perspective, it is reasonable to hypothesize the existence of higher rates of CVD health risk behavior among individual with PTSD.

Moreover, the avoidance symptoms of PTSD, mentioned in the criterion C, may lead to social isolation. The consequent poor social support constitutes by itself a recognized psychosocial risk factor for adverse medical outcome, inasmuch as it further compromises the chance of receiving a prompt diagnosis and an optimal treatment [71, 72]. The same studies have also been focusing on the prevalence of unhealthy behavior in PTSD sufferers with the aim of

quantifying its impact on the etiopathogenesis of CVD: although behavior-related factors rarely full attenuate the association between PTSD and CVD and related condition [11], on the other hand, it is out of doubt that they exert a detrimental effect on cardiovascular function and, more generally, negatively affects the physical health.

A list of maladaptive behaviors, albeit not complete, includes smoking, substance abuse, hazardous drinking, dangerous driving, sexual unprotected intercourses, poor medical therapy adherence, unhealthy eating behaviors, and physical inactivity [7, 73–76]. Interestingly, the results of a large longitudinal study conducted by Breslau highlights that the association between heavy alcohol use, substance abuse, and traumatic experiences was mediated by PTSD development and was not ascribable to the trauma in itself. Another important aspect to be taken in account is the effect of gender and sociodemographic factors: young males with lower instruction were more prone to develop a maladaptive behavioral pattern [6, 7, 77]. In addition, among people with PTSD, there is a high prevalence of sleep disturbance [78], a recent meta-analysis enlighted an association between short duration of sleep and incidence of CVD and stroke, and more studies are warranted in order to explore this relationship [79].

Cardiovascular Disease-Induced PTSD (CDI-PTSD)

Epidemiology

The number of adults with diagnosed CVD in the USA alone has been recently estimated to be as high as about 121.5 million [80] and 83.5 million in Europe [81]: among these, ischemic heart disease accounted for about 50% of these cases. Despite this, in recent decades, survival rates for cardiac events and, especially, for acute coronary syndrome [ACS, including myocardial infarction (MI) divided into subgroups of ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (N-STEMI), and unstable angina (UA)] have firmly increased [82, 83]: thus, quality of life after ACS has become vitally important. Even though the therapeutic progresses brought by new interventions, technologies, and treatment guideline have given an important survival benefit, the mentioned progresses may also have increased the number of patients at potential risk for developing psychiatric morbidity.

Psychiatric disorders, such as anxiety and depression, have been widely described in patients suffering from CVD in the last years with increasing attention, being devoted to the high prevalence rates detectable in this population. In patients suffering from coronary artery disease or heart failure, an overall prevalence of depressive disorder has been estimated to be around 20%: three times greater than in general population [84]. Literature reported prevalence rates of any anxiety disorders in CVD populations of about 16%, with prevalence rates of general anxiety disorder and panic disorder being much higher than in the general population and with comorbidity between depressive and anxiety disorders being around 50% of the CVD cases [85]. In this context, in recent years, researchers strongly focused on the importance of evaluating PTSD emerging in the aftermath of cardiovascular events (CDI-PTSD).

Among life-threatening diseases, CVDs seem to include potentially traumatizing characteristics, such as the concrete danger of death; the drasticity of the event, associated with the sense of loss of control; and helplessness experienced by the patient [86]. In addition to this, possible invasive treatments, including catheterization [percutaneous transluminal angioplasty or percutaneous coronary intervention (PCI)], heart surgery [coronary artery bypass graft (CABG)], implantation of pacemaker or implantable cardioverter-defibrillator (ICD), stress testings that the patient may undergo because of the cardiovascular event, as well as the side effects of pharmacological treatments, can work as traumatizing factors promoting the development of PTSD [87].

Since PTSD's first appearing as a diagnosis in the APA's third edition of its *Diagnostic and Statistical Manual of Mental Disorders* [9, 88], nosographic changes in the DSM later editions specifically involved PTSD diagnostic criteria,

generating as much controversy in its clinical boundaries, as well as the definition of an event as being traumatic. In the initial DSM-III formulation, in fact, a traumatic event was defined as a catastrophic stressor, an experience outside the range of usual human experience. In this context, events such as serious illnesses were not included among trauma, basing on the assumption that most individuals have ability to face these events that were assumed as ordinary stressors and that only events that can overwhelm subjects' adaptive capacities can be considered as traumatic. However increasing data have suggested PTSD in patients affected by cardiovascular diseases [84, 89, 90], leading to the current definition in the DSM-5 [1], where life-threatening illnesses and debilitating medical conditions, while being considered as not necessarily causal events of PTSD, are described as traumatic events that can elicit it.

For its hallmarks, PTSD due to medical conditions (including PTSD consequent to cardiovascular disease such as heart attack) has unique characteristics because of the trauma's nature and effects. Whence, this argument has been deepened in literature, and a number of researchers have studied how it can diverge from the traditional model of PTSD. Edmondson, in one study, highlighted the differences from PTSD due to other traumatic events (for instance, the classical example of PTSD in war veterans), including the source of the trigger event (external vs somatic), the timing and the probability of recurrence of the threatening event (past versus present/future), and the different symptoms and course of post-traumatic symptoms, proposing an enduring somatic threat to the approach [91]. In PTSD triggered by external events, such as combat or sexual assault, events are in fact circumscribed: even if the probability of re-experiencing similar violent situations exists, subjects rationally know that there are safe places in the world wherein the danger is unlikely to exist. Otherwise, life-threatening medical conditions, such as CVD, represent long term risk conditions that are intrinsically linked to the subject. Moreover, this kind of traumatic experiences may generate expectation of future unpredictable recurrences and further negative consequences; they also require medical surveillance on regular basis and compliance to therapeutic regimes, and make the patient feel unarmed and unsafe in any place [92, 93]. It's well-known that the great frequency of recurrence of these chronic diseases requests strict adherence to therapeutic regimens [94, 95], lifestyle changes, monitoring of physiological markers, and working as a continuous cue of ongoing threat and has been associated with poor psychological adjustment and distress [96]. Furthermore, cardiac acute events are often perceived with intense fear [97], loss of control [98], and helplessness [99] which are themselves risk factors for PTSD development.

Some researches highlighted how PTSD characteristics can also vary in the way symptomatological clusters of PTSD are presented in the aftermath of CVDs. For example, re-experiencing symptoms of PTSD due to a medical illness (e.g., recalling the cardiac event or defibrillator shocks, dreams of event recurrence, flashbacks of surgery, or generally medical interventions) are caused by recurrent fear rather than to a single event happened in the past, as much as avoidance (e.g., avoid reminders of the cardiac event such as the location of the event, the hospital, medical therapies, situations in which heart rate increases such as sexual activity), negative alterations in cognition or mood, and hyperarousal symptoms (e.g., worrying with heart rate or chest pain; insomnia) can have different behavioral and psychological consequences [100].

Interestingly, for what concerns re-experiencing symptoms, for example, some studies found that intrusive thoughts are linked to endothelial dysfunction [19], higher blood pressure [101], higher blood levels of contro-insular hormones (like cortisol or catecholamines) [102], and higher levels of C-reactive protein levels [103], highlighting the connection between psychological answers and autonomic nervous system, which is an important cardiovascular risk factor accelerating progression of heart disease and increasing the risk of acute events, which is more significant for patients surviving a cardiac attack than for those suffering other external events without an underlying cardiovascular risk.

In support of this, a study conducted on ACS patients found a threefold increased risk for recurrence or mortality due to a cardiac event, in the 42 months after the index event, in those subjects with higher scores of re-experiencing symptoms [104].

In relation to avoidance symptom as well, there is now considerable evidence for the association of PTSD with avoidance of medical treatments in ACS [105, 106], suggesting that nonadherence to secondary prevention can represent a reminder of the index event, with consequences on global survival rate of these patients.

Interestingly, in the trauma and loss spectrum questionnaire [107], developed in the framework of the Spectrum Project acknowledging a multidimensional spectrum approach to PTSD, one of the items encoded among maladaptive behaviors is: "Since the loss or event, did you ever stop taking prescribed medications or fail to follow-up with medical recommendations, such as appointments, diagnostic tests, or a diet?". A number of studies conducted by some of us showed the relevance of this behavior in traumatized subjects shedding light on the possible medical implications of treatment nonadherence as post-traumatic stress spectrum symptomatology, particularly among women [5, 6].

Hyperarousal symptoms, as well, represent an interesting indicator in cardiac-induced and generally in medically induced PTSD, because of the two-way connection between anxiety reactions and sympathetic answers and consequent cardiovascular activity: any fluctuation of cardiovascular indicators of threat (heart rate, blood pressure) in a hypervigilant heart attack survivor can itself increase anxiety and consequently autonomic and cardiovascular activity. Hyperarousal symptoms are furthermore associated with sleep disruption [79] as well as with inflammatory biomarker increase in cardiac event survivors [106, 108], probably due to autonomic imbalance with sympathetic prevalence of function, both of them representing themselves a cardiovascular risk and predictors of adverse outcome in survivors of acute cardiovascular events.

Among cardiovascular events, great focus of studies has been devoted to ACS, because of its high incidence in the general population: so it has been widely used as a paradigm to analyze cardiac-induced PTSD (CDI-PTSD). Fewer data have been reported on other cardiac conditions, such as heart surgery or ICD.

PTSD consequent to ACS (ACS-PTSD) prevalence estimates across studies widely varied from 0% to 32%, due to the different methodologies, in particular to the variability of the instruments adopted to assess post-traumatic stress symptoms: prevalence estimates derived by screening questionnaires, in fact, result to be higher than those derived by the use of clinical diagnostic interviews, with 16% and 4% prevalence rates, respectively.

Vilchinsky and colleagues [109], in a most recent systematic review, analyzed the PTSD prevalence rates across studies assessing patients at different timeframes from the cardiovascular event, ranging from the hospitalization to as many about 10 years later. Interestingly, only few studies have taken into account post-traumatic symptoms due to a coronary event during hospitalization or within 2 weeks as a consequence of ACS, in order to evaluate the prevalence of acute stress disorder with a variable prevalence ranging from 0% to 26% [110–114]. Evidence produced from studies that assessed the situation a month after the index event were influenced by diagnostic tools used: Roberge and colleagues reported CDI-PTSD rates of 4,1% by the means of a clinical interview, although other authors found higher rates, ranging about 11–16% using self-report questionnaires [115].

In a range of time going from 3 to 18 months, evidence suggested ACS-PTSD rates ranging from 3% to 21%, with differences that have may also been related to the variation of the diagnostic criteria suggested by the DSM for the PTSD diagnosis [105, 110, 116, 117] and with higher rates being reported by self-report measures with respect to the SCID. One study [89], using the structured clinical interview for the PTSD diagnosis 2 years post-MI, found that none of the subjects observed satisfied the criteria; higher prevalence was estimated around 13% in studies with wider samples of MI patients 3 years to

as many as 8 years after the event [118, 119] through self-report measures. These rates are anyway higher than those found in other studies reporting the prevalence rates in the general population [120–123].

To the best of our knowledge, the only meta--analysis available [124] including 24 observational cross-sectional studies reported an aggregated prevalence estimates of ACS-induced PTSD of 12%. Almost all the studies assessed PTSD within 2 years after the index medical event, suggesting timing from the index cardiovascular event to be unrelated to PTSD prevalence rates. Interestingly, most recent publications reported lower PTSD prevalence estimates, highlighting that less severe diseases more recently included to the definition of ACS (i.e., N-STEMI or UA) resulted to be unrelated to prevalence rates, suggesting that the advances achieved over the years in the medical treatment of MI may represent an effective instrument to reduce its traumatic impact, bettering post ACS psychological outcomes.

Little is known about the burden of PTSD caused by other cardiovascular diseases besides coronary artery disease. In a systematic review, Vilchinsky and colleagues [109] reported prevalence rates ranging from 15% to 38% among patient survivors of sudden cardiac arrest [125–127], with variability also being related to the assessment instruments adopted. In patients with an ICD was reported a prevalence of CDI- PTSD ranging from 7.6% to 30% [128–131]. The peculiarity inherent in this case is that ICD works in restoring physiological heart function with an electric shock when malignant arrhythmias occur, sometimes with daily multiple device firing ("electric storm"). While the aforementioned device is a lifesaver, it may be a continuous reminder of heart chronic disease and its life threat [132], not to mention the shock which represents a painful experience linked with helplessness and fright. For all the above reasons, it's likely that ICD implantation in the future will be found to fit neatly into CDI-PTSD risk factors' list.

In cases where the cardiac pathology requires a surgical intervention, such as CABG and in the most extreme cases heart transplantation, some authors investigated the presence of PTSD in these populations, finding again prevalence rate variations based on the evaluation times, ranging from 7% prior elective surgery [133, 134] to 12.7% after emergency CABG [135]. Interestingly, in case of heart transplant, higher PTSD prevalence rates have been reported, with a particular increasing trend across times with rates going from 10.8% to 19.3% 12 months after transplantation and up to 22% after 36 months with the most elevated rates among all studies [136, 137].

Despite a growing researchers' interest for PTSD induced by cardiovascular events in the last few years, more than half studies have been conducted so far on patients following a MI, with less attention being paid on other conditions (e.g., medical procedures consequent to cardiac illness): given the paucity of results, evidence can't be yet considered conclusive, and more research is needed.

Risk Factors

A growing body of literature has investigated the risk factors related to PTSD and to its symptoms' severity after ACS event. For what concerns demographic factors, many were found to be associated with CDI-PTSD related to ACS, even if there's no univocal consensus about this. In fact, if younger age was shown to be related to greater PTSD prevalence rates in some studies, suggesting that the threatening of the event could be more serious because of the little prior experience of these patients with medical illnesses [118, 124], in others it was not [138]. The same disagreement concerned gender: some authors detected females to be more prone to develop PTSD than male patients, while others did not find any gender differences [139]. Other demographic factors found to be related to PTSD onset, including ethnic minority and low socioeconomic status [140, 141]. Interestingly, all the aforementioned factors are those predicting myocardial ischemia in patients with known CVD [142]. Interestingly, no study considered

the clinical severity of the cardiac event predictive of PTSD's development, but many traumatic factors have been suggested by literature as risk factors for diagnosis and prognosis of PTSD after the cardiac event, like helplessness and chest pain during the event [143], dissociation during acute stress disorder [144], history of psychiatric disorder and depression symptoms during hospitalization [125], as well as prior traumatization [86], psychological traits as type of personality (such as distressed type D personality) [145], alexithymia [146] or neuroticism [99], maladaptive coping [147], and negative cognitive appraisals [149].

For what concerns CDI-PTSD related to other conditions besides ACS, significant correlations emerged to be related to preoccupation with somatic symptoms and impaired quality of life [109]. In the case of ICD, risk factors were associated with emotional distress before the device implantation and actual firing of the device [131, 149], while the ones connected with the CABG were represented by disease severity, longer operation, use of more complex surgical procedures instead of less invasive procedures, as well as postoperative delirium [90, 151, 152]. Finally, Dew and colleagues in 2001 [137], detecting anxiety disorders (among which PTSD) onset after heart transplantation, identified psychiatric history, female sex, longer post-transplant hospitalization, and low support from family members as risk factors.

Clinical Characteristics

Authors have explored the course of CDI-PTSD, despite there is currently some controversy about its chronicity. For what concerns ACS related PTSD, Ginzburg and colleagues, in an 8-year follow-up, revealed a significant decrease of post-traumatic stress symptoms, with most patients reporting PTSD at 7 months after being recovered for ACS acute coronary syndrome, except for a small percentage (6% patients, the so-called chronic group), showing enduring PTSD symptoms up to 8 years after the index event [153]. On a shorter time-gap, PTSD criteria were met in 12,2% and 12,8% of patients at a follow up of 12 and 36 months from the first ACS event respectively, highlighting, however, the fact that some patients resulting positive at 12 months resulted no longer affected at 36 months and others, conversely, resulted positive at 36 months having been negative at 12 months. Other factors, such as depressed mood during admission and recurrent cardiac symptoms, were independent predictors of post-traumatic symptoms, indicating emotional responses as predictors of longer-term post-traumatic stress and the importance of the patients' identification to improve their quality of life. Accordingly, Abbas and colleagues demonstrated that post-traumatic stress symptoms persisted in two-thirds of patients 2 years after the cardiac event, although PTSD global symptoms waned over time and in conjunction with a longer follow-up (leading advocacy for the prolongation of the clinical investigation). Furthermore, among all the symptomatic clusters, avoidance showed the lowest to decline [154].

For what concerns PTSD due to cardiac arrest, besides the scant data available, there is some controversy in relation to its course. Versteeg et al. [149] showed that 60% of the patients affected by cardiac-induced PTSD after 3 months from the implantation of the ICD still reported PTSD after 6 months. von Kanel et al. [120], on the other hand, following a group of ICD patients for 5 years, found that only 19% of patients having PTSD at baseline resulted in having PTSD at the follow-up test, but 18% of patients not affected by cardiac-induced PTSD at the baseline developed a PTSD afterward [150].

Only few studies have assessed the prevalence rate of CDI-induced PTSD due to CABG, and these produced heterogeneous results: some found a reduction of prevalence at the 1-year follow-up [141] (5,8%), while others detected a higher prevalence in the same time lapse (19,7%) [155].

The same can be said about heart transplantation-induced PTSD: in fact, prevalence outcomes derived from post-transplantation 1 to 5 years of follow-up cover a wide variety (ranging from 9,8% to 13%) [156, 157].

The increasing attention toward post-traumatic stress symptoms following major cardiovascular events has led to investigate the consequences and prognostic aspects of CDI-PTSD, as well as correlated aspects in mortality and morbidity even for other cardiovascular events. Various authors have focused on these aspects, and, although there is no consensus, the evidence of PTSD-related symptoms as negative prognostic factors in the population of patients with cardiovascular disease is quite clear. In 1979, Horowitz et al. found a positive correlation between scores obtained in the size of the intrusive symptoms of the IES scale [158] and the risk of developing major adverse cardiac events, as well as overall mortality [159]. Similarly, Edmondson et al. in 2011 confirmed the same concept, finding that severity intrusive symptoms measured 1 month after the cardiac event could predict the relapse of the major cardiac events and global mortality [104]. More recently, another study has shown the existence of dissociative symptoms increases the 15-year overall mortality rate among patients with myocardial infarction [153]. von Kanel and his colleagues highlighted that, for each 10-point increase of the post-traumatic stress symptoms' score evaluated at 3 months from an acute coronary event, the probability of a new hospitalization in relation to the re-occurrence of the previous cardiovascular pathology was significantly higher (HR = 1,42) [160, 161] .

Similarly, moving from the rising hypothesis of a correlation between PTSD and uncomplied therapy, Shemesh and colleagues have found the association between prevalence rates of above-threshold symptoms of PTSD in patients evaluated 6 months after the acute coronary event with an incidence of heart attack recurrence being almost double compared to patients who did not reach this threshold, as well as an association with nonadherence to medications [148].

In their meta-analysis, Edmondson and colleagues detected an almost doubled risk (RR=2) of unfavorable outcomes such as recurrence of cardiovascular events and mortality in this patient sample [124].

However, the evidence of a worse prognosis has not yet found great attention in literature as to univocally explain its reasons. Shortly mentioning the basis of pathophysiologic mechanisms linking PTSD to recurrence of cardiovascular events and consequent increase of mortality risk, although there is need for more data and research, there is considerable evidence about the link between PTSD, due to several stressful stimuli, and consequent occurrence of cardiovascular events. PTSD, indeed, is associated with an excess of inflammation and immune system dysfunction. This imbalance in favor of pro-inflammatory factors seems to be related to a dysfunction of the hypothalamic-pituitary-adrenal axis system as well as epigenetic factors leading T cells to a specific differentiation [162]. The increase of inflammatory factors, common to both diseases, including specific cytokines, such as PCR, TNF, and IL-1 [19], accelerates sufferance processes that contribute to an increased risk of cardiovascular disease. It is likely that the addictive effect of two disorders determines worsening of the underlying disease outcome. Chronic medical conditions such as PTSD can also cause activation of renin-angiotensin system resulting in vasoconstriction, inflammation, and fibrosis. The final effect can be explained in high blood pressure, increased sympathetic activity, and pro-inflammatory and hypertrophic effects [163, 164]. Some of these mechanisms have been highlighted and referred to as "the allostatic load model" [49]. Such model hypothesizes the presence of an imbalance in the physiological systems implied in the response, which allows this reaction in relation to a varied range of stress stimuli: PTSD as a chronic pathology linked to stress implies a request for responses to the body which requires the implementation of new steady states [164]: as all compensation mechanisms, this becomes an overload factor of allostatic systems that can result in pathophysiological consequences that contribute to increasing the risk of medical illness and negative consequences of cardiovascular outcomes].

It is important to mention that some behavioral mechanisms related to PTSD may represent further cardiovascular risk factors. Authors have supposed the basis of prognosis to be the poor adherence to therapies, a trait frequently found in

patients with PTSD who survived cardiovascular events, also considering the unique characteristics of the trauma induced by life-threatening medical events previously discussed, also highlighting how treatment can be a reminder of the traumatic medical event [165–167]. Unhealthy lifestyles, among which are substance use, decreased physical activity, and sleep disturbances, may represent negative prognostic factors contributing to enhanced cardiovascular risk. There is evidence that substance use disorders represent a frequent comorbid diagnosis in the context of patients with PTSD [73, 86], and this is partly linked to the tendency to self-medication of both anxiety and hyperarousal symptoms. In addition, some authors have evaluated the association between a history of exposure to traumatic events and increased risk of development of dependence and the presence of higher prevalence rates of nicotine smoking and nicotine dependence, resulting in a greater risk of initiation of tobacco use and associated lower quit and remission rates [17, 168]. It is noteworthy that some of the aforementioned behaviors are currently included in the DSM-5 among PTSD symptomatological criteria, constituing the socalled maldaptative behaviors. On the other hand, these behaviors are widely aknowledged as risk factors for the recurrence of cardiac illnesses behavior. A recent meta-analysis has highlighted and confirmed an association between PTSD decreased physical activity and incorrect alimentary habits which, in PTSD patients, appear to be related to the development of obesity and related metabolic consequences [169]. Finally, some studies found that sleep disturbances, common in patients with PTSD (i.e., nightmares, difficulties in falling/staying asleep), play a role as risk factors for development and flare of the cardiovascular disease [69, 170].

These behavioral factors, on the whole, are an example of the need to acquire greater awareness in order to preside over interventions aimed at their primary and secondary prevention, globally reducing the risk of unfavorable outcomes in patients who develop post-traumatic symptoms following cardiovascular events and, therefore, by definition vulnerable themselves.

Conclusions

The relationships between PTSD and CVDs appear to be complex and bidirectional. PTSD patients are clearly prone to develop CVDs, and increasing evidence highlighted the possible onset of PTSD related to CVDs. The increased risk of CVD among PTSD patients seems to be ascribable to a multifactorial pathogenetic model. Pathophysiological factors, such as neuroendocrinological abnormalities, autonomic imbalance, and pro-phlogistic diathesis, which have been shown to be associated with PTSD, as well as a wide range of maladaptive behaviors, many of which are well-known CVDs risk factors, contribute to outline an unfavorable scenario in terms of cardiovascular and, more generally, physical health. Hence, the higher prevalence of CVD health risk behaviors among individual with PTSD and their physiopathological vulnerability to CVDs deserve stronger attention from the health practitioners. This risk gap should be addressed with prevention and treatment strategies in order to reduce the excess burden of morbidity and mortality of people with PTSD.

On the other hand, psychiatric disorders, such as PTSD, have been widely described in patients suffering from CVDs, due to CVDs' potentially traumatizing characteristics such as life-threatening, concrete danger of death, sense of loss of control and helplessness experienced by the patient, and possible invasive treatments, all traumatizing factors that promote the development of PTSD. PTSD represents negative prognostic factors in the population of patients with CVDs, so it is essential for clinicians to recognize the more vulnerable subjects to implement targeted and early therapeutic strategies.

Cross-References

- ▶ Immune System and Mind-Body Medicine: An Overview
- ▶ Psychiatric Aspects of Sudden Cardiac Arrest and Implantable Cardioverter-Defibrillators
- ▶ The Role of Emotions, Stress, and Mental State in Inflammatory Processes Perturbing Brain-Heart Dialogue

References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Washington, DC: Author; 2013.
2. Sareen J, Cox BJ, Stein MB, Afifi TO, Fleet C, Asmundson GJ. Physical and mental comorbidity, disability, and suicidal behavior associated with post-traumatic stress disorder in a large community sample. Psychosom Med. 2007;69:242–8.
3. Burg MM, Soufer R. Post-traumatic stress disorder and cardiovascular disease. Curr Cardiol Rep. 2016;18(10):94.
4. Edmondson D, von Känel R. Post-traumatic stress disorder and cardiovascular disease. Lancet Psychiatry. 2017;4(4):320–9. https://doi.org/10.1016/S2215-0366(16)30377-7. Epub 2017 Jan 19. Review. PubMed PMID: 28109646; PubMed Central PMCID: PMC5499153
5. Carmassi C, Stratta P, Massimetti G, Bertelloni CA, Conversano C, Cremone IM, Miccoli M, Baggiani A, Rossi A, Dell'Osso L. New DSM-5 maladaptive symptoms in PTSD: gender differences and correlations with mood spectrum symptoms in a sample of high school students following survival of an earthquake. Ann General Psychiatry. 2014;13:28. https://doi.org/10.1186/s12991-014-0028-9. eCollection 2014. PubMed PMID: 25670961; PubMed Central PMCID: PMC4322820
6. Dell'osso L, Carmassi C, Stratta P, Massimetti G, Akiskal KK, Akiskal HS, Maremmani I, Rossi A. Gender differences in the relationship between maladaptive behaviors and post-traumatic stress disorder. A study on 900 L' Aquila 2009 Earthquake Survivors. Front Psych. 2013;3:111. https://doi.org/10.3389/fpsyt.2012.00111. eCollection 2012. PubMed PMID: 23293608; PubMed Central PMCID: PMC3537190
7. Carmassi C, Bertelloni CA, Gesi C, Conversano C, Stratta P, Massimetti G, Rossi A, Dell'Osso L. New DSM-5 PTSD guilt and shame symptoms among Italian earthquake survivors: Impact on maladaptive behaviors. Psychiatry Res. 2017;251:142–7. https://doi.org/10.1016/j.psychres.2016.11.026. Epub 2016 Nov 22. PubMedPMID: 28199913
8. Edmonson D, Kronish IM, Shaffer A, Falzon L, Burg MM. Post traumatic stress disorder and Risk for Coronary Heart Disease: a meta-analytic review. Am Heart J. 2013;166(5):806–14.
9. Glaesmer H, Brahler E, Gundel H, Riedel-Heller SG. The association of traumatic experiences and posttraumatic stress disorder with physical morbidity in old age: a German population-based study. Psychosom Med. 2011;73:401–6.
10. Koenen KC, Galea S. Post-traumatic stress disorder and chronic disease: open questions and future directions. Soc Psychiatry Psychiatr Epidemiol. 2015;50:511–3.
11. Koenen KC, Sumner JA, Gilsanz P, Glymour MM, Ratanatharathorn A, Rimm EB, Roberts AL, Winning A, Kubzansky LD. Post-traumatic stress disorder and cardiometabolic disease: improving causal inference to inform practice. Psychol Med. 2016;47(2):209–25.
12. Lohr JB, Palmer BW, Eidt CA, Aailaboyina S, Mausbach BT, Wolkowitz OM, Thorp SR, Jeste DV. Is post-traumatic stress disorder associated with premature senescence? A review of the literature. Am J Geriatr Psychiatr. 2015;23:709–25.
13. Gander ML, von Kanel R. Myocardial infarction and post-traumatic stress disorder: frequency, outcome, and atherosclerotic mechanisms. Eur J Cardiovasc Prev Rehabil. 2006;13:165–72.
14. Edmonson D, Sumner JA, Kronish IM, Burg MM, Oyesiku L, Schwartz JE. The association of PTSD with clinic and ambulatory blood pressure in healthy adults. Psychosom Med. 2017;80(1):55–61.
15. Goldstein BI, Carnethon MR, Matthews KA, McIntyre RS, Miller GE, Raghuveer G, Stoney CM, Wasiak H, McCrindle BW, American Heart Association Atherosclerosis, Hypertension and Obesity in Youth Committee of the Council on Cardiovascular Disease in the Young. Major depressive disorder and bipolar disorder predispose youth to accelerated atherosclerosis and early cardiovascular disease: a scientific statement from the American Heart Association. Circulation. 2015;132(10):965–86.
16. Fu SS, McFall M, Saxon AJ, Beckham JC, Carmody TP, Baker DG, Joseph AM. Post-traumatic stress disorder and smoking: a systematic review. Nicotine Tob Res. 2007;9(11):1071–84.
17. McFarlane AC. Epidemiological evidence about the relationship between ptsd and alcohol abuse: the nature of the association. Addict Behav. 1998;23(6):813–25.
18. Cohen BE, Marmar C, Ren L, Bertenthal D, Seal KH. Association of cardiovascular risk factors with mental health diagnoses in Iraq and Afghanistan war veterans using VA health care. JAMA. 2009;302(5):489–92. https://doi.org/10.1001/jama.2009.1084. PubMed PMID: 19654382
19. von Känel R, Hepp U, Traber R, Kraemer B, Mica L, Keel M, Mausbach BT, Schnyder U. Measures of endothelial dysfunction in plasma of patients with posttraumatic stress disorder. Psychiatry Res. 2008;158(3):363–73.
20. von Känel R, Hepp U, Kraemer B, Traber R, Keel M, Mica L, Schnyder U. Evidence for low-grade systemic proinflammatory activity in patients with posttraumatic stress disorder. J Psychiatr Res. 2007;41(9):744–52.
21. Spitzer C, Barnow S, Völzke H, John U, Freyberger HJ, Grabe HJ. Trauma, posttraumatic stress disorder, and physical illness: findings from the general population. Psychosom Med. 2009;71:1012–7.
22. Sawchuk CN, Roy-Byrne P, Goldberg J, Manson S, Noonan C, Beals J, et al. The relationship between post-traumatic stress disorder, depression and cardiovascular disease in an American Indian tribe. Psychol Med. 2005;35:1785–94.

23. Pietrzak RH, Goldstein RB, Southwick SM, Grant BF. Medical comorbidity of full and partial posttraumatic stress disorder in United States adults: results from wave 2 of the National Epidemiologic Survey on Alcohol and Related Conditions. Psychosom Med. 2011;73:697–707.
24. Kubzansky LD, Koenen KC, Spiro A 3rd, Vokonas PS, Sparrow D. Prospective study of posttraumatic stress disorder symptoms and coronary heart disease in the Normative Aging Study. Arch Gen Psychiatry. 2007;64(1):109–16.
25. Boscarino JA. Posttraumatic stress disorder and mortality among U.S. army veterans 30 years after military service. Ann Epidemiol. 2006;16:248–56.
26. Boscarino JA. Posttraumatic stress disorder and physical illness: results from clinical and epidemiologic studies. Ann N Y Acad Sci. 2004;1032:141–53.
27. Beristianos MH, Yaffe K, Cohen B, Byers AL. PTSD and risk of incident cardiovascular disease in aging veterans. Am J Geriatr Psychiatry. 2016;24:192–200.
28. Sumner JA, Kubzansky LD, Kabrhel C, Roberts AL, Chen Q, Winning A, Gilsanz P, Rimm EB, Glymour MM, Koenen KC. Associations of trauma exposure and posttraumatic stress symptoms with venous thromboembolism over 22 years in women. J Am Heart Assoc. 2016;5(5):e003197.
29. Sachs-Ericsson N, Blazer D, Plant EA, Arnow B. Childhood sexual and physical abuse and the 1-year prevalence of medical problems in the National Comorbidity Survey. Health Psychol. 2005;24:32–40.
30. Ahmadi N, Hajsadeghi F, Mirshkarlo HB, Budoff M, Yehuda R, Ebrahimi R. Post-traumatic stress disorder, coronary atherosclerosis, and mortality. Am J Cardiol. 2011;108:29–33.
31. Gradus JL, Farkas DK, Svensson E, Ehrenstein V, Lash TL, Milstein A, Adler N, Sørensen HT. Associations between stress disorders and cardiovascular disease events in the Danish population. BMJ Open. 2015;5(12):e009334.
32. Dennis PA, Watkins LL, Calhoun PS, Oddone A, Sherwood A, Dennis MF, Rissling MB, Beckham JC. Posttraumatic stress, heart rate variability, and the mediating role of behavioral health risks. Psychosom Med. 2014;76:629–37.
33. Scherrer JF, Chrusciel T, Zeringue A, Garfield LD, Hauptman PJ, Lustman PJ, Freedland KE, Carney RM, Bucholz KK, Owen R. Anxiety disorders increase risk for incident myocardial infarction in depressed and nondepressed Veterans Administration patients. Am Heart J. 2010;159:772–9.
34. Boscarino JA. Post-traumatic stress disorder and cardiovascular disease link: time to identify specific pathways and interventions. Am J Cardiol. 2011;108 (7):1052–3.
35. Burg MM, Brandt C, Buta E, Schwartz J, Bathulapalli H, Dziura J, Edmondson DE, Haskell S. Risk for incident hypertension associated with posttraumatic stress disorder in military veterans and the effect of posttraumatic stress disorder treatment. Psychosom Med. 2017;79(2):181–8.
36. Boscarino JA. Psychobiologic predictors of disease mortality after psychological trauma: implications for research and clinical surveillance. J Nerv Ment Dis. 2008;196:100–7.
37. Yehuda R. Advances in understanding neuroendocrine alterations in PTSD and their therapeutic implications. Ann N Y Acad Sci. 2006;1071:137–66.
38. Yehuda R, LeDoux J. Response variation following trauma: a translational neuroscience approach to understanding PTSD. Neuron. 2007;56:19–32.
39. Munck A, Guyre PM, Holbrook NJ. Physiological functions of glucocorticoids in stress and their relation to pharmacological actions. Endocr Rev. 1984;5(1):25–44.
40. Mason JW, Giller EL, Kosten TR, Ostroff RB, Podd L. Urinary free-cortisol levels in posttraumatic stress disorder patients. J Nerv Ment Dis. 1986;174(3):145–9.
41. Yehuda R, Teicher MH, Trestman RL, Levengood RA, Siever LJ. Cortisol regulation in posttraumatic stress disorder and major depression: a chronobiological analysis. Biol Psychiatry. 1996;40:79–88.
42. Dell'Osso L, Da Pozzo E, Carmassi C, Trincavelli ML, Ciapparelli A, Martini C. Lifetime manic-hypomanic symptoms in post-traumatic stress disorder: relationship with the 18 kDa mitochondrial translocator protein density. Psychiatry Res. 2010;177(1–2):139–43.
43. Martini C, Da Pozzo E, Carmassi C, Cuboni S, Trincavelli ML, Massimetti G, Marazziti D, Dell'Osso L. Cyclic adenosine monophosphate responsive element binding protein in post-traumatic stress disorder. World J Biol Psychiatry. 2013;14(5):396–402.
44. Shah AJ, Lampert R, Goldberg J, Veledar E, Bremner JD, Vaccarino V. Posttraumatic stress disorder and impaired autonomic modulation in male twins. Archival report. Biol Psychiatry. 2013;73:1103–10.
45. Rozanski A, Blumenthal JA, Davidson KW, Saab PG, Kubzansky L. The epidemiology, pathophysiology, and management of psychosocial risk factors in cardiac practice: the emerging field of behavioral cardiology. J Am Coll Cardiol. 2005;45:637–51.
46. Haensel A, Mills PJ, Nelesen RA, Ziegler MG, Dimsdale JE. The relationship between heart rate variability and inflammatory markers in cardiovascular diseases. Psychoneuroendocrinology. 2008;33(10):1305–12.
47. Tsuji H, Venditti FJ Jr, Manders ES, Evans JC, Larson MG, Feldman CL, Levy D. Reduced heart rate variability and mortality risk in an elderly cohort. The Framingham Heart Study. Circulation. 1994;90(2):878–83.
48. Bigger JT Jr, Fleiss JL, Steinman RC, Rolnitzky LM, Kleiger RE, Rottman JN. Frequency domain

measures of heart period variability and mortality after myocardial infarction. Circulation. 1992;85(1):164–71.
49. Buckley TC, Kaloupek DG. A meta-analytic examination of basal cardiovascular activity in posttraumatic stress disorder. Psychosom Med. 2001;63 (4):585–94.
50. Pole N. The psychophysiology of posttraumatic stress disorder: a meta-analysis. Psychol Bull. 2007;133(5):725–46.
51. Boscarino JA. Posttraumatic stress disorder, exposure to combat, and lower plasma cortisol among Vietnam veterans: findings and clinical implications. J Consult Clin Psychol. 1996;64(1):191–201.
52. Heim C, Newport DJ, Wagner D, Wilcox MM, Miller AH, Nemeroff CB. The role of early adverse experience and adulthood stress in the prediction of neuroendocrine stress reactivity in women: a multiple regression analysis. Depress Anxiety. 2002;15(3):117–25.
53. Fries E, Hesse J, Hellhammer J, Hellhammer DH. A new view on hypocortisolism. Psychoneuroendocrinology. 2005;30(10):1010–6.
54. Tracey KJ. The inflammatory reflex. Nature. 2002;420:853–9.
55. Maripuu M, Wikgren M, Karling P, Adolfsson R, Norrback KF. Relative hypocortisolism is associated with obesity and the metabolic syndrome in recurrent affective disorders. J Affect Disord. 2016; 204:187–96.
56. Passos IC, Vasconcelos-Moreno MP, Costa LG, Kunz M, Brietzke E, Quevedo J, Salum G, Magalhães PV, Kapczinski F, Kauer-Sant'Anna M. Inflammatory markers in post-traumatic stress disorder: a systematic review, meta-analysis, and meta-regression. Lancet Psychiatry. 2015;2(11):1002–12.
57. Pace TW, Heim CM. A short review on the psychoneuroimmunology of posttraumatic stress disorder: from risk factors to medical comorbidities. Brain Behav Immun. 2011;25:6–13.
58. Baker DG, Nievergelt CM, O'Connor DT. Biomarkers of PTSD: neuropeptides and immune signaling. Neuropharmacology. 2012;62:663–73.
59. Ross R. Atherosclerosis – an inflammatory disease. N Engl J Med. 1999;340(2):115–26.
60. Pace TWW, Wingenfeld K, Schmidt I, Meinlschmidt G, Hellhammer DH, Heim CM. Increased peripheral NF-kappa B pathway activity in women with childhood abuse-related posttraumatic stress disorder. Brain Behav Immun. 2012;26:13–7.
61. Bierhaus A, Nawroth PP. Modulation of the vascular endothelium during infection – the role of NF-kappa B activation. Contrib Microbiol. 2003;10:86–105.
62. Munck A, Náray-Fejes-Tóth A. Glucocorticoids and stress: permissive and suppressive actions. Ann N Y Acad Sci. 1994;746:115–30.. discussion 131-3
63. Van Zuiden M, Kavelaars A, Geuze E, Olff M, Heijnen CJ. Predicting PTSD: pre-existing vulnerabilities in glucocorticoid-signaling and implications for preventive interventions. Brain Behav Immun. 2013;30:12–21.
64. Willerson JT, Kereiakes DJ. Endothelial dysfunction. Circulation. 2003;108:2060–1.
65. Verma S, Buchanan MR, Anderson TJ. Endothelial function testing as a biomarker of vascular disease. Circulation. 2003;108:2054–9.
66. Grenon SM, Owens CD, Alley H, Perez S, Whooley MA, Neylan TC, Aschbacher K, Gasper WJ, Hilton JF, Cohen BE. Posttraumatic stress disorder is associated with worse endothelial function among veterans. J Am Heart Assoc. 2016;5(3):e003010.
67. Kibler JL, Joshi K, Ma M. Hypertension in relation to posttraumatic stress disorder and depression in the US national comorbidity study. Behav Med. 2008; 34:125–31.
68. Kibler JL. Posttraumatic stress and cardiovascular disease risk. J Trauma Dissociation. 2009;10:135–50.
69. Andersen J, Wade M, Possemato K, Ouimette P. Association between posttraumatic stress disorder and primary care providerdiagnosed disease among Iraq and Afghanistan veterans. Psychosom Med. 2010;72:498–504.
70. Granado NS, Smith TC, Swanson GM, Harris RB, Shahar E, Smith B, Boyko EJ, Wells TS, Ryan MA, Millennium Cohort Study Team. Newly reported hypertension after military combat deployment in a large population-based study. Hypertension. 2009;54(5):966–73.
71. Rozanski A, Blumenthal JA, Davidson KA, Saab PG, Kubzansky L. The epidemiology, pathophysiology, and management of psychosocial risk factors in cardiac practice. J Am Coll Cardiol. 2005;45:637–51.
72. Davidson JR, Hughes D, Blazer DG, George LK. Post-traumatic stress disorder in the community: an epidemiological study. Psychol Med. 1991; 21:713–21.
73. Breslau N, Davis GC, Schultz LR. Posttraumatic stress disorder and the incidence of nicotine, alcohol, and other drug disorders in persons who have experienced trauma. Arch Gen Psychiatry. 2003;60:289–94.
74. Calhoun PS, Elter JR, Jones ER Jr, Kudler H, Straits-Tröster K. Hazardous alcohol use and receipt of risk-reduction counseling among U.S. veterans of the wars in Iraq and Afghanistan. J Clin Psychiatry. 2008;69:1686–93.
75. Smith B, Ryan MAK, Wingard DL, Patterson TL, Slymen DJ, Macera CA. Cigarette smoking and military deployment: a prospective evaluation. Am J Prev Med. 2008;35:539–46.
76. Kronish IM, Edmondson D, Li Y, Cohen BE. Posttraumatic stress disorder and medication adherence: results from the Mind Your Heart study. J Psychiatr Res. 2012;46:1595–9.
77. Glodich A, Allen JG. Adolescents exposed to violence and abuse: a review of the group therapy literature with an emphasis on preventing trauma reenactment. J Child Adolesc Group Therapy. 1998; 8(3):135–54.

78. Maher MJ, Rego SA, Asnis GM. Sleep disturbances in patients with post-traumatic stress disorder: epidemiology, impact and approaches to management. CNS Drugs. 2006;20(7):567–90.
79. Cappuccio FP, Cooper D, D'Elia L, Strazzullo P, Miller MA. Sleep duration predicts cardiovascular outcomes: a systematic review and meta-analysis of prospective studies. Eur Heart J. 2011;32:1484.
80. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Das SR, Delling FN, Djousse L, MSV E, Ferguson JF, Fornage M, Jordan LC, Khan SS, Kissela BM, Knutson KL, Kwan TW, Lackland DT, Lewis TT, Lichtman JH, Longenecker CT, Loop MS, Lutsey PL, Martin SS, Matsushita K, Moran AE, Mussolino ME, O'Flaherty M, Pandey A, Perak AM, Rosamond WD, Roth GA, UKA S, Satou GM, Schroeder EB, Shah SH, Spartano NL, Stokes A, Tirschwell DL, Tsao CW, Turakhia MP, LB VW, Wilkins JT, Wong SS, Virani SS, American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics-2019 update: a report from the American Heart Association. Circulation. 2019;139(10):e56–e528.
81. Timmis A, Townsend N, Gale C, Grobbee R, Maniadakis N, Flather M, Wilkins E, Wright L, Vos R, Bax J, Blum M, Pinto F, Vardas P, ESC Scientific Document Group. European Society of Cardiology: cardiovascular disease statistics 2017. Eur Heart J. 2018;39(7):508–79.
82. Awaida JP, Dupuis J, Théroux P, Pelletier G, Joyal M, De Guise P, Doucet S, Bilodeau L, Thibault B, Tanguay JF, Gallo R, Grégoire J, L'Allier PL, Macle L, Nigam A. Demographics, treatment and outcome of acute coronary syndromes: 17 years of experience in a specialized cardiac centre. Can J Cardiol. 2006; 22(2):121–4.
83. Théroux P, Willerson JT, Armstrong PW. Progress in the treatment of acute coronary syndromes: a 50-year perspective (1950–2000). Circulation. 2000;102: IV2–IV13.
84. Cohen BE, Edmondson D, Kronish IM. State of the art review: depression, stress, anxiety, and cardiovascular disease. Am J Hypertens. 2015;28(11):1295–302.
85. Tully PJ, Harrison NJ, Cheung P, Cosh S. Anxiety and cardiovascular disease risk: a review. Curr Cardiol Rep. 2016;18(12):120.
86. Kutz I, Shabtai H, Solomon Z, Neumann M, David D. Post-traumatic stress disorder in myocardial infarction patients: prevalence study. Isr J Psychiatry Relat Sci. 1994;31(1):48–56.
87. Alonzo AA. The experience of chronic illness and post-traumatic stress disorder: the consequences of cumulative adversity. Soc Sci Med. 2000;50(10): 1475–84.
88. American Psychiatric Association. Diagnostic and statistical manual of mental disorder (3rd ed.). Washington, DC: American Psychiatric Association, 1980.
89. van Driel RC, den Velde Wybrand O. Myocardial infarction and post traumatic stress disorder. J Trauma Stress. 1995;8(1):151–9.
90. Gulielmos V, Eller M, Theile S, Dill HM, Jost T, Tagtekin SM, Schueler S. Influence of median sternotomy on the psychosomatic outcome in coronary artery single-vessel bypass grafting. Eur J Cardiothorac Surg. 1999;16(Suppl2):s34–8.
91. Edmondson D. An enduring somatic threat model of posttraumatic stress disorder due to acute life-threatening medical events. Soc Personal Psychol Compass. 2014;8(3):118–34.
92. Fox KAA, Dabbous OH, Goldberg RJ, Pieper KS, Eagle KA, Van de Werf F, Avezum A, Goodman SG, Anderson F Jr, Granger CB. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). BMJ. 2006;333(7578):1091.
93. Goldberg RJ, Currie K, White K, Brieger D, Steg PG, Goodman SG, Gore JM. Six-month outcomes in a multinational registry of patients hospitalized with an acute coronary syndrome (The Global Registry of Acute Coronary Events [GRACE]). Am J Cardiol. 2004;93(3):288–93.
94. Ay H, Gungor L, Arsava EM, Rosand J, Vangel M, Benner T, Schwamm LH, Furie KL, Koroshetz WJ, Sorensen AG. A score to predict early risk of recurrence after ischemic stroke. Neurology. 2010;4(2):128–35.
95. Tang EW, Wong CK, Herbison P. Global Registry of Acute Coronary Events (GRACE) hospital discharge risk score accurately predicts long-term mortality post acute coronary syndrome. Am Heart J. 2007;153(1):29–35.
96. Edmondson D, Park CL, Chaudoir SR, Wortmann JH. Death without God: religious struggle, death concerns, and depression in the terminally ill. Psychol Sci. 2008;19(8):754–8.
97. Bennett P, Owen RL, Koutsakis S, Bisson J. Personality, social context and cognitive predictors of post-traumatic stress disorder in myocardial infarction patients. Psychol Health. 2002;17(4):489–500.
98. Doerfler LA, Paraskos JA, Piniarski L. Relationship of quality of life and perceived control with post-traumatic stress disorder symptoms 3 to 6 months after myocardial infarction. J Cardpulm Rehabil. 2005;25(3):166–72.
99. Pedersen SS, Middel B, Larsen ML. Posttraumatic stress disorder in first time myocardial infarction patients. Heart Lung. 2003;32(5):300–7.
100. Green BL, Rowland JH, Krupnick JL, Epstein SA, Stockton P, Stern NM, Spertus IL, Steakley C. Prevalence of posttraumatic stress disorder in women with breast cancer. Psychosomatics. 1998;39(2):102–11.
101. Moazen-Zadeh E, Khoshdel A, Avakh F, Rahmani A. Increased blood pressures in veterans with post traumatic stress disorder. Int J Psychiatry Med. 2016; 51(6):576–86.

102. Hawk LW, Dougall AL, Ursano RJ, Baum A. Urinary catecholamines and cortisol in recent-onset post-traumatic stress disorder after motor vehicle accidents. Psychosom Med. 2000;62(3):423–34.
103. Miller RJ, Sutherland AG, Hutchison JD, Alexander DA. C-reactive protein and interleukin 6 receptor in post-traumatic stress disorder: a pilot study. Cytokine. 2001;13(4):253–5.
104. Edmondson D, Rieckmann N, Edmondson D, Rieckmann N, Shaffer JA, Schwartz JE, Burg MM, Davidson KW, Klemow L, Shimbo D, Kronish IM. Posttraumatic stress due to an acute coronary syndrome increases risk of 42-month major adverse cardiac events and all-cause mortality. J Psychiatr Res. 2011;45(12):1621–6.
105. Shemesh E, Yehuda R, Milo O, Dinur I, Rudnick A, Vered Z, Cotter G. Posttraumatic Stress, non-adherence, and adverse outcomes on survivors of a myocardial infarction. Psychosom Med. 2004;66(4):521–6.
106. Kronish IM, Edmondson D, Goldfinger JZ, Fei K, Horowitz CR. Posttraumatic stress disorder and adherence to medications in survivors of strokes and transient ischemic attacks. Stroke. 2012;43(8): 2192–7.
107. Dell'Osso L, Carmassi C, Rucci P, Conversano C, Shear MK, Calugi S, Maser JD, Endicott J, Fagiolini A, Cassano GB. A multidimensional spectrum approach to post-traumatic stress disorder: comparison between the Structured Clinical Interview for Trauma and Loss Spectrum (SCI-TALS) and the Self-Report instrument (TALS-SR). Compr Psychiatry. 2009;50(5):485–90.
108. von Känel R, Begrè S, Abbas CC, Saner H, Gander ML, Schmid JP. Inflammatory biomarkers in patients with posttraumatic stress disorder caused by myocardial infarction and the role of depressive symptoms. Neuroimmunomodulation. 2010;17(1):39–46.
109. Vilchinsky N, Ginzburg K, Fait K, Foa EB. Cardiac-disease-induced PTSD (CDI-PTSD): a systematic review. Clin Psychol Rev. 2017;55:92–106.
110. Castilla C, Vazquez C. Stress related symptoms and positive emotions after myocardial infarction: a longitudinal analysis. Eur J Psychotraumatol. 2011;2 https://doi.org/10.3402/ejpt.v2i0.8082.
111. Gao W, Zhao J, Li Y, Cao FL. Post-traumatic stress disorder symptoms in first-time myocardial infarction patients: roles of attachment and alexithymia. J Adv Nurs. 2015;71(11):2575–84.
112. Meister RE, Weber T, Princip M, Schnyder U, Barth J, Znoj H, Schmid JP, von Känel R. Perception of a hectic hospital environment at admission relates to acute stress disorder symptoms in myocardial infarction patients. Gen Hosp Psychiatry. 2016;39:8.14.
113. Oflaz S, Yüksel Ş, Şen F, Özdemiroğlu F, Kurt R, Oflaz H, Kaşikcioğlu E. Does illness perception predict posttraumatic stress disorder in patients with myocardial infarction? Noro Psikiyatr Ars. 2014; 51(2):103–9.
114. Sheldrick R, Tarrier N, Berry E, Kincey J. Post-traumatic stress disorder and illness perceptions over time following myocardial infarction and sub arachnoid hemorrhage. Br J Health Psychol. 2006;11:387–400.
115. Roberge MA, Dupuis G, Marchande A. Post-traumatic stress disorder following myocardial infarction: prevalence and risk factors. Can J Cardiol. 2010; 26(5):e170–5.
116. Doerfler LA. Posttraumatic stress disorder-like symptoms 1 week to 3 months after myocardial infarction. Int J Rehab Health. 1997;3:89.
117. Girard TD, Shintani AK, Jackson AC, Gordon SM, Pun BT, Henderson MS, Dittus RS, Bernard GR, Ely EW. Risk factors for post-traumatic stress disorder symptoms following critical illness requiring prospective cohort study. Crit Care. 2007;11(1):R28.
118. Wikman A, Bhattacharyya M, Perkins-Poraz L, Steptoe A. Persistence of posttraumatic stress symptoms 12 and 36 months after acute coronary syndrome. Psychosom Med. 2008;70(7):764–72.
119. Ginzburg K, Ein-Dor T, Solomon Z. Comorbidity of posttraumatic stress disorder, anxiety and depression: a 20-year longitudinal study of war veterans. J Affect Disord. 2010;123(1–3):249–57.
120. Breslau N, Kessler RC, Chilcoat HD, Schultz LR, Davis GC, Andreski P. Trauma and posttraumatic stress disorder in the community: the 1996 Detroit area survey of trauma. Arch Gen Psychiatry. 1998;55(7):626–32.
121. Frans O, Rimmö PA, Aberg L, Fredrikson M. Trauma exposure and post-traumatic stress disorder in the general population. Acta Psychiatr Scand. 2005;111(4):291–9.
122. Goldstein RB, Smith SM, Chou SP, Saha TD, Jung J, Zhang H, Pickering RP, Ruan WJ, Huang B, Grant BF. The epidemiology of DSM-5 posttraumatic stress disorder in the United States: results from the National Epidemiologic Survey on Alcohol and Related Conditions-III. Soc Psychiatry Psychiatr Epidemiol. 2016;51(8):1137–48.
123. Carmassi C, Dell'Osso L, Manni C, Candini V, Dagani J, Iozzino L, Koenen KC, de Girolamo G. Frequency of trauma exposure and post-traumatic stress disorder in Italy: analysis from the World Mental Health Survey Initiative. J Psychiatr Res. 2014;59:77–84.
124. Edmonson D, Richardson S, Falzon L, Davidson KW, Mills MA, Neria Y. Posttraumatic stress disorder prevalence and risk of recurrence in acute coronary syndrome patients: a meta-analytic review. PLoS One. 2012;7(6):e38915.
125. O'Reilly SM, Grubb N, O'Carroll RE. Long-term emotional consequencesof in-hospital cardiac arrest and myocardial infarction. Br J Clin Psychol. 2004;43:83–95.
126. Ladwig KH, Schoefinius A, Dammann G, Danner R, Gürtler R, Herrmann R. Long-acting psychotraumatic properties of a cardiac arrest experience. Am J Psychiatry. 1999;156(6):912–9.

127. Gamper G, Willeit M, Sterz F, Herkner H, Zoufaly A, Hornik K, Havel C, Laggner AN. Life after death: posttraumatic stress disorder in survivors of cardiac arrest: prevalence, associated factors, and the influence of sedation and analgesia. Crit Care Med. 2004;32(2):378–83.
128. Habibović M, van den Broek KC, Alings M, Van der Voort PH, Denollet J. Posttraumatic stress 18 months following cardioverter defibrillator implantation: shocks, anxiety, and personality. Health Psychol. 2012;31(2):186–93.
129. Lang S, Becker R, Wilke S, Hartmann M, Herzog W, Loewe B. Anxiety disorders in patients with implantable cardioverter defibrillators: frequency, course, predictors, and patients' requests for treatment. Pacing Clin Electrophysiol. 2014;37(1):35–47.
130. Morken IM, Bru E, Norekval TM, Larsen AI, Idsoe T, Karlsen B. Perceived support from healthcare professionals, shock anxiety and posttraumatic stress in implantable cardioverter defibrillator recipients. J Clin Nurs. 2014;23(3–4):450–60.
131. von Känel R, Baumert J, Kolb C, Cho EYN, Ladwig KH. Chronic posttraumatic stress and its predicators in patients living with implantable cardioverter defibrillator. J Affect Disord. 2011;131(1–3):344–52.
132. Matchett M, Sears SF, Hazelton G, Kirian K, Wilson E, Nekkanti R. The implantable cardioverter defibrillator: its history, current psychological impact and future. Expert Rev Med Devices. 2009;6(1):43–50.
133. Oxlad M, Wade TD. Longitudinal risk factors for adverse psychological functioning six months after coronary artery bypass graft surgery. J Health Psychol. 2008;13(1):79–92.
134. Oxlad M, Stubberfield J, Stuklis R, Edwards J, Wade TD. Psychological risk factors for increased post-operative length of hospital stay following Coronary Artery Bypass Graft Surgery. J Behav Med. 2006;29(2):179–90.
135. Boyer BA, Matour SJ, Crittenden KB, Larsen KA, Cox JM, Link DD. Appraisals of fear, helplessness, and perceived life-threat during emergent cardiac surgery: relationship to pre-surgical depression, trauma history, and posttraumatic stress. J Clin Psychol Med Settings. 2013;20(2):173–85.
136. Dew MA, Ruth LH, Schulberg HC, Simmons RG, Kormos RL, Trzepacz PT, Griffith BP. Prevalence and predictors of depression and anxiety-related disorders during the year after heart transplantation. Gen Hosp Psychiatry. 1996;18(6):48S–61S.
137. Dew MA, Kormos RL, Ruth LH, Murali S, DiMartini AF, Griffith BP. Early post-transplant medical compliance and mental health predict physical morbidity and mortality one to three years after heart transplantation. J Heart Lung Transplant. 1999;18(6):549–62.
138. Roberge MA, Dupuis G, Marchand A. Acute stress disorder after myocardial infarction: prevalence and associated factors. Psychosom Med. 2008;70(9): 1028–34.
139. Wikman A, Messerli-Bürgy N, Molloy GJ, Randall G, Perkins-Porras L, Steptoe A. Symptom experience during acute coronary syndrome and the development of posttraumatic stress symptoms. J Behav Med. 2012;35(4):420–30.
140. Dew MA, Kormos RL, DiMartini AF, Switzer GE, Schulberg HC, Roth LH, Griffith BP. Prevalence and risk of depression and anxiety-related disorders during the first three years after heart transplantation. Psychosomatics. 2001;42(4):300–13.
141. Stukas AA, Dew MA, Switzer GE, DiMartini A, Kormos RL, Griffith BP. PTSD in heart transplant recipients and their primary family caregivers. Psychosomatics. 1999;40(3):212–21.
142. Wei J, Rook C, Ramadan R, Shah AJ, Bremner JD, Quyyumi AA, Kutner M, Vaccarino V. Meta-analysis of mental stress-induced myocardial ischemia and subsequent cardiac events in patients with coronary artery disease. Am J Cardiol. 2014;114(2):187–92.. Eliminato da page. 15
143. Wiedemar L, Schmid J-P, Muller J, Wittmann L, Schnyder U, Saner H, von Kanel R. Prevalence and predictors of posttraumatic stress disorder in patients with acute myocardial infarction. Heart Lung. 2008;37(2):113–21.
144. Berkman LF, Blumenthal J, Burg M, Carney RM, Catellier D, Cowan MJ, Czajkowski SM, DeBusk R, Hosking J, Jaffe A, Kaufmann PG, Mitchell P, Norman J, Powell LH, Raczynski JM, Schneiderman N, Enhancing Recovery in Coronary Artery Disease Patients Investigators (ENRICHD). Effects of treating depression and low perceived social support on clinical events after myocardial infarction: The Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) randomized trial. JAMA. 2003;289 (3):3106–16.
145. Ginzburg K, Solomon Z, Koifman B, Keren G, Roth A, Kriwisky M, Kutz I, David D, Bleich A. Trajectories of posttraumatic stress disorder following myocardial infarction: a prospective study. J Clin Psychiatry. 2003;64(10):1217–23.
146. Wang X, Chung MC, Hyland ME, Bahkeit M. Posttraumatic stress disorder and psychiatric co-morbidity following stroke: the role of alexithymia. Psychiatry Res. 2011;188(1):51–7.
147. Solomon Z, Mikulincer M, Avitzur E. Coping, locus of control, social support, and combat-related posttraumatic stress disorder: a prospective study. J Pers Soc Psychol. 1988;55(2):279–85.
148. Tsai YC, Pai HC. Burden and cognitive appraisal of stroke survivors' informal caregivers: an assessment of depression model with mediating and moderating effects. Arch Psychiatr Nurs. 2016; 30(2):237–43.
149. Versteeg H, Theuns DAMJ, Erdman RMA, Jordaens L, Pedersen SS. Posttraumatic stress in implantable cardioverter defibrillator patients: the role of preimplantation distress and shocks. Int J Cardiol. 2011; 2(4):242–50.

150. Ladwig KH, Baumert J, Marten-Mittag B, Kolb C, Zrenner B, Schmitt C. Posttraumatic stress symptoms and predicted mortality in patients with implantable cardioverter-defibrillators. Arch Gen Psychiatry. 2008;65(11):1324–30.
151. Rothenhousler HB, Grieser B, Nollert G, Reichart B, Schelling G, Kapfhahmmer HP. Psychiatric and psychosocial outcome of cardiac surgery with cardiopulmonary bypass: a prospective 12-month follow-up study. Gen Hosp Psychiatry. 2005;27(1):18–28.
152. Schelling G, Richter M, Roozendaal B, Rothenhäusler HB, Krauseneck T, Stoll C, Nollert G, Schmidt M, Kapfhammer HP. Exposure to high stress in the intensive care unit may have negative effects on health-related quality-of-life outcomes after cardiac surgery. Crit Care Med. 2003;31(7):1971–80.
153. Ginzburg K, Ein-Dor T. Posttraumatic stress syndromes and health-related quality of life following myocardial infarction: 8-year follow-up. Gen Hosp Psychiatry. 2011;33(6):565–71.
154. Abbas CC, Schmid JP, Guler E, Wiedemar L, Begré S, Saner H, Schnyder U, von Kanel R. Trajectory of posttraumatic stress disorder caused by myocardial infarction: a two-year follow-up study. Int J Psychiatry Med. 2009;39(4):359–76.
155. Tarsitani L, Santis VD, Mistretta M, Parmigiani G, Zampetti G, Roselli V, Vitale D, Tritapepe L, Biondi M, Picardi A. Treatment with b-blockers and incidence of post-traumatic stress disorder after cardiac surgery: a prospective observational study. J Cardiothorac Vasc Anesth. 2012;26(2):265–9.
156. Favaro A, Gerosa G, Caforio ALP, Volpe B, Rupolo G, Zarneri D, Boscolo S, Pavan C, Tenconi E, d'Agostino C, Moz M, Torregrossa G, Feltrin G, Gambino A, Santonostaso P. Posttraumatic stress disorder and depression in heart transplantation recipients: the relationship with outcome and adherence to medical treatment. Gen Hosp Psychiatry. 2011; 33(1):1–7.
157. Kollner V, Schade I, Maulhardt T, Maercker A, Joraschky P, Gulielmos V. Posttraumatic stress disorder and quality of life after heart or lung transplantation. Transplant Proc. 2002;34(6):2192–3.
158. Horowitz M, Wilner N, Alvarez W. Impact of event scale: a measure of subjective stress. Psychosom Med. 1979;41(3):209–18.
159. Ginzburg K, Kutz I, Koifman B, Roth A, Kriwisky M, David D, Bleich A. Acute stress disorder symptoms predict all-cause mortality among myocardial infarction patients: a 15-year longitudinal study. Ann Behav Med. 2016;50(2):177–86.
160. von Känel R, Hari R, Schmid JP, Wiedemar L, Guler E, Barth J, Saner H, Schnyder U, Begré S. Non-fatal cardiovascular outcome in patients with posttraumatic stress symptoms caused by myocardial infarction. J Cardiol. 2011;58(1):61–8.
161. Shemesh E, Rudnick A, Kuloski E, Milovanov O, Salah A, Alon D, Dinur I, Blatt A, Metzkor M, Golik A, Verd Z, Cotter G. A prospective study of Post-traumatic stress symptoms and non-adherence in survivors of a myocardial infarction. Gen Hosp Psychiatry. 2001;23(4):215–22.
162. Gill JM, Saligan L, Woods S, Page G. PTSD is associated with an excess of inflammatory immune activities. Perspect Psychiatr Care. 2009;45(4):262–77.
163. Brudey C, Park J, Wiaderkiewicz J, Kobayashi I, Mellman TA, Marvar PJ. Autonomic and inflammatory consequences of posttraumatic stress disorder and the link to cardiovascular disease. Am J Phys. 2015;309(4):R315–21.
164. Croghan IT, Hurt RD, Dakhil SR, Croghan GA, Sloan JA, Novotny PJ, Rowland KM, Bernath A, Loots ML, Le-Lindqwister NA, Tschetter LK, Garneau SC, Flynn KA, Ebbert LP, Wender DB, Loprinzi CL. Randomized comparison of a nicotine inhaler and bupropion for smoking cessation and relapse prevention. Mayo Clin Proc. 2007;82(2):186–95.
165. Edmondson D, Horowitz CR, Goldfinger JZ, Fei K, Kronish IM. Concerns about medications mediate the association of posttraumatic stress disorder with adherence to medication in stroke survivors. Br J Health Psychol. 2013;18(4):799–813.
166. Shemesh E, Yehuda R, Milo O, Dinur I, Rudnick A, Vered Z, Cotter G. Posttraumatic stress, nonadherence, and adverse outcome in survivors of a myocardial infarction. Psychosom Med. 2004;66(4):521–6.
167. Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB. Posttraumatic stress disorder in the National Comorbidity Survey. Arch Gen Psychiatry. 1995;52(12):1048–60.
168. Hapke U, Schumann A, Rumpf HJ, John U, Konerding U, Meyer C. Association of smoking and nicotine dependence with trauma and posttraumatic stress disorder in a general population sample. J Nerv Ment Dis. 2005;193(12):843–6.
169. Hall KS, Hoerster KD, Yancy WS Jr. Post-traumatic stress disorder, physical activity, and eating behaviors. Epidemiol Rev. 2015;37:103–15.
170. Caples SM, Garcia-Touchard A, Somers VK. Sleep-disordered breathing and cardiovascular risk. Sleep. 2007;30(3):291–303.

Psychiatric Aspects of Sudden Cardiac Arrest and Implantable Cardioverter-Defibrillators

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Simone Savastano, Enrico Baldi, and Natascia Brondino

Contents

Abstract

People affected by diseases linked to an increased risk of sudden death, including cardiomyopathies and cardiac "channellopatiens," can benefit from the implantation of an ICD (implantable cardioverter-defibrillator). Penetrance and phenotypic expression of such diseases are very variable, which leads to an increase of psychological distress among these patients. For instance, an increased prevalence of mood disorders, anxiety disorders, and substance abuse disorders is found in people affected by hypertrophic cardiomyopathy. Moreover, symptomatic long QT syndrome (LQTS) patients are generally more depressed than asymptomatic ones, taking into account that depression and arrhythmic events are strongly interrelated and that most antidepressants are known to prolong the QT interval. Also the Brugada syndrome, another potentially lethal familiar cardiac disease, is known to be possibly triggered or worsened by the use of antidepressants and mood stabilizers. Patients affected by catecholaminergic polymorphic ventricular tachycardia (CPVT) have a higher rate of anxiety, depression, and post-traumatic stress symptoms compared to the general population.

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*,
https://doi.org/10.1007/978-3-030-28008-6_21

In addition, the implantation of the ICD in itself proved to be a very stressful event for the patients, who worry about many factors: first of all, they are afraid of having to experience the shocks delivered by the device, but also of potentially losing their independence. ICD implants may also have a bad impact on body image perception and lead to the feeling of being "impaired" and useless. ICDs have in fact been linked to many psychiatric comorbidities like anxiety and depression, but also post-traumatic stress disorder and adjustment disorders.

Keywords

Cardiomyopathies · Channelopathies · Sudden death · Implantable cardioverter-defibrillator · Depression · Anxiety

Introduction

Heart and brain are in close relation, and this is true mostly in the case of heart diseases causing an increased risk of sudden cardiac death. The increased risk of sudden cardiac death itself or the subsequent need of an implantable cardioverter defibrillator (ICD) can cause mood disorders such as anxiety, depression, and substance abuse. Many factors may play a role in this regard such as the presence of a heart disease, the presence of other family members affected, the need of a chronic therapy or, on the contrary, the absence of a specific therapy, and finally the need of a cardiac implantable device. In this complex scenario, further complicated by the interindividual variability, it is quite difficult to weigh the role of every single factor. The aim of this chapter is to discuss how different structural and non-structural heart diseases could influence the brain's dynamics resulting in mood disorders.

Living with the Risk of Sudden Cardiac Death

The advancement in genetic techniques has recently provided the opportunity of identifying familiar diseases linked to a risk of sudden cardiac death since the postnatal period. These diseases include cardiomyopathies as well as the cardiac "channelopathies" [1]. Differently from other form of inheritable pathologies (such as Huntington disease) for which no treatment is available, familiar cardiac arrhythmia syndromes should benefit from prophylactic measures and, eventually, implantable cardioverter-defibrillators which have consistently reduced mortality and morbidity. However, due to their reduced penetrance, a large number of diagnosed individuals would never experience symptoms or sudden death [2]. This uncertainty about possible life-threatening outcomes creates great distress among patients and their caregivers, especially when dealing with the interpretation of cardiac signs and symptoms [3]. Living with a potentially life-threatening illness exerts a dramatic impact on several aspects of everyday life and well-being: each subject must face several difficulties in dealing with present/future personal relationships, altered body identity, limitation in social as well as physical activity. Eventually she/he must rebuild a new normality, starting from her/his resiliency and personal attitudes [4], a process which is not always smooth and linear.

Among familiar diseases with a risk of sudden cardiac death, hypertrophic cardiomyopathy (HCM), affecting 1 in 500 people, is the most common cause of premature sudden cardiac death [5]. The HCM is characterized by asymmetrical left ventricular hypertrophy with an extreme phenotypic variability, ranging from being completely asymptomatic during the entire lifespan to experiencing chest pain, dyspnea, syncope, or sudden death at any age [5]. Despite the potential psychological/psychiatric consequences of HCM, the first study evaluating psychiatric comorbidities in an HCM sample dated to 2008 [6]. The authors observed an elevated prevalence of mood disorders (especially major depression), anxiety disorders (particularly panic disorder), and substance use disorders. HMC patients with comorbid depression or anxiety were generally older and perceived themselves to be at high risk of death. Among clinical symptoms, only chest pain was significantly associated with depression and anxiety [6]. This may be related to considering chest pain as a more pregnant sign of impending mortality compared to dyspnea; on the other hand, altered visceral perception

associated with depression and anxiety may foster an interpretation of normal emotional symptoms as evidence of an imminent cardiac arrest. Of note, despite this correlation with chest pain, presence of psychiatric comorbidities was not correlated with the severity of the disease. In a subsequent study [7], HCM individuals were found more depressed than the general population but with rates of depression similar to patients with coronary artery disease. Consistently with previous report, there was no correlation between severity of depression and severity of HCM. Of note, longitudinal follow-up of HCM patients did not show a temporal pattern for psychiatric comorbidities: Patients were not more depressed immediately after the diagnosis than after 5 years from testing results. A recent review [8] summarized the results of studies which focused on self-report depressive symptoms [7, 9, 10], on self-report anxiety symptoms [9], and on DSM-defined psychiatric conditions [6]. Overall, 21% of HCM patients met the criteria for depression and 37% for anxiety disorders. Despite these figures, there are no studies evaluating potential strategies for preventing/treating psychiatric comorbidities in this population.

Among familiar cardiac disease with a risk of sudden death, another disorder is represented by long QT syndrome (LQTS), affecting at least 1 in 2500 individuals [11]. LQTS symptoms are represented by cardiac ventricular arrhythmias, leading to dizziness, syncope, and eventually sudden death, often before the age of 40 (Tester and Ackerman) [12]. Diagnosis is made combining familiar history, clinical symptoms, and instrumental findings (ECG, Holter ECG, etc.). However, as for HCM, penetrance and phenotypic expression is quite variable, with nearly 50% of mutation carriers who would never manifest any symptoms of LQTS and 15% of mutation carriers whom would not display even any ECG signs of the disease. This uncertainty about outcomes is potentially a threat for an individual's capacity to maintain control over everyday life. The first longitudinal study focusing on the psychological consequences of predictive testing for LQTS showed that levels of distress in patients returned to normal values for the general population after 18 months from testing, irrespectively of the carriership status [13]. However, symptomatic LQTS patients (that is with arrhythmic events) were generally more depressed than asymptomatic LQTS patients or healthy controls [14]. Additionally, symptomatic LQTS subjects were more prone to develop depression in response to stressful life events compared to asymptomatic ones [15]. The link between LQTS and depression appeared to be gender-mediated: in fact, the correlation between symptomatic LQTS and elevated levels of depressive symptoms was present only in men, while women seemed unaffected [16]. Considering temperamental characteristics associated with LQTS, patients with this syndrome reported higher level of harm avoidance than the general population, irrespectively of their symptom status [17]. Harm avoidance is a temperamental trait which is associated with fear and unpleasant emotions and low level of happiness during stress [18]. Additionally, harm avoidance is linked to low parasympathetic control of the heart rate which could eventually lead to cardiac events [19].

The problem of dealing with depression in LQTS is of extreme importance and several factors need to be taken into consideration in order to provide better care for these patients. First of all, depression and arrhythmic events are deeply intertwined, with depression increasing the risk of ventricular arrhythmia [20]. Thus, a screening for the presence of subthreshold depressive symptoms should be relevant in LQTS. Secondly, almost all commonly used antidepressants are at risk of prolonging the QT interval, thus preventing its use in LQTS patients [21]. As a consequence, identifying LQTS patients at risk for depression could be useful to initiate a strict monitoring: this could lead to a prompt response in early stage of depression in which psychotherapy could be used.

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is another familiar cardiac disease with risk of sudden death. CPVT main symptoms are generally exercise-induced syncope or sudden death. CPVT is associated with a normal ECG during rest but an altered ECG during exercise [22]. Unfortunately, CPVT is one of the most lethal hereditary cardiac disease with sudden cardiac death in more than 30% of CPVT individuals [22]. Despite this datum, the first study on well-being and psychological outcomes of CPVT patients has been published in 2018

[23]. The authors showed that patients with CPVT had poorer psychological functioning compared to the general population, with higher levels of depression, anxiety, and post-traumatic stress symptoms. There was a negative correlation between psychosocial functioning and age, with younger people displaying the worst outcomes. Specifically in children with CPVT, parent reports showed overall poor quality of life (impacting all domains from physical to school functioning) in their children. All parents declared the need for specific support strategies for affected children.

The last heritable arrhythmia syndrome which we will analyze in this chapter is Brugada syndrome (BrS). BrS is characterized by an ECG pattern of coved type ST-segment elevation in the right precordial leads (V1 through V3) and an increased risk for sudden cardiac death resulting from episodes of polymorphic ventricular tachyarrhythmias [24]. The first manifestation of BrS may occur in adulthood and sudden death typically happened during sleep. As the familiar cardiac diseases described in previous paragraphs, BrS has an incomplete penetrance and a highly variable phenotypic expression, ranging from asymptomatic individuals to sudden death in the first years of life. There is no current epidemiological data on the prevalence of psychiatric comorbidities in BrS. However, it has been reported that BrS may present with physical symptoms of anxiety and therefore misdiagnosed and referred to the psychiatrist instead of the cardiologist [25]. Of note, as for LQTS, many antidepressants as well as mood stabilizers are deemed responsible for exacerbating or triggering BrS. Therefore, therapeutic options in patients with BrS and comorbid severe depression and/or anxiety are limited: two case reports supported the use of mirtazapine [25, 26], an atypical antidepressant, or transcranial magnetic stimulation [26]. However, more studies are needed to address this issue.

Implantable Cardioverter-Defibrillators: Friends or Foe?

Familiar cardiac diseases with a risk of sudden death benefit from behavioral and lifestyle adaptation. In several cases, the use of implantable cardioverter defibrillator (ICD) is the best therapeutic option. The number of implantable cardioverter defibrillators (ICD) and pacemakers has increased significantly during the past decades as a result of the large amount of evidence supporting the positive effect on survival [27].

Several recent reviews have explored the complex issue of psychosocial adjustment in patients with an ICD [28–32]. In fact, living with an ICD is generally associated with multifaceted emotions, an entangling mixture of optimism and fear.

As regarding quality of life (QoL), a recent systematic review of randomized controlled trials [28] has summarized the results of seven trials, evaluating the impact of ICD not only on mortality but also on QoL. Of the two secondary prevention studies included in the review, one reported a positive impact of ICD on QoL [33], while the other did not observe differences in QoL between ICD and antiarrhythmic medications [34]. Results from the five primary prevention selected studies [35–39] showed more consistent positive findings, favoring ICD versus other types of treatment. Only one primary prevention study reported a poor quality of life in patients with ICD: however, it was the only trial using a larger device with a more invasive and unaesthetic method of implantation (open chest with abdominal pocket) [36]; this difference may explain the conflicting findings as the physical and aesthetic appearance of the device seemed to exert a significant impact on psychosocial functioning especially in women [27]. The review from da Silva reported a mixed evidence for association between ICD shocks and QoL: overall this correlation seemed to be time-mediated with a decreasing impact on QoL as time passed from the ICD shock.

Focusing on the psychological status of patients with ICD, there are several aspects to consider [32]. Firstly, the experience of ICD shocks is a significant worry for the patient. The shock episodes could be divided in objective shocks (recorded by the ICD) and phantom shocks (when the patient feels the shock sensation even with no recorded trace by the ICD). Both types of ICD shocks are dramatic and generally unexpected, with no foreboding sensations of the impeding shock [40]. Consistently across

numerous qualitative investigations, patients receiving ICD shocks tend to use similar terms to describe the experience like "bomb," "explosion," "lightning," "electric shock," or "sticking your finger in the light socket" [32]. All these expressions are characterized by the intensity which match the physical sensation of pain.

Secondly, the uncertainty about the outcomes following ICD implantation may determine a significant psychological distress for patients and caregivers. Immediately after implantation, patients experience a complex mix of negative emotions, predominantly anxiety and fear [41]. Anxiety is mainly driven by the unpredictability of shock and by the fear of a potential loss of independence [32] and displays important gender differences (women are more anxiety prone than men after ICD implant). This difference appears mediated by heightened somatosensory amplification (the tendency to perceive normal somatic sensations as being potentially dangerous) in women [42]. Conversely, fear experienced by patients is commonly related to sudden death, to failure of the device and possibility of hurting the partner during sexual activity [32]. The unpredictability of the disease's course and the number of ICD shocks may become the trigger for repetitive negative thinking and rumination: recurrent ICD shocks may represent a potential rapid progression of the disease, while no shock or phantom shock may lead the patient to doubt the utility of the device.

The feeling of uncertainty about the future is potentially a threat to the individual's locus of control, that is the degree to which a person believes to exert control on the outcomes of the events of their lives: specifically it could be hypothesized that the balance between internal and external locus of control would move toward a greater impact of the external; people with ICD would blame the ICD (the external factor) as the responsible for negative events in their lives.

Thirdly, as mentioned above, ICD implants may have a detrimental effect on body image perception. Women are more sensitive to this concern, especially in younger age, when the scars left by the implant are a motive of social embarrassment [43].

Fourthly, driving restrictions due to ICD may foster a sense of "feeling impaired," of uselessness and a loss of independence, a need for other's help [32]. Several people could not be at ease when receiving help from others and feel themselves as burden for their loved ones.

Finally, two important aspects impacting recovery of patients with ICD are related to social and familiar support as well as on acceptance of the condition and on developing coping strategies. In fact, ICD subjects with adequate family and social support usually have better outcomes and shorter recovery time [44]. Fostering and developing a social network for patients with ICD seems a cost-effective strategy to improve psychological status and outcomes in this group. Additionally, a specific focus on developing coping strategies and improving acceptance of the condition in these subjects should be carefully considered. In fact, a recent Swedish study reported that ICD patients rarely used coping strategies, among which optimism was the most common: [45] evaluating coping strategies before the implant must be important in order to define the pattern of care after discharge and to identify patients which may benefit from individual or group psychotherapy. Better coping strategies would result in faster adaptation to limitations inherent to ICD implantation, such as pain, weakness, and negative emotions [46].

Psychiatric comorbidities related to ICD are more commonly anxiety and depression. The identification of these comorbidities is of primary interest as their presence is often related to worst outcome for the patients. The link between anxiety and worst cardiac outcomes is mediated by psychophysiological and behavioral mechanisms: The first ones are mostly represented by inappropriate activation of the autonomic nervous systems in response to emotional stimuli such as fear and anxiety: this will induce directly and through an increase in catecholamine levels vasoconstriction, rise in blood pressure, and alteration of heart rate and rhythm. The behavioral mechanism connecting anxiety and cardiac outcome are represented by the fact that subjects experiencing more anxiety frequently indulge in unhealthy lifestyle habits, such as eating junk food, smoking, abusing of alcohol, and being sedentary which in turn could worsen the course of the cardiac disease [47]. Unfortunately, however, our data about prevalence of these conditions rely mainly on self-

report questionnaires [31]. Anxiety was assessed by means of diagnostic interview only in a few trials [48–51] and rates of clinically relevant anxiety vary between 4.2% and 37.5%. Higher prevalence was observed in patients with device shock compared to patients who never received a shock. Dealing with anxiety in patient with ICD may represent a challenge: Apart from using medications, cognitive behavioral psychotherapy (CBT) shows greater benefits for the patient. A recent systematic review has highlighted the positive effect of CBT on anxiety in ICD patients [52], even if several methodological problems were observed in the included studies. Of note, a randomized controlled trial performed in 2015 has reported a positive effect of CBT on anxiety in ICD patients after a short treatment period (three sessions) [53].

As for anxiety, most studies evaluate depressive symptoms by means of self-administered measures. Prevalence rates of clinically assessed current depressive episode vary from 8% to 32.5% [49, 54], with higher rates in patients having received a ICD shock. Of note, these numbers are low and seem to point out that ICD patients manifest a good adjustment. However, identification of people with ICD at risk for developing a depressive episode is recommended. Risk factors for depression in ICD are older age, absence of significant relationships, and self-care dependency [55]. Potential treatment may consist in educational strategies concerning ICD functioning as well as CBT.

Post-traumatic stress disorder (PTSD) is another mental disorder frequently observed in ICD patients, affecting 10–15% of ICD recipients [56]. PTSD correlates with 5-year mortality in patients with an ICD [57] and with higher rates of cardiac morbidity and mortality. ICD patients with PTSD tend to be younger and PTSD symptoms surprisingly do not appear related to ICD shock. Trajectories of PTSD symptoms over time from implant show slight but constant decrease of severity [58]. As for other disorders, PTSD responds to CBT: [59] in fact, a randomized controlled trial showed greater reduction of PTSD symptoms in CBT compared to usual care, especially for patients with high symptoms severity. Patients with low severity of PTSD symptoms showed small improvement in both CBT and standard care group [60]. Apart from CBT, positive findings were observed in trials using the Eye Movement Desensitization and Reprocessing (EMDR) techniques. [61]

Other clinically relevant mental disorders observed in ICD patients were adjustment disorders [62], a psychiatric category that lays between normality and mental disorders, characterized by distress and emotional disturbances, occurring after important life events, physical illness, or possibility of important physical illness.

As the occurrence of psychiatric conditions in ICD patients seems associated with positive familiar psychiatric history and inadequate social support, it is striking the need for adequate screening before implantation. Additionally, future studies should be design to better target the unmet need for psychological support of this patient group, determining also the best therapeutic strategy to offer.

Cross-References

- ▶ Anxiety, Anger, Personality, and Heart Disease
- ▶ Borderline Personality Disorder and the Heart
- ▶ Cardiac Transplantation and Psychopathology
- ▶ Consequences of Altered Cardiac Activity on Brain Activity
- ▶ Depression and Cardiovascular Diseases
- ▶ Major Psychiatric Complications of Cardiac Surgery

References

1. Ackerman MJ, Priori SG, Willems S, Berul C, Brugada R, Calkins H, et al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies: this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). Hear Rhythm. 2011; 8(8):1308–39.
2. Michels M, Soliman OII, Phefferkorn J, Hoedemaekers YM, Kofflard MJ, Dooijes D, et al. Disease penetrance and risk stratification for sudden cardiac death in

asymptomatic hypertrophic cardiomyopathy mutation carriers. Eur Heart J. 2009;30(21):2593–8.
3. Hamang A, Eide GE, Rokne B, Nordin K, Øyen N. General anxiety, depression, and physical health in relation to symptoms of heart-focused anxiety- a cross sectional study among patients living with the risk of serious arrhythmias and sudden cardiac death. Health Qual Life Outcomes. 2011;9(1):100.
4. Subasic K. Living with hypertrophic cardiomyopathy. J Nurs Scholarsh. 2013;45(4):371–9.
5. Van Driest SL, Ommen SR, Tajik AJ, Gersh BJ, Ackerman MJ. Yield of genetic testing in hypertrophic cardiomyopathy. Mayo Clin Proc. 2005;80(6):739–44.
6. Morgan JF, O'Donoghue AC, McKenna WJ, Schmidt MM. Psychiatric disorders in hypertrophic cardiomyopathy. Gen Hosp Psychiatry. 2008;30(1):49–54.
7. Igoumenou A, Alevizopoulos G, Anastasakis A, Stavrakaki E, Toutouzas P, Stefanadis C. Depression in patients with hypertrophic cardiomyopathy: is there any relation with the risk factors for sudden death? Heart Asia. 2012;4(1):44–8.
8. Suárez Bagnasco M, Núñez-Gil IJ. Psychological disorders in adults with inherited cardiomyopathies and Takotsubo syndrome. Medwave. 2016;16(5):e6460.
9. Ingles J, Lind JM, Phongsavan P, Semsarian C. Psychosocial impact of specialized cardiac genetic clinics for hypertrophic cardiomyopathy. Genet Med. 2008;10(2):117–20.
10. Serber ER, Sears SF, Nielsen CD, Spencer WH, Smith KM. Depression, anxiety, and quality of life in patients with obstructive hypertrophic cardiomyopathy three months after alcohol septal ablation. Am J Cardiol. 2007;100(10):1592–7.
11. Zaklyazminskaya E V., Abriel H. Prevalence of significant genetic variants in congenital long QT syndrome is largely underestimated. Front Pharmacol. 2012;3:72. https://doi.org/10.3389/fphar.2012.00072
12. Tester DJ, Ackerman MJ. Genetic testing for potentially lethal, highly treatable inherited cardiomyopathies/channelopathies in clinical practice. Circulation. 2011;123(9):1021–37.
13. Hendriks KSWH, Hendriks MMWB, Birnie E, Grosfeld FJM, Wilde AAM, van den Bout J, et al. Familial disease with a risk of sudden death: a longitudinal study of the psychological consequences of predictive testing for long QT syndrome. Hear Rhythm. 2008;5(5):719–24.
14. Hintsa T, Keltikangas-Järvinen L, Puttonen S, Ravaja N, Toivonen L, Kontula K, et al. Depressive symptoms in the congenital long QT syndrome. Ann Med. 2009;41(7):516–21.
15. Hintsa T, Jokela M, Elovainio M, Määttänen I, Swan H, Hintsanen M, et al. Stressful life events and depressive symptoms among symptomatic long QT syndrome patients. J Health Psychol. 2016;21(4):505–12.
16. Wesołowska K, Elovainio M, Koponen M, Tuiskula AM, Hintsanen M, Keltikangas-Järvinen L, et al. Is symptomatic long QT syndrome associated with depression in women and men? J Genet Couns. 2017;26(3):491–500.
17. Määttänen I, Hintsa T, Toivonen L, Swan H, Pulkki-Råback L, Hintsanen M, et al. Cloninger's temperament traits and inherited long QT syndrome. J Psychosom Res. 2011;71(4):245–9.
18. Puttonen S, Ravaja N, Keltikangas-Järvinen L. Cloninger's temperament dimensions and affective responses to different challenges. Compr Psychiatry. 2005;46(2):128–34.
19. Tsuji H, Larson MG, Venditti FJ, Manders ES, Evans JC, Feldman CL, et al. Impact of reduced heart rate variability on risk for cardiac events: the Framingham heart study. Circulation. 1996;94(11):2850–5.
20. Watkins LL, Blumenthal JA, Davidson JRT, Babyak MA, McCants CB, Sketch MH. Phobic anxiety, depression, and risk of ventricular arrhythmias in patients with coronary heart disease. Psychosom Med. 2006;68(5):651–6.
21. Beach SR, Celano CM, Sugrue AM, Adams C, Ackerman MJ, Noseworthy PA, et al. QT prolongation, Torsades de Pointes, and psychotropic medications: a 5-year update. Psychosomatics. 2018;59(2):105–22.
22. Priori SG, Napolitano C, Memmi M, Colombi B, Drago F, Gasparini M, et al. Clinical and molecular characterization of patients with catecholaminergic polymorphic ventricular tachycardia. Circulation. 2002;106(1):69–74.
23. Richardson E, Spinks C, Davis A, Turner C, Atherton J, McGaughran J, et al. Psychosocial implications of living with catecholaminergic polymorphic ventricular tachycardia in adulthood. J Genet Couns. 2018;27(3):549–57.
24. Chen PS, Priori SG. The Brugada syndrome. J Am Coll Cardiol. 2008;51(12):1176–80.
25. Chen JJ, Sangha RS. Treatment of anxiety and depression in a patient with Brugada syndrome. Case Rep Psychiatry. 2014;2014:478397.
26. Alampay MM, Haigney MC, Flanagan MC, Perito RM, Love KM, Grammer GG. Transcranial magnetic stimulation as an antidepressant alternative in a patient with Brugada syndrome and recurrent syncope. Mayo Clin Proc. 2014;89(11):1584–7.
27. Savastano S, Rordorf R, Scotti Foglieni A, Klersy C, Vicentini A, Petracci B, et al. Submammary device implantation. Good long-term performance and better patients' satisfaction. A single-center experience. Int J Cardiol. 2016;221:820–6.
28. da Silva KR, Costa R, Rodrigues CG, Schasechter A, Nobre MC, Passman R, et al. Quality of life in patients with implantable cardioverter–defibrillator: systematic review of randomized controlled trials. Eur J Cardiovasc Nurs. 2018;17(3):196–206.
29. Kajanová A, Bulava A, Eisenberger M. Factors influencing psychological status and quality of life in patients with implantable cardioverter-defibrillators [Internet]. Neuroendocrinol Lett. 2014 [cited 2019 Nov 20];35:54–58. Available from: https://pdfs.

semanticscholar.org/77b2/1d420a24ea2d31ebb9015a48456b927b7644.pdf
30. Manuel A, Dobbin-Williams K, Swab M. The experiences of adults living with an implantable cardioverter defibrillator for cardiovascular disease: a systematic review of qualitative evidence protocol. JBI Database Syst Rev Implement Rep. 2015;13(6):82–95.
31. Manzoni GM, Castelnuovo G, Compare A, Pagnini F, Essebag V, Proietti R. Psychological effects of implantable cardioverter defibrillator shocks. A review of study methods. Front Psychol. 2015;6:39.
32. Ooi SL, He HG, Dong Y, Wang W. Perceptions and experiences of patients living with implantable cardioverter defibrillators: a systematic review and meta-synthesis. Health Qual Life Outcomes. 2016;14:160.
33. Irvine J, Dorian P, Baker B, O'Brien BJ, Roberts R, Gent M, et al. Quality of life in the Canadian implantable defibrillator study (CIDS). Am Heart J. 2002;144(2):282–9.
34. Schron EB, Exner DV, Yao Q, Jenkins LS, Steinberg JS, Cook JR, et al. Quality of life in the antiarrhythmics versus implantable defibrillators trial: impact of therapy and influence of adverse symptoms and defibrillator shocks. Circulation. 2002;105(5):589–94.
35. Mark DB, Anstrom KJ, Sun JL, Clapp-Channing NE, Tsiatis AA, Davidson-Ray L, et al. Quality of life with defibrillator therapy or amiodarone in heart failure. N Engl J Med. 2008;359(10):999–1008.
36. Namerow PB, Firth BR, Heywood GM, Windle JR, Parides MK. Quality-of-life six months after CABG surgery in patients randomized to ICD versus no ICD therapy: findings from the CABG patch trial. PACE – Pacing Clin Electrophysiol. 1999;22(9):1305–13.
37. Noyes K, Corona E, Zwanziger J, Hall WJ, Zhao H, Wang H, et al. Health-related quality of life consequences of implantable cardioverter defibrillators: results from MADIT II. Med Care. 2007;45(5):377–85.
38. Passman R, Subacius H, Ruo B, Schaechter A, Howard A, Sears SF, et al. Implantable cardioverter defibrillators and quality of life: results from the defibrillators in nonischemic cardiomyopathy treatment evaluation study. Arch Intern Med. 2007;167(20):2226–32.
39. Strickberger SA, Hummel JD, Bartlett TG, Frumin HI, Schuger CD, Beau SL, et al. Amiodarone versus implantable cardioverter-defibrillator: randomized trial in patients with nonischemic dilated cardiomyopathy and asymptomatic nonsustained ventricular tachycardia – AMIOVIRT. J Am Coll Cardiol. 2003;41(10):1707–12.
40. Morken IM, Severinsson E, Karlsen B. Reconstructing unpredictability: experiences of living with an implantable cardioverter defibrillator over time. J Clin Nurs. 2010;19(3–4):537–46.
41. McDonough A. The experiences and concerns of young adults (18–40 years) living with an implanted cardioverter defibrillator (ICD). Eur J Cardiovasc Nurs. 2009;8(4):274–80.
42. Versteeg H, Baumert J, Kolb C, Pedersen SS, Denollet J, Ronel J, et al. Somatosensory amplification mediates sex differences in psychological distress among cardioverter-defibrillator patients. Health Psychol. 2010;29(5):477–83.
43. Vazquez LD, Kuhl EA, Shea JB, Kirkness A, Lemon J, Whalley D, et al. Age-specific differences in women with implantable cardioverter defibrillators: an international multi center study. PACE – Pacing Clin Electrophysiol. 2008;31(12):1528–34.
44. Palacios-Ceña D, Losa ME, Fernández-de-las-Peñas C, Salvadores-Fuentes P. Living with life insurance: a qualitative analysis of the experience of male implantable defibrillator recipients in Spain. J Clin Nurs. 2011;20(13–14):2003–13.
45. Flemme I, Hallberg U, Johansson I, Strömberg A. Uncertainty is a major concern for patients with implantable cardioverter defibrillators. Hear Lung J Acute Crit Care. 2011;40(5):420–8.
46. Williams AM, Young J, Nikoletti S, McRae S. Getting on with life: accepting the permanency of an implantable cardioverter defibrillator. Int J Nurs Pract. 2007;13(3):166–72.
47. Molinari E, Parati G, Compare A. Clinical psychology and heart disease. Clinical psychology and heart disease. Springer; 2006. p. 1–515. https://doi.org/10.1007/978-88-470-0378-1
48. Berg SK, Herning M, Svendsen JH, Christensen AV, Thygesen LC. The screen-ICD trial. Screening for anxiety and cognitive therapy intervention for patients with implanted cardioverter defibrillator (ICD): a randomised controlled trial protocol. BMJ Open. 2016;6(10):e013186.
49. Jacq F, Foulldrin G, Savouré A, Anselme F, Baguelin-Pinaud A, Cribier A, et al. A comparison of anxiety, depression and quality of life between device shock and nonshock groups in implantable cardioverter defibrillator recipients. Gen Hosp Psychiatry. 2009;31(3):266–73.
50. Van Den Broek KC, Nyklíček I, Denollet J. Anxiety predicts poor perceived health in patients with an implantable defibrillator. Psychosomatics. 2009;50(5):483–92.
51. Van Den Broek KC, Nyklíček I, Van Der Voort PH, Alings M, Denollet J. Shocks, personality, and anxiety in patients with an implantable defibrillator. PACE – Pacing Clin Electrophysiol. 2008;31(7):850–7.
52. Maia ACCO, Braga AA, Soares-Filho G, Pereira V, Nardi AE, Silva AC. Efficacy of cognitive behavioral therapy in reducing psychiatric symptoms in patients with implantable cardioverter defibrillator: an integrative review. Brazilian J Med Biol Res. 2014;47(4):265–72.
53. Qintar M, George JJ, Panko M, Bea S, Broer KA, St. John J, et al. A prospective study of anxiety in ICD patients with a pilot randomized controlled trial of cognitive behavioral therapy for patients with

moderate to severe anxiety. J Interv Card Electrophysiol. 2015;43(1):65–75.
54. Amiaz R, Asher E, Rozen G, Czerniak E, Levi L, Weiser M, et al. Reduction in depressive symptoms in primary prevention ICD scheduled patients – one year prospective study. Gen Hosp Psychiatry. 2017;48:37–41.
55. Wong MFF. Factors associated with anxiety and depression among patients with implantable cardioverter defibrillator. J Clin Nurs. 2017;26(9–10):1328–37.
56. Morken IM, Bru E, Norekvål TM, Larsen AI, Idsoe T, Karlsen B. Perceived support from healthcare professionals, shock anxiety and post-traumatic stress in implantable cardioverter defibrillator recipients. J Clin Nurs. 2014;23(3–4):450–60.
57. Ladwig KH, Baumert J, Marten-Mittag B, Kolb C, Zrenner B, Schmitt C. Posttraumatic stress symptoms and predicted mortality in patients with implantable cardioverter-defibrillators: results from the prospective living with an implanted cardioverter-defibrillator study. Arch Gen Psychiatry. 2008;65(11):1324–30.
58. Habibović M, Denollet J, Pedersen SS. Posttraumatic stress and anxiety in patients with an implantable cardioverter defibrillator: trajectories and vulnerability factors. PACE – Pacing Clin Electrophysiol. 2017; 40(7):817–23.
59. Irvine J, Firestone J, Ong L, Cribbie R, Dorian P, Harris L, et al. A randomized controlled trial of cognitive behavior therapy tailored to psychological adaptation to an implantable cardioverter defibrillator. Psychosom Med. 2011;73(3):226–33.
60. Ford J, Rosman L, Wuensch K, Irvine J, Sears SF. Cognitive–behavioral treatment of posttraumatic stress in patients with implantable Cardioverter defibrillators: results from a randomized controlled trial. J Trauma Stress. 2016;29(4):388–92.
61. Jordan J, Titscher G, Peregrinova L, Kirsch H. Manual for the psychotherapeutic treatment of acute and posttraumatic stress disorders following multiple shocks from implantable cardioverter defibrillator (ICD). Psychosoc Med. 2013;10:Doc09.
62. Morris PL, Badger J, Chmielewski C, Berger E, Goldberg RJ. Psychiatric morbidity following implantation of the automatic implantable cardioverter defibrillator. Psychosomatics. 1991;32(1):58–64.

Major Psychiatric Complications of Cardiac Surgery

22

Benedetta Vanini, Claudio Placenti, and Andrea M. D'Armini

Contents

Abstract

Neurocognitive and psychiatric conditions after cardiac surgery are frequent and have an impact on postoperative recovery, adherence to pharmacological and rehabilitation therapy, and, ultimately, a significant effect on mortality. In a broader framework, neuropsychiatric disorders affect both patient's socio-occupational functioning and quality of life. Patients requiring cardiac surgery could have significant risk factor for developing neuropsychiatric disorder or already show subthreshold conditions or diagnosed disorders that could worsen after the intervention. All these factors need to be acknowledged and targeted to improve the overall outcome. In the postoperative period, patients may experience several complications including depressive disorders, anxiety disorders, post-traumatic stress disorder, delirium, and neurocognitive damage. These conditions have all been related to general and specific pathological factors, both modifiable and non-modifiable, that will be discussed in this chapter. A brief review of recent etiological theories has also been provided for the major neuropsychiatric complications. The complex assessment of neurological and psychiatric problems will also be discussed in order to justify the heterogeneity in prevalence estimates of these conditions and to increase the awareness of the clinician involved in the care

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*,
https://doi.org/10.1007/978-3-030-28008-6_28

management of this delicate category of patients. Moving from the strictly scientific perspective, this chapter will further provide an overview of the general and specific intervention needed to improve the outcome of patients undergoing cardiac surgery and presenting with neuropsychiatric complications [98].

In conclusion, this chapter advocates for a better understanding of the impact, the role, and the therapeutic strategies of neuropsychiatric complications of cardiac surgery, providing a general reference for clinicians.

Keywords

Neuropsychiatric complications · Cardiac surgery · Neurological outcomes · Post-traumatic brain disorder · Depression · Postoperative cognitive dysfunction · Delirium

Introduction

Cardiac surgery is often associated with neurological adverse events, including stroke and transient ischemic attack. Over the years, some techniques have been developed with the aim of reducing the risk of neurological complications of major cardiovascular surgical procedures. The techniques include, for example, the off-pump coronary artery bypass graft (off-pump CABG) [1], anterograde cerebral perfusion and hypothermia during aortic bow surgery and distal and cerebrospinal aortic perfusion fluid drainage in thoracic-abdominal aortic surgery [99]. As a result of the significant reduction of major neurological adverse events, the attention has shifted to less well understood and often subtle neuropsychiatric complications such as neurocognitive disorders and postoperative cognitive dysfunction (POCD). The scientific literature has also grown about the psychiatric disorders associated with such a traumatic situation, especially post-traumatic stress disorder (PTSD), depression, and anxiety. These topics are clinically relevant as neuropsychological and psychological problems can also affect functional independence, resulting in increased care requirements, reduced workforce participation, and greater reliance on social well-being and long-term mortality [2]. The precise etiology of neuropsychological and psychological problems is not entirely clear. However, this etiology is currently a focus on research: increased cerebral metabolic demand, deranged cerebral autoregulation, excessive cerebral microembolic load, consistently lower regional cerebral oxygen saturation (rSO_2) levels in patients, disrupted blood–brain barrier, and endothelial damage, for example, are all dysfunctions that expose patients to neuro-inflammation, which has been suggested to lead to delirium susceptibility [3]. Furthermore, POCD may be associated to a low-grade baseline systemic inflammatory reaction that occurs after cardiac surgery. This inflammatory burden could be present in elderly and in those affected by neurodegenerative diseases or atherosclerosis [4]. Initial preoperative low-baseline scores during neuropsychological testing are associated with hypertension, age, and low education levels, indicating mild cognitive decline: this may increase, for example, the risk of POCD [5]; J.A. DiGangi et al. [6] systematically reviewed prospective studies of trauma and PTSD to determine how pre-trauma factors affected the development of PTSD symptomatology following an index trauma exposure. The authors identified six categories of predictors: cognitive abilities, coping and response styles, personality factors, psychopathology, psychophysiological factors, and social ecological factors (e.g., family of origin, social support, poverty); in the reciprocal association between depression and CVD, several biological mechanisms might be involved, including inflammation, platelet reactivity, autonomic dysregulation, circadian rhythm disruption, hormone imbalance, neurotrophins, lifestyle, and metabolic syndrome [7].

From a review of the literature, we have examined what appear to be the main psychiatric problems that can be observed after cardiac surgery, without going into the specifics of the main cardiac pathologies.

The aim of this chapter is to set out an analytical account of neuropsychiatric and psychiatric conditions associated with cardiac surgery.

Postoperative Delirium

Despite the use of good clinical practice [8], some important studies indicate that 37% of patients undergoing cardiac surgery develop delirium, a complication that can prolong the admission time in the intensive care unit (ICU), complicate recovery, and increase the risk of death [9]. Several authors have recognized the importance of making an early diagnosis of delirium [10].

Delirium is considered an acute mental disorder characterized by inattention, with several causes, including medical illness and withdrawal from medications or substances [10]. According to the definition provided in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) [11], five criteria need to be present in order to diagnose this condition. The diagnosis of delirium is based on clinical assessment since no clear biomarker has been introduced in the clinical practice, except some aspecific biomarkers (e.g., increased urea and creatinine levels) [12]. However, the follow-up of the clinical status could rely on standardized monitoring tools including the intensive care checklist for delusion screening and the confusion assessment method for the intensive care units (CAM-ICU) [10, 13, 14].

The critically ill patient can show three types of delirium: hypoactive (predominant but often underdiagnosed), hyperactive, and mixed [10]. Hypoactive delirium is characterized by lethargy, confusion, sedation, low level of awareness, periods of poor attention, drowsiness, deprivation, and apathy. Hyperactive delirium manifests itself with agitation, hallucinations, delusional ideas, paranoia, disorientation, disruptive behavior, self-removal of invasive devices, aggressiveness, and pugnacity. Mixed delirium has manifestations of both hyperactive and hypoactive delirium.

The true prevalence of delirium is not yet well defined. Some studies suggest that delirium occurs in cardiac surgery in 10–50% of patients and may not be recognized, especially in patients who are not particularly agitated (the so-called "hypoactive" delirium) [15, 16]. In ICU it is not defined, but several studies report a range from 16% to 89% [10, 17].

After cardiac surgery, delirium is associated with the risk of self-harm (e.g., due to self-extubation, inappropriate removal of lines, and falls), to a substantially longer stay in ICU and to greater mortality [16, 18]. The prevention of delirium and its treatment are important for improving results.

The pathophysiology of delirium is believed to be due to a combination of vulnerability factors and stress factors related to acute disease [19]. In the context of cardiac surgery, the vulnerability reflects the preoperative status of patients and includes age, comorbidity, and low values of preoperative cerebral oximetry [20]. Furthermore, the stress-related elements that may trigger delirium among vulnerable patients undergoing cardiac surgery include complicated procedures, and other mechanisms are likely involved in the pathogenesis of post-cardiac surgery delirium [21].

Risk factors associated with delirium could be classified as modifiable and non-modifiable. The modifiable risk factors are total amount of sedation received, type of analgesic and sedative drugs, number of intravenous infusions, use of mechanical restrictions, duration of stay at ICU, lack of natural light, nonuse of glasses or hearing aid, interventions during sleep hours, and prolonged immobilization. Instead, the non-modifiable risk factors are old age, prior neurological or psychiatric disorders and hypertension, the severity of the illness, mechanical ventilation, urgent surgery, multiple organ failure, metabolic acidosis, and coma [16].

Several studies have investigated some surgical techniques as risk factors of delirium. Norkiene et al. [22] performed a study of 1267 patients undergoing CABG. Patients with low cardiac output in the perioperative period had a significantly greater risk of postoperative delirium. Another study of 8139 [23] patients with CABG and valvular surgery focused on the development of psychotic symptoms, such as hallucinations and delusions, identifying a similar list of independent risk factors. These factors include older age, preoperative renal failure, dyspnea, heart failure, left ventricular hypertrophy, perioperative hypothermia, postoperative hypoxemia,

low hematocrit, renal failure, hypernatremia, infection, and stroke.

Some authors [23] showed that beating heart "off-pump" surgery was not associated with a lower incidence of delirium, which was found in a previous large cohort study [24].

In cardiac surgery, in addition to prevention, the treatment of delirium requires several non-pharmacological interventions and sometimes requires the use of antipsychotic drugs to reduce associated psychotic symptoms and agitation [25]. The multicomponent intervention should follow the assessment by a trained and competent healthcare professional, who would recommend actions tailored to the person's needs. The intervention should encompass adequate hydration, reorientation activities, prevention of sensory deprivations, sleep hygiene, and medication review [26]. In clinical practice, pharmacological interventions are currently used to manage the symptoms of delirium, but the evidence for this is limited. Some studies showed that atypical and typical antipsychotics have a superior efficacy when compared against placebo, but there is no evidence for benzodiazepines superiority [27].

In clinical practice is frequent the use of a variety of antipsychotic agents: oral or intramuscular administration of haloperidol is considered the first-line agent, as no clinical trial has suggested the superiority of other antipsychotics over haloperidol. However, care must be taken to monitor for cardiac adverse effects and extrapyramidal symptoms. It is also recommended to avoid intravenous use whenever possible [27]. Even though in lesser extent than haloperidol, olanzapine may cause extrapyramidal symptoms, but could also show greater sedation, which is the most commonly reported adverse effect [27]. Interestingly this medication could also be available as tablets for oral disintegration. Administration of quetiapine may cause postural hypotension and sedation as the most common reported adverse effects. Consequently, before and during the antipsychotic treatment of delirium, blood pressure, QT-corrected, and serum potassium and magnesium levels should be monitored.

Prakanrattana et al. [28] found that a single dose of risperidone administered soon after recovery from anesthesia could reduce the incidence of postoperative delirium. Furthermore, a trial comparing haloperidol, olanzapine, risperidone, and quetiapine showed that all were equally safe and efficacious in the treatment of delirium, but the response rate to olanzapine was poorer in the older age group (>75 years) [27, 29]. Furthermore, several studies [30, 31] have suggested that benzodiazepines may be associated to a higher risk of delirium than other sedatives.

At present, there is no conclusive evidence to support a single-drug therapy to treat delirium once it has established [10, 15]. However, we need to stress the crucial role of preventive measures. For example, day/night differentiation using change in environment illumination helps to avoid sleep disturbance. Nighttime and the reduction of noise for patients are recommended. Reorientation, reassurance, and facilitating communication using visual/hearing aids are of utmost importance. The crucial role of resting periods has also been studied: many hospitals now enforce a "quiet time" in the afternoon (usually 2 h where no visitors are allowed and only essential procedures are carried out), allowing time for the patients to rest and prevent overstimulation, which can also aggravate delirium. Each physician should consider the underlying pathophysiology: hypotension, hypoxemia, hypoglycemia, and pain that should be specifically addressed. Finally, early mobilization can reduce delirium (including sitting out in a chair and visits outside the ICU once stable) [10, 17].

Delirium in post-cardiac surgery patients over 60 years old was related with lower-adjusted MMSE scores at 1 month but not at the follow-up (6- or 12-month), even in patients with delirium lasting 3 days or longer [32]. Moreover, in cardiac surgery patients, postoperative delirium was correlated with a decrease in IADLs (instrumental activities of day life) at 1 month but not at the follow-up (12-month) [33, 34]. Devore EE et al. [35] found that global cognitive performance was most deeply related with long-term cognitive decline following delirium and that pre-surgical

factors may substantially predict this outcome. This aspect has been specifically addressed in the following paragraph.

Postoperative Cognitive Dysfunction

Postoperative cognitive dysfunction (POCD) is a condition characterized by neurocognitive deficits (in particular memory, concentration, and psychomotor speed) after surgery that may persist for weeks or months.

Cognitive deficits after cardiac surgery are quite common and their incidence is very difficult to identify. However, some studies indicate that after major cardiac intervention, 30–80% of patients could have POCD at the time of hospital discharge and after 6 months 20–40% of patients may still experience cognitive problems. In some patients, the POCD may persist for a year or more.

From a general review of the literature about the diagnosis of POCD [5, 36–39], a core battery of tests could be recommended. The tests encompass the evaluation of specific basic cognitive domains including motor skills, verbal memory, attention, and concentration. Alongside with neurological examination, the effects of concurrent anxiety and depression should be carefully excluded. Whenever the condition should be present, follow-up tests at least 3 months after the procedure is recommended. Despite the first indications, a revision of the POCD following cardiac surgery, which comprised 62 studies, found that there was a high heterogeneity between the applied evaluation batteries [38]. Although the heterogeneity in the definition of POCD remains, the condition can be generally described as a reduction of any cognitive domain after surgery – usually reasoning and memory [40]. This is important to distinguish POCD from postoperative delirium that is considered an attention disorder that usually resolve in days if adequately treated. Unfortunately, the complexity of reaching a consensus definition of POCD is limiting the clear assessment of its incidence, the understanding of causative factors putatively involved, and the evaluation of the implications for the long-term prognosis. What has been suggested however is that, in some patients, the deficit lasts for more than a year [5].

In the early stages of the preoperative period, it is difficult to diagnose POCD given the many variables that should be accounted for: the tail effects of anesthetics, narcotics and benzodiazepines as well as the misinterpretation of POCD in the presence of postoperative delirium [38, 39].

The long-term diagnosis of POCD is also complicated: it is unusual to routinely assess preoperative cognitive functions of account for increased incidence of silent brain infarcts (SBI) already associated with increasing age. In other words, a misdiagnosed pre-existing cognitive impairment could result in overestimating the effect of cognitive dysfunction actually related to surgery procedure [41].

Patients with POCD are at risk of increased hospitalization, long-term care needs, morbidity, and higher mortality as compared to those without post-surgical deficits [42].

Risk factors for POCD include advanced age, low level of education, and greater invasiveness of surgery procedure [43]. Cardiac surgery is recognized to be associated with a higher incidence of POCD when compared to non-cardiac surgery [44]. Cardiopulmonary bypass (CPB) could be the technique responsible for this increased incidence. In particular, the bypass aspects that are declared to involve neuronal damage are microemboli; hypotension; difficulties in management of hypothermia (e.g., fast rewarming); and increased expression of inflammatory and vasoactive molecules induced by shear stress associated with non-pulsatile flow during CPB [20, 45].

However, some studies suggest that POCD cannot be attributed solely to CPB. In fact, several data have shown that long-term cognitive dysfunction among patients undergoing CPB is no worse than that affecting patients undergoing cardiac surgery without CPB [20, 46].

An Italian study investigated the possible effects of circulatory arrest on cognitive functions [47]. The studies describe the surgical procedure for the treatment of chronic thromboembolic hypertension, involving the use of 7–10 min of

repeated moderate hypothermia and circulatory arrest (MHCA), each followed by short periods (5–7 min) of reperfusion. During periods of circulatory arrest and reperfusion, the saturation of cerebral oxygen is monitored by near-infrared spectroscopy (NIRS), a widely recognized monitoring measure of cerebral oxygenation (rSO2).

The study investigated the association between repeated short periods of circulatory arrest with moderate hypothermia during pulmonary endarterectomy (PEA) in patients with chronic thromboembolic pulmonary hypertension (CTEPH) and different neuropsychological dimensions [47]. This technique appeared to be safe of any neuropsychological complication and may even lead to post-surgical psychological improvements such as a reduction in anxiety, depression, and improvement in the quality of life at 3 months. This study followed the indications of another significant research on cognitive functions after cardiac surgery with techniques such as circulatory arrest and hypothermia [48]. More studies are awaited to corroborate these results.

Several studies are investigating the possibility of reducing POCD after surgery based on the modulation of different risk factors. A recent review [49] pinpoints the attention toward the possible role of dexmedetomidine. However, while there is evidence for the neural anti-inflammatory properties of dexmedetomidine, human trials have produced incomplete results regarding its use for the prevention of POCD. Dexmedetomidine could be used as alternative sedative to benzodiazepines in controlling hyperactive postoperative delirium, but further studies are awaited prior to recommend the use of dexmedetomidine for the reduction of POCD.

Alongside with neuropsychiatric complication, some psychiatric conditions need to be carefully considered. Hereinafter, we will focus on PTSD, depression, and anxiety.

Post-traumatic Stress Disorder

The delicate interlinks between this condition and several cardiological problems have been thoroughly addressed in another chapter. Briefly, the ICD-10 diagnosis of post-traumatic stress disorder (PTSD) requires that the patient, first, has been exposed to a traumatic event and, second, suffers from distressing re-experiencing symptoms. Patients will usually also show some symptoms of hyperarousal, avoidance of reminders of the event, and/or emotional numbing. ICD-10 diagnosis requires the presence of several criteria [50] but is beyond the scope of this chapter to provide a detailed description of the diagnostic criteria for PTSD.

Patients undergoing heart surgery are at risk of developing, in addition to mood disorders, PTSD. This appears to be present in 15% of patients [51, 52] and could hinder full recovery. In the perioperative period surrounding cardiac procedures, high levels of stress occur. Schelling et al. found that, despite the correct cardiac procedures, up to 20% of patients had no improvement in the quality of life scores [53]. Out of 148 patients, 20 were affected by PTSD 6 months after undergoing cardiac surgery. This appeared to be strongly correlated with preoperative stress and duration of CPB (e.g., higher risk with 150 vs. 120 min of CPB) [54]. Before addressing the putative biological substrate, we would like to remark the undoubtable psychological relevance of being exposed to the traumatic experience of two life-threatening conditions: the disease requiring a cure and the cure itself, which is frequently perceived by the patient as the greatest risk.

Exposure to stressful events may alter the sensitivity, and thus the responses of the hypothalamic-pituitary-adrenal (HPA) axis when further stressful situations are encountered [54, 55]. The role of exposure to stressful life events on the development of psychopathology (i.e., PTSD and depression) is currently unknown. However, the impact of permanent stress on an individual depends partly on personality traits, such as anxiety [6, 56–58]. Trait anxiety, for example, is common among cardiac patients and associated with major symptoms of PTSD [59]. As discussed in the introduction, to determine how pre-trauma factors affected the development of PTSD symptomatology, an important role is played by six categories of predictors: psychopathology, coping and response styles,

cognitive abilities, psychophysiological factors, personality factors, and social ecological factors (e.g., family of origin, social support, poverty). Examination of these categories revealed that many of these categories, long considered aspects of post-trauma psychopathology, were actually present before the index trauma [6]. As already anticipated, an important role in stress is played by plasma cortisol levels, for example corticosteroid-related insufficiency linked to severe or acute illness, including septic shock and post-cardiac surgery [60]. Postoperative treatment following cardiac surgery has shown a reduction in circulating corticosteroids and a higher incidence of PTSD and chronic stress. A prominent study [61] has shown that the administration of hydrocortisone in the perioperative period was able to reduce chronic stress symptoms, improve quality of life scores, and reduce the incidence of PTSD at a 6-month follow-up [60]. However, these results need to be considered with caution and confirmation studies are awaited.

Regarding pharmacological intervention, the first-line drug treatment of PTSD [27] is the use of SSRI (paroxetine, sertraline, and fluoxetine are the preferred SSRIs) [27, 62, 63]. Antipsychotics appear to be effective for the intrusion symptoms (flashbacks and nightmares) but not the hyperarousal and avoidance symptoms of PTSD, as shown in studies investigating these drugs as monotherapy or as adjunctive treatment [27, 64]. The use of mirtazapine is recommended by NICE [27, 65].

Depression and Anxiety in Cardiac Surgery Patients

Often, when you are dealing with a very stressful event such as a disease, feelings of marked fear, anxiety, and mood disorders can be normal reactions. In some cases, however, reactions to a stressful event may be so marked as to compromise the functioning of the person. It is therefore important to differentiate a normal reaction, a hypothetical "adaptation disorder," from the psychopathology of major psychiatric diseases: depression is a common mental disease worldwide, with depressed mood and/or loss of pleasure in most activities as key symptoms. A proper diagnosis, according to ICD-10 classification system, requires at least two of these three key symptoms: low mood, loss of interest and pleasure, or loss of energy [66]; anxiety is an emotion experienced with symptoms that can be psychological, physical, or a combination of both. When symptoms become overly distressing or disabling, or reduce quality of life, in the context of the absence of any clear external threat, an intervention is necessary [27].

The World Health Organization [67] indicated that only in 2012, 17.5 million people died of cardiovascular disease and 80% of deaths occurred in middle and low income countries. Since the heart is fundamental for life, the related problems concerning it are provoking different behaviors and emotions. In fact, when there is a heart disease, many variables interfere with the progression and healing of the patient [68]. Several studies have found a significant relationship between mood disorders, anxiety, and heart disease. The presence of psychological disorders in patients with heart disease increases the risk of death associated with cardiovascular condition. Consequently, the rehabilitation of a patient with cardiac disease should include, in addition to the organic and physiological aspects, also cognitive, adaptive, and psychological care, especially in the postoperative period [69].

Over the years it has been possible to prove that attention to psychological aspects is particularly important in cases of serious heart disease such as refractory heart failure (HF), in which cardiac transplantation is recognized as the best therapeutic strategy. In these cases, screening psychiatric problems and their treatment is essential to obtain the best post-surgical results. Other chapters discussed in detail the association between psychiatric disorders and individual heart disease. However, the major depressive disorder is probably the most common psychopathology in this patient's group. This disorder is present in more than 20% of patients with cardiovascular disease and is considered a relevant comorbidity [70]. Cardiac surgery has not been clearly addressed as a significant cause of depression. However,

depression may in turn be an important cofactor in inducing relapse and contributing to postoperative morbidity and mortality. In fact, some studies indicate that the incidence of major depressive disorder is two to three times greater in patients with cardiovascular disease (CVD) than in the general population [71]. Among the various hypotheses about possible causes, some author suggested a correlation between depressive disorder and silent cerebral infarcts (SBI). In a study of 194 patients with different psychiatric problems, it was found that 42.8% had an SBI and were being treated for depressive disorder [72]. This study supported the previous results of Yamashita et al. who reported the prevalence of SBI in depression as greater than 48.6% [73]. This association is present, above all, in elderly patients [74]. In support of this hypothesis, there is also the Rotterdam study which demonstrates the reduction of cerebral blood flow velocity as predictive of depressive symptoms and disorders [75]. Bipolar disorder, which appears to be associated with vascular risk factors and ischemic lesions of the white matter, as well as manic episodes due to cerebral infarcts, is also of concern in elderly patients. Specifically, organic lesions were observed in about half of the patients diagnosed with bipolar disorder after 50 years [76].

Among the various cardiac surgery interventions, that of CABG is certainly one of the most studied even with respect to psychological implications. CABG is usually associated with improved clinical outcomes. However, some patients experience depression and anxiety both before and after surgery. The depressive disorder was found in 14–47% [77] and anxiety in 15–52% of patients [78].

Some studies suggest that major depressive disorder and anxiety are associated with poor post-surgical outcomes including cardiac events, level of functioning, and quality of life [79]. Several studies focus on biological mechanisms of cardio-pathogenesis imputable to depression and anxiety. These biological mechanisms are multifactorial and include the dysregulation of the HPA axis [80–82], reduced heart rate variability [83–85], altered serotonergic pathways, inflammatory response [85], and altered platelet aggregability [86]. Tully et al. [87] in systematic comparison of anxiety, depression, and stress suggested that only depression was systematically related to quality of life domains tapping into vitality, social role functioning, and physical and general health. Furthermore, mortality appears to increase in patients with high levels of depression and anxiety undergoing CABG surgery, although not all studies have been consistent. A recent review showed an increase in mortality from various causes in relation to preoperative depressive disorder [88]. The treatment of this condition is thus critical for improving the overall success of the intervention.

For the pharmacological treatment, it is important to underline some evidences: several studies have reported the possible pro-arrhythmic and cardiotoxic effects of tricyclic anti-depressants in cardiac patients [89, 90], while selective serotonin reuptake inhibitors (SSRI), by contrast, have been considered as safe among cardiac patients due to the serotonin transporter affinity and attenuation of platelet functioning [79]. However, careful prescription, slow dosage titration, and cardiology monitoring are needed as some studies reported safety, tolerability, and efficacy of SSRIs among cardiac patients [91, 92], but others did not [93–95]. Psychological support and psychotherapy should also be considered. Further research will investigate gender-specific factors of people undergoing CABG surgery. In fact, differences emerged in the delayed referral of women to surgery, disparity in functional gains after CABG surgery, with women showing worse results and lower adherence to cardiac rehabilitation program. Another group of studies on patients with myocardial infarction showed gender disparity in the impact of depression on clinical outcomes, with women showing more adverse effects [96, 97].

Conclusion

This chapter stressed the relevance of the most frequent neuropsychiatric and psychiatric conditions associated with cardiac surgery. The wide prevalence of attention disorders, cognitive

impairment, and psychiatric disorders highlighted the need for a basic knowledge of this condition for all the clinicians working in the field of cardiac surgery and associated intensive care. The clinical and functional detrimental roles of these conditions also pinpoint the need for liaison psychiatric and psychological support for the patients undergoing surgical procedure. The existence of effective and safe treatments is well recognized and should be part of the reasons to spread the culture of integrated multi-specialist approaches.

References

1. Dominici C, Salsano A, Nenna A, et al. Neurological outcomes after on-pump vs off-pump CABG in patients with cerebrovascular disease. J Card Surg. 2019;34(10):941–7.
2. Steinmetz J, Christensen KB, Lund T, Lohse N, Rasmussen LS, ISPOCD Group. Long-term consequences of postoperative cognitive dysfunction. Anesthesiology. 2009;110(3):548–55.
3. Bernardi MH, Wahrmann M, Dworschak M, Kietaibl C, Ristl R, Edlinger-Stanger M, Lassnigg A, Hiesmayr MJ, Weber U. Carotid artery blood flow velocities during open-heart surgery and its association with delirium: a prospective, observational pilot study. Medicine. 2019;98:50(e18234).
4. van Harten AE, Scheeren TW, Absalom AR. A review of postoperative cognitive dysfunction and neuroinflammation associated with cardiac surgery and anaesthesia. Anaesthesia. 2012;67(3):280–93.
5. Gao L, Taha R, Gauvin D, Othmen LB, Wang Y, Blaise G. Postoperative cognitive dysfunction after cardiac surgery. Chest. 2005;128(5):3664–70.
6. DiGangi JA, Gomez D, Mendoza L, Jason LA, Keys CB, Koenen KC. Pretrauma risk factors for posttraumatic stress disorder: a systematic review of the literature. Clin Psychol Rev. 2013;33(6):728–44.
7. Lichtman JH, et al. Depression and coronary heart disease: recommendations for screening, referral, and treatment: a science advisory from the American Heart Association Prevention Committee of the Council on Cardiovascular Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Interdisciplinary Council on Quality of Care and Outcomes Research: endorsed by the American Psychiatric Association. Circulation. 2008;118(17):1768–75.
8. Devlin JW, Skrobik Y, Gélinas C, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. Crit Care Med. 2018;46(9):e825–73.
9. Gosselt AN, Slooter AJ, Boere PR, Zaal IJ. Risk factors for delirium after on pump cardiac surgery: a systematic review. Crit Care. 2015;19:346.
10. Jackson P, Khan A. Delirium in critically ill patients. Crit Care Clin. 2015;31(3):589–603.
11. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM 5. 5th ed. Washington, DC: American Psychiatric Association; 2014.
12. Early recognition of delirium and delirium biomarkers in adults after cardiac surgery. AORN J. 2020;111(2):243–6.
13. Van den Boogaard M, Pickkers P, Slooter ACJ, et al. Development and validation of PRE-DELIRIC (PREdic-tion of DELIRium in ICu patients) delirium prediction model for intensive care patients: observational multicentre study. BMJ. 2012;344:e420.
14. Trogrlic Z, Van der Jagt M, Bakker J, Balas MC, Ely EW, Van der Voort PHJ, et al. A systematic review of implementation strategies for assessment, prevention, and management of ICU delirium and their effect on clinical outcomes. Crit Care. 2015;19(1):157.
15. Mittal D, Majithia D, Kennedy R, et al. Differences in characteristics and outcome of delirium as based on referral patterns. Psychosomatics. 2006;47(5):367–75.
16. Mirasol EG, Shapiro PA, Fang Y. Delirium in the cardiothoracic ICU: prevalence, predictors and effect on length of stay. Amelia Island: Academy of Psychosomatic Medicine; 2007.
17. Reade MC, Finfer S. Sedation and delirium in the intensive care unit. N Engl J Med. 2014;370(5):444–54.
18. Leslie DL, Marcantonio ER, Zhang Y, et al. One-year health care costs associated with delirium in the elderly population. Arch Intern Med. 2008;168(1):27–32.
19. Inouye SK, Westendorp RGJ, Saczynski JS. Delirium in elderly people. Lancet. 2014;383(9920):911–22.
20. Patel N, Minhas JS, Chung EM. Risk factors associated with cognitive decline after cardiac surgery: a systematic review. Cardiovasc Psychiatry Neurol. 2015;2015:370612.
21. Mailhot T, Cossette S, Lambert J, et al. Cerebral oximetry as a biomarker of postoperative delirium in cardiac surgery patients. J Crit Care. 2016;34:17–23.
22. Norkiene I, Ringaitiene D, Misiuriene I, et al. Incidence and precipitating factors of delirium after coronary artery bypass grafting. Scand Cardiovasc J. 2007;41(3):180–5.
23. Giltay EJ, Huijskes RV, Kho KH, et al. Psychotic symptoms in patients undergoing coronary artery bypass grafting and heart valve operation. Eur J Cardiothorac Surg. 2006;30(1):140–7.
24. Bucerius J, et al. Predictors of delirium after cardiac surgery delirium: effect of beating-heart (off-pump) surgery. J Thorac Cardiovasc Surg. 2004;127(1):57–64.
25. Shapiro PA. Heart disease. In: Levenson JL, editor. APPI textbook of psychosomatic medicine. Washington, DC: APPI; 2004.
26. NICE Clinical Guidelines. Delirium: prevention, diagnosis and management (CG103). Published: 28 July 2010. https://www.nice.org.uk/guidance/cg103

27. Taylor DM, Paton C, Kapur S. The Maudsley prescribing guidelines in psychiatry. Chichester: Wiley; 2015.
28. Prakanrattana U, Prapaitrakool S. Efficacy of risperidone for prevention of postoperative delirium in cardiac surgery. Anaesth Intensive Care. 2007;35(5):714–9.
29. Yoon HJ, et al. Efficacy and safety of haloperidol versus atypical antipsychotic medications in the treatment of delirium. BMC Psychiatry. 2013;13:240.
30. Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med. 2013;41(1):263–306.
31. Pandharipande P, Shintani A, Peterson J, et al. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. Anesthesiology. 2006;104(1):21–6.
32. Saczynski JS, Marcantonio ER, Quach L, et al. Cognitive trajectories after postoperative delirium. N Engl J Med. 2012;367:30–9.
33. Quinlan N, Rudolph JL. Postoperative delirium and functional decline after noncardiac surgery. J Am Geriatr Soc. 2011;59(Suppl 2):S301–4.
34. Rudolph JL, Inouye SK, Jones RN, et al. Delirium: an independent predictor of functional decline after cardiac surgery. J Am Geriatr Soc. 2010;58(4):643–9.
35. Devore EE, Fong TG, Marcantonio ER, et al. Prediction of long-term cognitive decline following postoperative delirium in older adults. J Gerontol A Biol Sci Med Sci. 2017;72(12):1697–702.
36. Newman MF, Kirchner JL, Phillips-Bute B, et al. Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery. N Engl J Med. 2001;344(6):395–402.
37. van Dijk D, Keizer AM, Diephuis JC, Durand C, Vos LJ, Hijman R. Neurocognitive dysfunction after coronary artery bypass surgery: a systematic review. J Thorac Cardiovasc Surg. 2000;120(4):632–9.
38. Rudolph JL, Babikian VL, Treanor P, Pochay VE, Wigginton JB, Crittenden MD, et al. Microemboli are not associated with delirium after coronary artery bypass graft surgery. Perfusion. 2009;24(6):409–15.
39. Marcantonio ER, Goldman L, Orav EJ, Cook EF, Lee TH. The association of intraoperative factors with the development of postoperative delirium. Am J Med. 1998;105(5):380–4.
40. Tsai TL, Sands LP, Leung JM. An update on postoperative cognitive dysfunction. Adv Anesth. 2010;28(1):269–84.
41. Fanning JP, Wesley AJ, Wong AA, Fraser JF. Emerging spectra of silent brain infarction. Stroke. 2014;45(11):3461–71.
42. Roach GW, Kanchuger M, Mangano CM, et al. Adverse cerebral outcomes after coronary bypass surgery. Multicenter study of perioperative ischemia research group and the ischemia research and education foundation investigators. N Engl J Med. 1996;335(25):1857–63.
43. Moller JT, Cluitmans P, Rasmussen LS, et al. Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD investigators. International study of post-operative cognitive dysfunction. Lancet. 1998;351(9106):857–61.
44. Rasmussen LS. Postoperative cognitive dysfunction: incidence and prevention. Best Pract Res Clin Anaesthesiol. 2006;20(2):315–30.
45. Goto T, Maekawa K. Cerebral dysfunction after coronary artery bypass surgery. J Anesth. 2014;28(2):242–8.
46. van Dijk D, Spoor M, Hijman R, et al. Cognitive and cardiac outcomes 5 years after off-pump vs on-pump coronary artery bypass graft surgery. J Am Med Assoc. 2007;297(7):701–8.
47. Vanini B, Grazioli V, Sciortino A, et al. Neuropsychological outcomes after pulmonary endarterectomy using moderate hypothermia and periodic circulatory arrest. J Heart Lung Transplant. 2018;37(7):860–4.
48. Vuylsteke A, Sharples L, Charman G, et al. Circulatory arrest versus cerebral perfusion during pulmonary endarterectomy surgery (PEACOG): a randomised controlled trial. Lancet. 2011;378(9800):1379–87.
49. Carr ZJ, Cios TJ, Potter KF, Swick JT. Does dexmedetomidine ameliorate postoperative cognitive dysfunction? A brief review of the recent literature. Curr Neurol Neurosci Rep. 2018;18(10):64.
50. National Collaborating Centre for Mental Health (UK). Post-traumatic stress disorder: the management of PTSD in adults and children in primary and secondary care. NICE clinical guidelines, no. 26. Leicester: Gaskell; 2005. Appendix 13, Diagnostic criteria. https://www.ncbi.nlm.nih.gov/books/NBK56500
51. Griffiths J, Fortune G, Barber V, Young JD. The prevalence of post-traumatic stress disorder in survivors of ICU treatment: a systematic review. Intensive Care Med. 2007;33(9):1506–18.
52. Tully PJ. Psychological depression and cardiac surgery: a comprehensive review. J Extra Corpor Technol. 2012;44(4):224–32.
53. Schelling G, Richter M, Roozendaal B, Rothenhausler HB, Krauseneck T, Stoll C, et al. Exposure to high stress in the intensive care unit may have negative effects on health-related quality-of-life outcomes after cardiac surgery. Crit Care Med. 2003;31(7):1971–80.
54. Binder BC, Bradley RG, Liu W, Epstein MP, Deveau TC, Mercer KB, Tang Y, Gillespie CF, Heim CM, Nemeroff CB, Schwartz AC, Cubells JF, Ressler KJ. Association of FKBP5 polymorphisms and childhood abuse with risk of posttraumatic stress disorder symptoms in adults. JAMA. 2008;299(11):1291–305.
55. Maripuu M, Wikgren M, Karling P, Adolfsson R, Norrback KF. Relative hypo- and hypercortisolism are both associated with depression and lower quality of life in bipolar disorder: a cross-sectional study. PLoS One. 2014;9(6):e98682.
56. Kadak MT, Nasiroglu S, Boysan M, Aydin A. Risk factors predicting posttraumatic stress reactions in adolescents after 2011 Van earthquake. Compr Psychiatry. 2013;54(7):982–90.
57. Van Zuiden M, Geuze E, Willemen HLDM, Vermetten E, Maas M, Amarouchi K, Kavelaars A,

Heijnen CJ. Glucocorticoid receptor pathway components predict posttraumatic stress disorder symptom development: a prospective study. Biol Psychiatry. 2012;71(4):309–16.
58. Vinkers CH, Joëls M, Milaneschi Y, Kahn RS, Penninx BWJH, Boks MPM. Stress exposure across the life span cumulatively increases depression risk and is moderated by neuroticism. Depress Anxiety. 2014;31(9):737–45.
59. Jakšic N, Brajković L, Ivezić E, Topić R, Jakovljević M. The role of personality traits in posttraumatic stress disorder (PTSD). Psychiatr Danub. 2012;24(3):256–66.
60. Schelling G, Roozendaal B, Krauseneck T, Schmoelz M, DE Quervain D, Briegel J. Efficacy of hydrocortisone in preventing posttraumatic stress disorder following critical illness and major surgery. Ann N Y Acad Sci. 2006;1071:46–53.
61. Weis F, Kilger E, Roozendaal B, de Quervain DJ, Lamm P, Schmidt M, et al. Stress doses of hydrocortisone reduce chronic stress symptoms and improve health-related quality of life in high-risk patients after cardiac surgery: a randomized study. J Thorac Cardiovasc Surg. 2006;131(2):277–82.
62. Hoskins M, et al. Pharmacotherapy for post-traumatic stress disorder: systematic review and meta-analysis. Br J Psychiatry. 2015;206(2):93–100.
63. Lee DJ, et al. Psychotherapy versus pharmacotherapy for posttraumatic stress disorder: systematic review and meta-analyses to determine first-line treatments. Depress Anxiety. 2016;33(9):792–806.
64. Han C, et al. The potential role of atypical antipsychotics for the treatment of posttraumatic stress disorder. J Psychiatr Res. 2014;56:72–81.
65. National Institute for Health and Care Excellence. Post-traumatic stress disorder: management. Clinical guideline 26, 2005. http://www.nice.org.uk/guidance/CG26
66. NICE Clinical Guidelines, Depression in adults: recognition and management. https://www.nice.org.uk/guidance/cg90/chapter/Introduction#ftn.footnote_1
67. World Health Organization (WHO). World health statistics 2016: monitoring health for the SDGs, sustainable development goals. http://www.who.int/gho/publications/world_health_statistics/2016/en/
68. Pfeifer PM, Ruschel PP, Bordignon S. Coping strategies after heart transplantation: psychological implications. Rev Bras Cir Cardiovasc. 2013;28(1):61–8.
69. Dew MA, Rosenberger EM, Myaskovsky L, DiMartini AF, DeVito Dabbs AJ, Posluszny DM, et al. Depression and anxiety as risk factors for morbidity and mortality after organ transplantation: a systematic review and meta-analysis. Transplantation. 2015;100(5):988–1003.
70. Thombs BD, Bass EB, Ford DE, Stewart KJ, Tsilidis KK, Patel U, et al. Prevalence of depression in survivors of acute myocardial infarction. J Gen Intern Med. 2006;21(1):30–8.
71. Celano CM, Huffman JC. Depression and cardiac disease: a review. Cardiol Rev. 2011;19(3):130–42.
72. Avdibegovic E, Becirovic E, Selimbasic Z, Hasanovic M, Sinanovic O. Cerebral cortical atrophy and silent brain infarcts in psychiatric patients. Psychiatr Danub. 2007;19(1–2):49–55.
73. Yamashita H, Fujikawa T, Yanai I, Morinobu S, Yamawaki S. Cognitive dysfunction in recovered depressive patients with silent cerebral infarction. Neuropsychobiology. 2002;45(1):12–8.
74. Fujikawa T, Yamawaki S, Touhouda Y. Incidence of silent cerebral infarction in patients with major depression. Stroke. 1993;24(11):1631–4.
75. Direk N, Koudstaal PJ, Hofman A, Ikram MA, Hoogendijk WJ, Tiemeier H. Cerebral hemodynamics and incident depression: the Rotterdam Study. Biol Psychiatry. 2012;72(4):318–23.
76. Fujikawa T, Yamawaki S, Touhouda Y. Silent cerebral infarctions in patients with late-onset mania. Stroke. 1995;26(6):946–9.
77. Blumenthal JA, Lett HS, Babyak MA, White W, Smith PK, Mark DB, Jones R, Mathew JP, Newman MF, NORG Investigators. Depression as a risk factor for mortality after coronary artery bypass surgery. Lancet. 2003;362(9384):604–9.
78. Tully PJ, Cosh SM, Baumeister H. The anxious heart in whose mind? Review and meta-regression of factors associated with coronary heart disease. J Psychosom Res. 2014;77(6):439–48.
79. Tully PJ, Baker RA. Depression, anxiety, and cardiac morbidity outcomes after coronary artery bypass surgery: a contemporary and practical review. J Geriatr Cardiol. 2012;9(2):197–208.
80. Tully PJ, Baker RA, Knight JL, et al. Neuropsychological function five years after cardiac surgery and the effect of psychological distress. Arch Clin Neuropsychol. 2009;24:741–51.
81. Barger SD, Sydeman SJ. Does generalized anxiety disorder predict coronary heart disease risk factors independently of major depressive disorder? J Affect Disord. 2005;88(1):87–91.
82. Goodwin RD. Association between physical activity and mental disorders among adults in the United States. Prev Med. 2003;36(6):698–703.
83. Carney RM, Freedland KE, Eisen SA, et al. Major depression and medication adherence in elderly patients with coronary artery disease. Health Psychol. 1995;14(1):88–90.
84. Kuhl EA, Fauerbach JA, Bush DE, et al. Relation of anxiety and adherence to risk-reducing recommendations following myocardial infarction. Am J Cardiol. 2009;103(12):1629–34.
85. Frasure-Smith N, Lesperance F, Irwin MR, et al. Depression, C-reactive protein and two-year major adverse cardiac events in men after acute coronary syndromes. Biol Psychiatry. 2007;62(4):302–8.
86. Soufer R, Arrighi JA, Burg MM. Brain, behavior, mental stress, and the neurocardiac interaction. J Nucl Cardiol. 2002;9(6):650–62.
87. Tully PJ, Baker RA, Turnbull DA, et al. Negative emotions and quality of life six months after cardiac surgery: the dominant role of depression not anxiety symptoms. J Behav Med. 2009;32(6):510–22.

88. Stenman M, Holzmann MJ, Sartipy U. Association between preoperative depression and long-term survival following coronary artery bypass surgery – a systematic review and meta-analysis. Int J Cardiol. 2016;222:462–6.
89. Cohen HW, Gibson G, Alderman MH. Excess risk of myocardial infarction in patients treated with antidepressant medications: association with use of tricyclic agents. Am J Med. 2000;108(1):2–8.
90. Ha JH, Wong CK. Pharmacologic treatment of depression in patients with myocardial infarction. J Geriatr Cardiol. 2011;8(2):121–6.
91. Dowlati Y, Herrmann N, Swardfager WL, et al. Efficacy and tolerability of antidepressants for treatment of depression in coronary artery disease: a meta-analysis. Can J Psychiatr. 2010;55(2):91–9.
92. Glassman AH, O'Connor CM, Califf RM, et al. Sertraline treatment of major depression in patients with acute MI or unstable angina. JAMA. 2002;288(6):701–9.
93. Veien KT, Videbaek L, Schou M, et al. High mortality among heart failure patients treated with antidepressants. Int J Cardiol. 2011;146(1):64–7.
94. Von Ruden AE, Adson DE, Kotlyar M. Effect of selective serotonin reuptake inhibitors on cardiovascular morbidity and mortality. J Cardiovasc Pharmacol Ther. 2008;13(1):32–40.
95. Tata LJ, West J, Smith C, et al. General population based study of the impact of tricyclic and selective serotonin reuptake inhibitor antidepressants on the risk of acute myocardial infarction. Heart. 2005;91(4):465–71.
96. Mendes de Leon CF, Krumholz HM, Seeman TS, Vaccarino V, Williams CS, Kasl SV, Berkman LF. Depression and risk of coronary heart disease in elderly men and women: new haven EPESE, 1982–1991. Established populations for the epidemiologic studies of the elderly. Arch Intern Med. 1998;158(21):2341–8.
97. Williams SA, Kasl SV, Heiat A, Abramson JL, Krumholz HM, Vaccarino V. Depression and risk of heart failure among the elderly: a prospective community-based study. Psychosom Med. 2002;64(1):6–12.
98. Indja B, Seco M, Seamark R et al., Neurocognitive and Psychiatric Issues Post Cardiac Surgery. Heart Lung Circ. 2017;26(8):779–785.
99. Seco M, Edelman JJ, Van Boxtel B, Forrest P, Byrom MJ, Wilson MK, et al. Neurologic injury and protection in adult cardiac and aortic surgery. Journal of cardiothoracic and vascular Anesthesia. 2015;29 (1):185–95.

Cardiac Transplantation and Psychopathology

23

Pierluigi Politi and Valentina Martinelli

Contents

Abstract

Heart transplantation (HT) is a well-established procedure for terminal cardiac disease and is considered the treatment of choice in cases of severe cardiac insufficiency refractory to medical or surgical treatment. Although cardiac transplantation leads to a dramatic improvement in functional status and quality of life, it still represents one of the more invasive and psychologically threatening surgical interventions. HT raises unique psychological issues which originate from the complexity of the entire clinical and therapeutic trajectory as well as from extraordinary symbolicity of the heart and the human source of the graft. Psychiatric and psychological disturbances, mainly mood and anxiety disorders, are common both in the pre- and posttransplant phase, with prevalence rates of 50% in HT candidates and 20–30% in HT recipients, even in the long term. Correct detection and treatment of these conditions is mandatory given their recognized impact on HT main outcomes, including survival. Available interventions include pharmacological treatment, mainly selective serotonin reuptake inhibitors (SSRIs), and psychotherapeutic approaches, but the evidence to guide clinicians' management of psychopathology

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*,
https://doi.org/10.1007/978-3-030-28008-6_27

in this population is still limited. Further research is needed to optimize treatment and management of psychological outcomes.

Keywords

Heart transplantation · Psychopathology · Depression · Anxiety · Delirium · Antidepressants · Psychopharmacological treatment · Psychotherapy · Psychosocial outcomes

Introduction

Heart transplantation (HT) is a well-established procedure for terminal cardiac disease and is considered the treatment of choice in cases of severe cardiac insufficiency refractory to medical or surgical treatment. However, even nowadays, more than 50 years after Christiaan Barnard performed the world's first human-to-human heart transplant at Groote Schuur Hospital in Cape Town, South Africa, cardiac transplantation still evokes intense emotions. Indeed, it represents one of the more invasive and psychologically threatening surgical interventions [1, 2].

HT is only a part of a complex clinical process, which involves a series of stages, each one carrying dangerous implications. In the preoperative period, the patient may experience recurrent episodes of acute decompensated heart failure, leading to urgent hospital admissions, invasive procedures, and, in some cases, mechanical circulatory support. The postoperative phase is also physically and psychologically challenging due to a first period of isolation, the risk for acute rejection, infections, and immunosuppressants' side effects. For many transplant recipients, transplantation and related comorbidities impose a significant and lifelong physical and emotional symptom burden [3].

It is often assumed that HT psychological peculiarities are interwoven with the extraordinary symbolicity of the heart. From the dawn of time, cardiac sound – we all may hear it – marks the beginning as the end of our lives. Through the history of mankind, the heart became soon the vital center of the human being, long before blood circulation was discovered. From the very beginning of heart transplantation, psychiatry was deeply involved into transplantology, as it was for surgery, immunology, ethics, and sociology. *Major* organ transplantation soon became a kind of in vivo experiment along the development of body scheme organization, enriching the experience had with amputated patients or having congenital or acquired malformations. A paradigmatic example of life-extending operations, heart transplantation is characterized by important psychological implications, over all the convergence of the themes of identity, death, and rebirth [4].

Of note, many transplant recipients celebrate the anniversary of the surgical intervention in terms of a new birth, the beginning of a second life. Richard Blacher, an American psychiatrist and psychoanalyst, talks about *rebirth* discussing psychological implications of open-heart surgery [5].

The concept of rebirth indissolubly recalls the thought of death and dying, which is central in the inner experience of transplant recipients. The graft "weighs." It carries feelings of guilt that many recipients may experience for having desired, mostly unconsciously, the death of another human being during the waiting period [6].

The graft is, effectively, the organ of a deceased which continues to beat. The mourning for a young person, whose heart still continues to pulse in another body, may be almost impossible to elaborate. The concept of rebirth evokes also the dimension of identity, the possibility of remaining ourselves, despite the change. In fact, the themes of extraneousness, non-self and "double", often recur in these clinical settings. The integration of the new organ into the body scheme often requires time [7]. From a psychological perspective, the graft is not inert: it carries some of the donors' features. The transplanted organ almost immediately achieves a mental representation: it does not become only a part of the body, but represents the donor and the relationship to that person [4, 8]. It is an anatomical part which becomes anthropomorphized. Identification with the donor is often noticeable. Some patients report they have become more masculine or feminine, according to the sex of

the donor, as if some of the donors traits, both physical and psychological, could have been transmitted to them as a result of transplantation. The recomposition of the body image's integrity gradually leads to overcome the crisis induced by the transplant and allows adaptation to the new condition [4]. HT is generally followed by marked improvements in physical and mental health and emotional well-being. However, in the late years post-HT, the development of medical complications may provoke renewed distress. To this regard, Jean-Luc Nancy, a contemporary French philosopher, describes the experience of his own heart transplant in terms of the problematic gift of a foreign organ and the intrusiveness of a cancer fostered by the immunosuppressive treatment regimen [9].

Taken together, these considerations show how HT raises unique psychological issues and potential psychiatric complications which require a multidisciplinary approach.

Waiting For a New Heart

Psychosocial Evaluation of Heart Transplant Candidates

Extensive clinical literature highlighted the impact of pretransplant psychosocial factors, including patient's history of medical adherence, mental health, substance use, and social support on HT outcomes. Therefore, all HT guidelines state that pretransplant screening should include a thorough psychological assessment [10, 11]. This evaluation integrates a complex multifaceted assessment, providing information relevant for patients' selection and overall care planning. With specific regard to complex situations, it facilitates appropriate referral for treatments or interventions that may improve patients' well-being and suitability as transplant candidates. While medical criteria warranting HT candidacy have been well established, psychosocial criteria are less standardized. Recently, a consensus of expert opinion promoted by the International Society for Heart and Lung Transplantation (ISHLT) provided recommendations for the psychosocial evaluation of adult cardiothoracic transplant candidates, addressing both the evaluation content and process [10]. Regarding content, the psychological assessment should address nine main domains, specifically patient's treatment adherence and health behaviors; mental health history; substance use history; cognitive status and capacity to give informed consent; knowledge and understanding of current illness; knowledge and understanding of treatment options; coping with illness; social support; and social history.

Predicting non-compliance has always represented one of the central issues in the psychosocial evaluation of the potential HT candidate. Repeated documented nonadherence to medications and other medical directives is a recognized contraindication to cardiothoracic transplantation, due to the associated increased risks for posttransplant morbidities and mortality. Psychiatric conditions contraindicate transplantation when uncontrolled, affecting patients' ability to adhere to the medical regimen, and are not mitigated by adequate clinical and social support [10]. Depression and anxiety are common in HT candidates [12, 13]. Even the more severe, less common psychiatric disorders, including psychosis and bipolar disorder, do not inevitably lead to posttransplant clinical outcomes if careful candidate assessment and close management of these conditions is provided. Active alcohol abuse, drug abuse, and tobacco smoking are contraindications to cardiothoracic transplantation, given the increased risks for poor postsurgical clinical outcomes and mortality, primarily mediated by relapse to use after the operation. The evaluation should carefully investigate history of use of all substances, current status, previous treatments received, periods of abstinence as well as the person's insight and willingness to receive treatment [10]. The assessment of patients' understanding, acquaintance, and capacity to engage in decision-making needs is also part of the psychosocial evaluation. Although dementia represents a contraindication to HT, patients with milder degrees of cognitive impairment or with transient impairments (delirium, encephalopathy) that resolve may have the capacity to give

informed consent and undergo HT. Moreover, previous studies suggest that intellectual disabilities per se may not adversely affect ultimate transplant outcomes if adequate social support is provided to ensure patient's medical adherence [10]. More recently, research explored the role of coping strategies, received family and social support, and social history on HT outcomes and sustained their inclusion in the formal assessment. In HT patients, the use of denial and avoidant coping before transplantation is associated with an increased risk for developing a psychiatric disorder after transplant. Optimism, active problem-solving, and having a strong sense of self-efficacy are associated with better psychological, behavioral, and clinical outcomes [10, 14]. Family and social support needs also to be assessed given its contribution to patient's adherence and the important protective role in mitigating other risk factors including mental health problems and cognitive and intellectual disability. Low level of family and social support, low socioeconomic status, and worse background health characteristics contribute to an unsatisfactory HT outcome due to worse adherence to the therapeutic regimen [10, 15].

In contrast with the large body of literature supporting the content to be explored by the psychosocial evaluation, few empirical works focus on processes and procedures [10]. According to Organ Procurement and Transplantation Network (OPTN)/United Network for Organ Sharing (UNOS) guidelines, "All transplant programs should identify appropriately trained individuals who are designated members of the transplant team and have primary responsibility for coordinating the psychosocial needs of transplant candidates, recipients, living donors and families" [11]. The evaluation protocol may follow one of the published specific screening tools, including the Psychosocial Assessment of Candidates for Transplantation (PACT) [16], the Transplant Evaluation Rating Scale (TERS) [17], and the Stanford Integrated Psychosocial Assessment for Transplantation (SIPAT) [11]. There is current insufficient evidence to support the use of any given instrument over the others [10].

Consensus of expert opinion highlights the importance of a multidisciplinary discussion of the psychosocial evaluation's final report. This approach provides a key opportunity to recommend treatments and interventions to ameliorate any identified psychosocial contraindication or risk factor to transplantation. With regard to mental health, pharmacological and psychotherapeutic strategies are now available and can be used safely and effectively to treat mental health issues before HT. Implementation, progress, and outcomes of recommended treatments or interventions should be monitored to allow timely updates to the transplant team [10]. Importantly, criteria for success need to consider the patient's medical urgency. In fact, HT represents a life-saving procedure: the process of conducting the evaluation therefore requires a tailored approach to the patients' ability to provide information, according to their current medical status and capacity to participate actively. In this sense, researchers and clinicians underline that strict, prescriptive guidelines for universal application are not appropriate in this field [10].

The Waiting Period: Psychopathology

Scarcity of donor organs and improvement in survival after a cardiac event due to advances in medications and technology, including ventricular assist devices (VAD), has led to an increase of average waiting times for all patients over the past years. Regarding psychopathology, the period between being listed for transplantation and receiving a heart is often particularly difficult and very stressful [12, 18]. The majority of patients experience a marked worsening in their physical condition. Previous studies reported rates of psychiatric morbidity of around 50% in HT candidates, mainly depressive and anxiety disorders [18]. The waiting period is often described as the most stressful of the entire transplant trajectory. The first allusion to the need for the intervention may generate in the patient profound discouragement and anguish, if not terror, with attempts to deny the seriousness of the situation. Denial has been observed to be a common defensive pattern and coping strategy in patients with cardiac disease and may play an initial adaptive

role, leading to a reduction in anxiety. By contrast, maladaptive denial may result in treatment noncompliance, counterphobic over efforts in work and activities, and failure to make appropriate plans. When denial is extreme, patients may refuse appropriate medical treatment and transplant [6, 12]. One of the main challenges during the waiting period is a sort of extreme uncertainty: the person lives constantly on the alert, dealing with the fear of death before an organ becomes available, while the physical status declines. Different from other solid organ transplant recipients, many patients await HT in the hospital setting. This wait, coupled with the need for intensive cardiac support, can compound the stress of the heart transplant process. Even for patients who are able to wait at home, there is significant stress associated with poor physical functioning, shortness of breath, fatigue, the stress of adhering to a medical and dietary regimen, waiting for an organ to be allocated, and contending with the possibility of death. Moreover, in recent years the implantation of ventricular assist devices (VAD) has evolved into a standard procedure to bridge patients to transplant. VAD therapy is associated with characteristic psychiatric and psychosocial issues, including additional distress due to the risk of adverse events such as infections, bleeding, neurological events, and early mortality [19]. The neuropsychologic course after VAD implantation proceeds in different stages [20]. Neurologic affections, including recurrent episodes of embolic or hemorrhagic strokes, may occur in the initial phase and can even preclude the possibility of HT [19, 21]. Subsequently, when adjustment to the life with a VAD sets in, the patient may experience an existential threat and that a machine controls his/her life. This represents a traumatic experience and implies a severe distortion of the body image [22]. This period is usually followed by a stage of stabilization, which often accompanies somatic health progress. However, this phase is characterized by continuing efforts of adaptation to life with the VAD and to the necessity to develop a new personal life concept. Patients are required to learn to manage a complex technical device where errors or inattentiveness are potentially fatal. This results in constant psychological pressure, where pause nor oblivion is possible [20]. Long hospitalization due to recurrent VAD-related complications leads to deprivation and presents an additional negative psychological factor.

The prevalence of anxiety in patients with heart failure ranges between 9% and 53%, and moderate anxiety has been reported in the majority of transplant candidates [18, 23]. Symptomatic cardiac disease may itself trigger anxiety. Angina, arrhythmia, and acute heart failure produce anxiety related to fears of heart attack, disability, and sudden death. New potential sources of anxiety in the waiting period include long waits for the donor organ, the informed consent process, and the experience of the death of other patients [6]. Of note, anxiety has been identified as an independent predictor of all-cause mortality in patients with heart failure [19]. The prevalence of major depressive disorders ranges from 20% to 40% in patients with heart failure and 24% to 38% of patients on a heart transplant waiting list, with further increases in the intensity of the symptoms during the waitlisted period [13, 15]. Sanchez et al. in a cross-sectional study of 125 subjects found 30.4% of HT candidates reported a DSM-IV-TR Axis I disorder and 31.2% were on psychopharmacological treatment, mainly benzodiazepines (16%) and selective serotonin reuptake inhibitors (6.4%) [18]. Preoperative depression predicts higher risk for unfavorable outcome after HT, in terms of poor medication compliance, higher rates of hospitalization, and mortality [13, 15]. Appropriate identification and treatment of depressive and anxiety disorders is therefore essential. Psychotropic medications provide an effective option, combined with psychotherapy or alone. The choice of psychotropic agent requires careful consideration of the risk for QTc prolongation and of pharmacokinetic issues. In the waiting period, end-stage organ disease represents the primary focus, given the potential alterations in drug absorption, distribution, and clearance [19, 24]. Selective serotonin reuptake inhibitors (SSRIs) are well tolerated and efficacious for depression, panic disorder, and posttraumatic stress disorder. Adjustments in dosage

are required when renal or hepatic impairment is present. For acute or short-term control of anxiety with these patients, benzodiazepines provide the most rapid and effective relief. First-generation antipsychotics, most atypical antipsychotics, tricyclic antidepressants, and the SSRIs citalopram and escitalopram have been associated with QTc prolongation and ventricular arrhythmias, thus requiring a careful analysis of the necessity of immediate treatment and the availability of alternative treatment options. Furthermore, specific caution and awareness of the QTc-prolonging effects of cardiac medications, particularly class I and class III antiarrhythmics, are required to guide appropriate drug choice in case of coadministration [19, 24].

Living with a New Heart

Early Postoperative Period

In the early phase following heart transplantation, many recipients report feelings of euphoria, omnipotence, and immortality, linked to the dramatic improvements of their physical conditions. These feelings are often accompanied by a temporary denial of worries about the risk of rejection, the need for lifelong pharmacological therapy, and the extraneous nature, not only biological, of the transplanted organ. The very early period after HT has been described as a sort of "honeymoon," a phase of transient idealization of the recipient's condition following the triumph over death. This feeling of rebirth may resemble the characteristics of a hypomanic state, most likely reactive to the intense anguish and threat experienced throughout the waiting period [4, 25]. Previous studies showed a significant decline in anxiety and depressive symptoms and the return to a psychological status comparable to that in the absence of illness [2, 25].

Neurological complications represent the main neuropsychiatric disturbances in the immediate postoperative period, with a 9% prevalence of delirium or encephalopathy in HT recipients [26]. The pathogenesis of delirium after HT is complex and involves neurotransmitter alterations, physiological stressors, metabolic derangements, electrolyte imbalances, potential neurocognitive side effects of immunosuppressive regimens and antibiotics, and the use of extracorporeal circulation [25, 27]. Of note, postoperative delirium has been reported in 36.8% of lung transplant recipients in a recent study by Anderson et al. (2018), with pretransplant benzodiazepine prescription found as an independent risk factor. There are few data to guide the treatment of delirium in cardiac intensive care unit patients [28]. Non-pharmacological strategies to reorientate the patient should be preferred. There are conflicting and limited data to guide the use of antipsychotics. Atypical antipsychotics may reduce the duration of delirium, but these should not be used in patients at significant risk for torsades de pointes [27]. Brief psychotic disorders may also occur in the immediate postoperative period or within 2–4 weeks after the intervention, mainly in patients with a previous history of psychiatric disorders or secondary to steroid treatment. Although rare, the early and correct identification of psychotic disorders deserves attention, given the potential for appropriate good management rather than the very negative effect on HT outcomes if not treated [25, 29].

First Year After Transplant

The first year following HT is characterized by a complex strict clinical follow-up, including laboratory tests, pharmacological monitoring, electrocardiograms and echocardiograms, chest radiography, and biopsies. The need for accurate close clinical surveillance is due to the risk of acute rejection and the higher recipients' frailty in this phase, especially if hospitalized in the period before the intervention. The need to adhere to frequent, continued medical controls and immunosuppressive regimens, the threat of acute rejection, and possible hospital admissions due to infectious complications may all lead to the loss of the initial feeling of omnipotence and contribute to the genesis of feelings of depression and uncertainty. The perception of the graft itself may change, from a magic and powerful organ to

a weak and fragile one [4, 8]. The development of anxiety and depressive symptoms may be influenced by the unique experience of end-stage heart failure and subsequent transplantation, which can be highly traumatic. Competing senses of hope and gratitude mixed with guilt and grief regarding the acceptance of a heart from a deceased donor may contribute to psychopathology in this population. A review of qualitative studies on recipients' perception of the transplant reported a complex variety of experiences, ranging from positive feelings and emotions, connected with a sense of gratitude, pride, and altruism, to more negative ones, such as feeling fearful, depressed, and guilty. Of note, a sense of grief seemed to relate to the loss of the donor's life as well as for the recipient's own heart that had needed to be replaced [30, 31]. Overall, several studies reported a significant improvement in depressive and anxiety symptoms within the first postoperative year compared to the waiting list period [2]. However, HT recipients may experience a higher prevalence of depressive symptoms at hospital discharge and in the early period after HT, with a rapid decline over time. Mood and anxiety disorders, as well as subclinical psychological symptoms, are relatively common in the first year after HT. About 4% of recipients meet criteria for major depressive disorder in the first month after transplant, rising to about 8% by the middle of the first year and to about 14–20% by 12–18 months after transplant [32]. The prevalence of anxiety disorders is similar, with 1.5–7% of recipients meeting criteria for either phobias, panic, generalized anxiety disorder, or post-traumatic stress disorder specifically related to the transplant experience (PTSD-T) during the first month posttransplant, rising to at least 17–18% by the end of the first year [29].

Despite recipients' awareness of being survived to a disabling condition, early problems with medical compliance may already arise during the first year after HT. Previous research found that 20% of recipients reported difficulties with pharmacological adherence, 19% restarted smoking, 18% did not follow nutritional advice, and 9% did not present to scheduled appointments regularly [33]. Data on the occurrence of psychosis beyond the postoperative period, not ascribed to acute organic etiology, are scarce and appear to occur almost exclusively in individuals with a pretransplant history of illness [25, 29].

Long-Term Follow-Up

According to the International Society for Heart and Lung Transplantation (ISHLT) registry, the average life expectancy after cardiac transplant is 10.9 years [34]. With improvement in patients' survival after heart transplant, the quality of life and psychosocial well-being emerged as important outcome measures in the long term. Despite a general improvement in functional and psychosocial status following the intervention, the posttransplant adaptation trajectory may be threatened by the onset of medical complications due to the immunosuppression regimen, pharmacological side effects, and comorbidities. As a result, many patients may experience psychological and psychiatric morbidity in the subsequent years.

Mood and anxiety disorders are the most common ascertained psychiatric conditions after HT. During the first several years following the intervention, up to 63% of recipients have been reported to experience depressive disorders, mainly major depressive disorder or persistent depressive disorder, while up to 26% suffered from one or more anxiety disorders, including generalized anxiety disorder, panic disorder, and post-traumatic stress disorder [29]. Dew et al. (2001) found that 3 years after HT, the cumulative rate of major depressive disorder (MDD) was 25%, slightly higher than that of all anxiety disorders (21%). The levels of distress and impairment due to depressive and anxiety disorders in HT recipients appeared to be severe in terms of length, number of symptoms, and presence of suicidality [32]. Risk factors for depression in the early posttransplant period include worse physical functioning, longer hospitalization, lower level of social support, and inadequate coping strategies [32]. Within 5 years after HT, the estimated frequency of major depression is 41% and 12% for transplantation-related post-traumatic stress disorder (PTSD) [35]. In the last decade, a growing body

of research explored psychological outcomes more than 10 years after HT [36]. Dobbels et al. reported a prevalence of depressive symptoms of 30% at 5 years and 22% at 10 years after surgery, with 20% of the entire study cohort showing symptoms at both time points, according to the Beck Depression Inventory, one of the most used self-administered questionnaires in the field. The use of passive coping strategies, a tendency to express more negative emotions, and lower club membership were associated with the presence of depression at both time points. None of those patients was taking antidepressants or had received psychotherapeutic treatment during the follow-up period [37]. Similar rates of depressive symptoms (30%) were reported by Fusar-Poli et al. in a sample of 137 recipients more than 10 years after HT [38]. A recent cross-sectional study by Conway et al. involving mostly HT long-term survivors found that 10% of participants suffered from major depression according to a structured clinical interview and 18% were receiving antidepressant medications, with depressed HT recipients experiencing worse pain control after controlling for clinical and psychological variables [3]. Of note, depression and anxiety are recognized risk factors for morbidity and mortality after organ transplantation [39]. Predictors of poor psychological functioning after HT include the onset of posttransplant secondary medical complications, poor physical functioning at time of HT or perioperatively, pretransplant history of psychiatric disorder, poorer social supports, use of avoidant/passive coping strategies, lower sense of personal control/self-efficacy, and lower optimism and sense of hope. Cumulative cyclosporine dose and pretransplant VAD support may affect neurocognitive status following HT [40]. Older patients reported better quality of life, psychosocial adjustment, and adherence after HT than middle-aged and younger patients [41, 42].

Despite being recommended by the clinical guidelines for caring for heart transplant recipients, regular screening for anxiety and depression is not a currently standard practice. Although underrecognition and treatment of major depression is a well-known phenomenon in many clinical populations, it may be particularly problematic in transplant recipients due to clinicians' concerns about recommending the addition of psychopharmacological agents to the complex regimen of medications. Treating depression in this patient population is challenging due to drug interactions from patients' antirejection medications. Cyclosporine and tacrolimus are both metabolized utilizing the hepatic CYP450 3A4 pathway: inhibitors of this enzyme increase the risk of their toxicity, while, by contrast, medications that induce 3A4, such as many antidepressants, determine subtherapeutic levels of these immunosuppressants, increasing the risk of graft rejection. Selective serotonin reuptake inhibitors (SSRIs) are the first-line treatment for depression in postcardiac transplant patients. The serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine can be safely used in most transplant recipients. Mirtazapine has been suggested as a second-line treatment to be reserved for patients suffering from cachexia who may benefit from its appetite-stimulating effect [24, 43, 44].

However, transplant patients experience unique issues that may benefit from a psychotherapeutic approach. Interesting findings and potential suggestions come from qualitative research exploring recipients' perceptions of the factors that contributed to their past and present emotions. Adequate support from family, friends, previous HT recipients, and the transplant team has been reported as essential. However, too much support from caregivers at a time when the HT recipient was trying to readjust back to normal life was noted as an obstacle to recovery and a source of potential conflict within family dynamics [31]. These considerations highlight the importance of tailored support transitioning to a level that promote recipients' sense of independence and perceived control over health and daily life. As a practical implication for healthcare providers too, these findings suggest that during hospitalizations the staff should provide the HT recipient with as many opportunities to care for themselves as possible. Other interventions, which have been shown to increase perceived control in cardiac populations, include reframing techniques in which an acute event is viewed not as something

that is uncontrollable out of control but as an isolated exacerbation of a chronic condition that can be controlled managed with adherence to prescribed medications and lifestyle modifications. Receiving support from others who had previously undergone HT was also considered particularly beneficial as HT was viewed by recipients as a unique experience. Further research is needed to explore the impact of peer support programs and group interventions [31].

Data on the impact of non-pharmacologic interventions on psychological outcomes for heart transplant recipients are limited, and insufficient evidence is currently available. This is surprising, given the long term since ISHLT first calls for more research in the field. Moreover, no study specifically addressed the impact of non-pharmacological interventions on psychological outcomes in heart transplant recipients fitting the criteria for psychopathology [40, 45]. Possible reasons include feasibility of psychosocial interventions, including psychiatric evaluation and psychotherapeutic treatment in the hospital setting, accessibility for patients living at a long distance from the transplant center or coming from other regions of the country, restrictions due to physical illnesses, costs, and availability of dedicated trained staff.

Exercise programs, a web-based intervention, cognitive behavioral therapy (CBT), interpersonal psychotherapy, and mindfulness-based stress reduction techniques have been shown to improve depressive symptoms and quality of life in solid-organ transplant and cardiovascular disease patients [45–47]. Recently, a pilot study by Conway et al. found that telephone-delivered CBT was not acceptable in HT recipients [48]. More research into how depression manifests after heart transplantation is required in order to determine the most effective supportive strategies.

Conclusion

HT raises unique psychological issues and potential psychiatric complications which originate from the human source of the graft, together with the complexity of the entire clinical and therapeutic trajectory. HT therefore deserves a multidisciplinary approach, including psychological and psychiatric competences.

Cross-References

- ▶ Antipsychotics and Cardiac Side Effects
- ▶ Anxiety, Anger, Personality, and Heart Disease
- ▶ Cardiovascular Manifestations of Panic and Anxiety
- ▶ Depression and Cardiovascular Diseases
- ▶ Major Psychiatric Complications of Cardiac Surgery
- ▶ Psychiatric and Neurological Effects of Cardiovascular Drugs
- ▶ Psychiatric Aspects of Sudden Cardiac Arrest and Implantable Cardioverter-Defibrillators
- ▶ Psychological and Cardiovascular Effects of Meditation and Yoga
- ▶ Psychotherapy and Psychological Support for Severe Heart Conditions

References

1. Barnard CN. A human cardiac transplant: an interim report of a successful operation performed at Grote Schuur Hospital, Cape Town. S Afr Med J. 1967;41:1271–4.
2. Sánchez R, Baillès E, Peri JM, Bastidas A, Pérez-Villa F, Bulbena A, Pintor L. Assessment of psychosocial factors and predictors of psychopathology in a sample of heart transplantation recipients: a prospective 12-month follow-up. Gen Hosp Psychiatry. 2016;38:59–64.
3. Conway A, Sheridan J, Maddicks-Law J, Fulbrook P, Ski CF, Thompson DR, Clark RA, Doering LV. Depression and pain in heart transplant recipients: an observational study. Biol Res Nurs. 2017;19:71–6.
4. Castelnuovo-Tedesco P. Ego vicissitudes in response to replacement or loss of body parts. Certain analogies to events during psychoanalytic treatment. Psychoanal Q. 1978;47:381–97.
5. Blacher R. Death, resurrection, and rebirth: observations in cardiac surgery. Psychoanal Q. 1983; 52:56–72.
6. Levenson JL, Olbrisch ME. Psychiatric aspects of heart transplantation. Psychosomatics. 1993;34:114–23.
7. Mauthner OE, De Luca E, Poole JM, Abbey SE, Shildrick M, Gewarges M, Ross HJ. Heart transplants:

identity disruption, bodily integrity and interconnectedness. Health. 2015;19:578–9.
8. Castelnuovo-Tedesco P. Transplantation. Psychological implications of changes in body image. In: Levy NB, editor. Psychonephrology 1. Boston: Springer; 1981.
9. Wynn F. Reflecting on the ongoing aftermath of heart transplantation: Jean-Luc Nancy's L'intrus. Nurs Inq. 2009;16:3–9.
10. Dew MA, DiMartini AF, Dobbels F, Grady KL, Jowsey-Gregoire SG, Kaan A, Kendall K, Young QR, Abbey SE, Butt Z, Crone CC, De Geest S, Doligalski CT, Kugler C, McDonald L, Ohler L, Painter L, Petty MG, Robson D, Schlöglhofer T, Schneekloth TD, Singer JP, Smith PJ, Spaderna H, Teuteberg JJ, Yusen RD, Zimbrean PC. The 2018 ISHLT/APM/AST/ICCAC/STSW recommendations for the psychosocial evaluation of adult cardiothoracic transplant candidates and candidates for long-term mechanical circulatory support. J Heart Lung Transplant. 2018;37:803–23.
11. Maldonado JR, Dubois HC, David EE, Sher Y, Lolak S, Dyal J, Witten D. The Stanford Integrated Psychosocial Assessment for Transplantation (SIPAT): a new tool for the psychosocial evaluation of pre-transplant candidates. Psychosomatics. 2012;53:123–32.
12. Spaderna H, Smits JM, Rahmel AO, Weidner G. Psychosocial and behavioural factors in heart transplant candidates-an overview. Transpl Int. 2007;20:909–20.
13. Delibasic M, Mohamedali B, Dobrilovic N, Raman J. Pre-transplant depression as a predictor of adherence and morbidities after orthotopic heart transplantation. J Cardiothorac Surg. 2017;12:62.
14. Burker EJ, Madan A, Evon D, Finkel JB, Mill MR. Educational level, coping, and psychological and physical aspects of quality of life in heart transplant candidates. Clin Transpl. 2009;23:233–40.
15. Spaderna H, Zittermann A, Reichenspurner H, Ziegler C, Smits J, Weidner G. Role of depression and social isolation at time of waitlisting for survival 8 years after heart transplantation. J Am Heart Assoc. 2017;29:6 (12).
16. Olbrisch ME, Levenson JL, Hamer R. The PACT: a rating scale for the study of clinical decision-making in psychosocial screening of organ transplant candidates. Clin Transpl. 1989;3:164–9.
17. Twillman RK, Manetto C, Wellisch DK, et al. The transplant evaluation rating scale. A revision of the psychosocial levels system for evaluating organ transplant candidates. Psychosomatics. 1993;34:144–53.
18. Sánchez R, Baillés E, Peri JM, Bastidas A, Pérez-Villa F, Bulbena A, Pintor L. Cross-sectional psychosocial evaluation of heart transplantation candidates. Gen Hosp Psychiatry. 2014;36:680–5.
19. Doehner W, Ural D, Haeusler KG, Čelutkienė J, Bestetti R, Cavusoglu Y, Peña-Duque MA, Glavas D, Iacoviello M, Laufs U, Alvear RM, Mbakwem A, Piepoli MF, Rosen SD, Tsivgoulis G, Vitale C, Yilmaz MB, Anker SD, Filippatos G, Seferovic P, Coats AJS, Ruschitzka F. Heart and brain interaction in patients with heart failure: overview and proposal for a taxonomy. A position paper from the Study Group on Heart and Brain Interaction of the Heart Failure Association. Eur J Heart Fail. 2018;20:199–215.
20. Heilmann C, Kuijpers N, Beyersdorf F, Berchtold-Herz M, Trummer G, Stroh AL, Schlensak C, Fritzsche K. Supportive psychotherapy for patients with heart transplantation or ventricular assist devices. Eur J Cardiothorac Surg. 2011;39:44–50.
21. Baba A, Hirata G, Yokoyama F, Kenmoku K, Tsuchiya M, Kyo S, Toyoshima R. Psychiatric problems of heart transplant candidates with left ventricular assist devices. J Artif Organs. 2006;9:203–8.
22. Caro MA, Rosenthal JL, Kendall K, Pozuelo L, Funk MC. What the psychiatrist needs to know about ventricular assist devices: a comprehensive review. Psychosomatics. 2016;57:229–37.
23. Sokoreli I, de Vries JJ, Pauws SC, Steyerberg EW. Depression and anxiety as predictors of mortality among heart failure patients: systematic review and meta-analysis. Heart Fail Rev. 2016;21:49–63.
24. Crone CC, Gabriel GM. Treatment of anxiety and depression in transplant patients: pharmacokinetic considerations. Clin Pharmacokinet. 2004;43:361–94.
25. Ackerman MG, Shapiro PA. Psychological effects of invasive cardiac surgery and cardiac transplantation. In: Alvarenga M, Byrne D, editors. Handbook of psychocardiology. Singapore: Springer; 2016.
26. Alejaldre A, Delgado-Mederos R, Santos MÁ, Martí-Fàbregas J. Cerebrovascular complications after heart transplantation. Curr Cardiol Rev. 2010;6:214–7.
27. Ibrahim K, McCarthy CP, McCarthy KJ, Brown CH, Needham DM, Januzzi JL Jr, McEvoy JW. Delirium in the Cardiac Intensive Care Unit. J Am Heart Assoc. 2018;7:1–11.
28. Anderson BJ, Chesley CF, Theodore M, Christie C, Tino R, Wysoczanski A, Ramphal K, Oyster M, Kalman L, Porteous MK, Bermudez CA, Cantu E, Kolson DL, Christie JD, Diamond JM. Incidence, risk factors, and clinical implications of post-operative delirium in lung transplant recipients. J Heart Lung Transplant. 2018;37:755–62.
29. Dew MA, DiMartini AF. Psychological disorders and distress after adult cardiothoracic transplantation. J Cardiovasc Nurs. 2005;20:S51–66.
30. Poole J, Ward J, DeLuca E, Shildrick M, Abbey S, Mauthner O, Ross H. Grief and loss for patients before and after heart transplant. Heart Lung. 2016;45:193–8.
31. Conway A, Schadewaldt V, Clark R, Ski C, Thompson DR, Doering L. The psychological experiences of adult heart transplant recipients: a systematic review and meta-summary of qualitative findings. Heart Lung. 2013;42:449–55.
32. Dew MA, Kormos RL, DiMartini AF, Switzer GE, Schulberg HC, Roth LH, Griffith BP. Prevalence and

risk of depression and anxiety-related disorders during the first three years after heart transplantation. Psychosomatics. 2001;42:300–13.
33. Dew MA, Roth LH, Thompson ME, Kormos RL, Griffith BP. Medical compliance and its predictors in the first year after heart transplantation. J Heart Lung Transplant. 1996;15:631–45.
34. International Society for Heart and Lung Transplantation (ISHLT). International Thoracic Organ Transplant (TTX) Registry. https://www.ishlt.org/registries/ttx-registry
35. Favaro A, Gerosa G, Caforio AL, Volpe B, Rupolo G, Zarneri D, Boscolo S, Pavan C, Tenconi E, d'Agostino C, Moz M, Torregrossa G, Feltrin G, Gambino A, Santonastaso P. Posttraumatic stress disorder and depression in heart transplantation recipients: the relationship with outcome and adherence to medical treatment. Gen Hosp Psychiatry. 2011;33:1–7.
36. Politi P, Piccinelli M, Fusar-Poli P, Klersy C, Campana C, Goggi C, Viganò M, Barale F. Ten years of "extended" life: quality of life among heart transplantation survivors. Transplantation. 2004;78:257–63.
37. Dobbels F, De Geest S, Martin S, Van Cleemput J, Droogne W, Vanhaecke J. Prevalence and correlates of depression symptoms at 10 years after heart transplantation: continuous attention required. Transpl Int. 2004;17:424–31.
38. Fusar-Poli P, Martinelli V, Klersy C, Campana C, Callegari A, Barale F, Viganò M, Politi P. Depression and quality of life in patients living 10 to 18 years beyond heart transplantation. J Heart Lung Transplant. 2005;24:2269–78.
39. Dew MA, Rosenberger EM, Myaskovsky L, DiMartini AF, DeVito Dabbs AJ, Posluszny DM, et al. Depression and anxiety as risk factors for morbidity and mortality after organ transplantation: a systematic review and meta-analysis. Transplantation. 2015;100:988–1003.
40. Cupples S, Dew MA, Grady KL, De Geest S, Dobbels F, Lanuza D, Paris W. Report of the Psychosocial Outcomes Workgroup of the Nursing and Social Sciences Council of the International Society for Heart and Lung Transplantation: present status of research on psychosocial outcomes in cardiothoracic transplantation: review and recommendations for the field. J Heart Lung Transplant. 2006;25:716–25.
41. Shamaskin AM, Rybarczyk BD, Wang E, White-Williams C, McGee E Jr, Cotts W, Grady KL. Older patients (age 65+) report better quality of life, psychological adjustment, and adherence than younger patients 5 years after heart transplant: a multisite study. J Heart Lung Transplant. 2012;31:478–84.
42. Martinelli V, Fusar-Poli P, Emanuele E, Klersy C, Campana C, Barale F, Viganò M, Politi P. Getting old with a new heart: impact of age on depression and quality of life in long-term heart transplant recipients. J Heart Lung Transplant. 2007;26:544–8.
43. Fusar-Poli P, Picchioni M, Martinelli V, Bhattacharyya S, Cortesi M, Barale F, Politi P. Anti-depressive therapies after heart transplantation. J Heart Lung Transplant. 2006;25:785–9.
44. Michaelsen K, Arnold RM. Treating depression after heart transplantation #273. J Palliat Med. 2013;16:1477–8.
45. Conway A, Schadewaldt V, Clark R, Ski C, Thompson DR, Kynoch K, Doering L. The effectiveness of non-pharmacological interventions in improving psychological outcomes for heart transplant recipients: a systematic review. Eur J Cardiovasc Nurs. 2014;13:108–15.
46. Dew MA, Goycoolea JM, Harris RC, Lee A, Zomak R, Dunbar-Jacob J, Rotondi A, Griffith BP, Kormos RL. An internet-based intervention to improve psychosocial outcomes in heart transplant recipients and family caregivers: development and evaluation. J Heart Lung Transplant. 2004;23:745–58.
47. Stonnington CM, Darby B, Santucci A, Mulligan P, Pathuis P, Cuc A, Hentz JG, Zhang N, Mulligan D, Sood A. A resilience intervention involving mindfulness training for transplant patients and their caregivers. Clin Transpl. 2016;30:1466–72.
48. Conway A, Sheridan J, Maddicks-Law J, Fulbrook P. Pilot testing a model of psychological care for heart transplant recipients. BMC Nurs. 2016;15:62.

Psychotherapy and Psychological Support for Severe Heart Conditions

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Contents

Abstract

Cardiovascular diseases are the leading causes of death around the world and in most developed countries are the major causes of disability among elderly people.

In this chapter psychological issues and psychological/psychotherapeutic interventions related to chronic coronary heart disease and chronic heart failure (the most common type of heart disease) are discussed.

The relationship between psychosocial risk factors and health outcomes in cardiac diseases is known. Many researches in fact show that psychosocial risk factors, such as low socioeconomic status, social isolation, stress, type D personality (a tendency to experience negative emotions associated with a tendency not to express these emotions when together with others), depression, and anxiety, increase the risk of incident coronary heart disease and also contribute to poorer health-related quality of life and prognosis in patients with established

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*,
https://doi.org/10.1007/978-3-030-28008-6_26

cardiovascular diseases. Evidence also exists for an association between depression, social factors, and disease outcome for chronic heart failure.

Evidence-based psychological support and psychotherapy, consisting of cognitive behavioral therapy (mainly), interpersonal therapy, and short-term psychodynamic therapy, are discussed.

Finally, different psychoeducational and psychological interventions in order to enhance cardiac patient adherence to pharmacological and non-pharmacological prescriptions are described.

Keywords

Psychosocial factors · Adherence · Psychotherapy · Psychological support · Heart diseases · Coronary heart disease · Chronic heart failure

Introduction

Cardiovascular diseases are the leading causes of death around the world and in most developed countries are the major origin of disability among elderly people [1]. The incidence of cardiovascular diseases (CVD) has been strongly related with classic risk factors (hypertension, dyslipidemia, and diabetes) and poor lifestyles (smoking, physical inactivity, and unhealthy diet) [1]. In the last 30 years, psychosocial risk factors and inadequate psychosocial and living conditions have also been found to be linked to CVD [2–6]. The relationship between psychosocial risk factors and health outcomes in chronic diseases has been the subject of a review of evidence for cancer and cardiovascular disease in a 2015 WHO document [7]. Thirty-seven systematic reviews and meta-analyses were identified. Among the psychosocial factors repeatedly identified as related to chronic diseases emerge: high job demand, low autonomy, low control or high effort-reward imbalance, interpersonal conflicts, and low social support or low trust. Evidence suggests that multiple psychosocial factors are independently associated with various chronic diseases throughout adulthood. Moreover, the social gradient in health observed during adulthood can partly operate through psychosocial factors on the path between socioeconomic characteristics and health. This report provides evidence that psychosocial factors play an important role in explaining CVD outcomes. In particular for cardiovascular diseases, evidence for association with depression and social isolation is strong and consistent. Psychosocial factors, therefore, could become part of comprehensive risk reduction interventions focused on multiple risk factors. These findings suggest that psychosocial factors can provide multiple opportunities for prevention, intervention, and possible cross-sectoral approaches to address social inequalities in health observed in the middle and elderly age. These results also support health policy 2020, which aims to reduce health inequalities and focuses on actions that would improve health, including improving psychosocial conditions to reduce stress through measures such as work control, adequate social protection, or improvement of job security.

In this chapter psychological issues and psychological/psychotherapeutic interventions related to chronic coronary heart disease (CHD) and chronic heart failure (CHF) are presented. Particularly, we describe the model developed by the working group of psychologists of GICR-IACPR [8, 9], which show the steps of a psychological intervention in CHD and CHF patients, especially in a cardiac rehabilitation setting in Italy. Recently the working group of psychologists of the GICR-IACPR (Italian Association for Cardiovascular Prevention, Rehabilitation, and Epidemiology) updated and renewed the Italian Psychological Guidelines published in 2003, in order to elaborate a document on the best practice in daily psychological activities in CPR based on efficacy, effectiveness, and sustainability, introducing new knowledge and new paths for psychologists who work in the cardiac and preventive rehabilitation settings [9].

Coronary Heart Disease (CHD)

Patients suffering from CHD should adapt to radical changes in their health status and may experience intense emotional states to their previous work, leisure, and level of sexual activity, even if they are physically fit to these activities, such as excitement, anger, anxiety, fears, and depression. These experiences are often associated with the failure to return. Many studies have shown that psychosocial risk factors, such as low socioeconomic status, social isolation, stress, type D personality, depression, and anxiety, increase the risk of incident coronary heart disease and also contribute to poorer health-related quality of life and prognosis in patients with established CHD. Psychosocial risk factors may also act as barriers to lifestyle changes and treatment adherence [2, 4, 9, 10].

The prevalence of depression is between 15% and 20% in coronary heart disease, and estimates of clinically relevant depressive symptoms are much higher [11, 12]. A recent meta-analysis indicated a prevalence rate of 16% of anxiety disorders [13]. While psychosocial risk factors such as anxiety and depression may affect the cardiovascular system through biological and behavioral pathways, on the other hand, CHD and its treatments may cause anxious and depressive reactions in the patient and in the caregiver [14].

Many position papers and psychological guidelines [2–6, 9, 10] underline the need of an effective management of these psychosocial risk factors, including the screening of psychosocial risk factors and the implementation of different psychological intervention programs, such as counseling, motivational interview, health psychoeducation, and psychotherapy. It may be important to teach the patients to change their existing stressors, or to enhance their coping mechanisms for existing stressors, than to change unhealthy lifestyle habits.

Educational interventions can affect a patient's psychological state positively and reduce misconceptions about CHD and its outcomes [15]. A larger number of "multidisciplinary" studies have been conducted to determine the effectiveness of psychosocial interventions for primary and secondary prevention, but often the effects of psychosocial components cannot be formally isolated from these studies. *Psychoeducation* is a method of disease management that provides patients with the tools they need to take control of their health and healthcare. A complete psychoeducational intervention for CHD should include health education with nutrition and smoking cessation counseling, physical activity program, and emotional/psychosocial support. Cardiac rehabilitation is a secondary prevention intervention that focuses on the overall well-being of patients after a cardiac event. One of the core components of CR is the psychological support that is intended to both evaluate and manage psychosocial risk factors that are also cardiovascular risk factors [15].

The studies on *psychological interventions* for CHD patients reported positive effects on quality of life, health behavior, and somatic risk profile, while others reported a protective effect on cardiovascular morbidity and mortality [14]. Some studies showed small-to-moderate improvements in depression and anxiety, a small reduction in cardiac mortality risk, and a reduction in all-cause mortality risk for men but not women. Men appear to profit more from the interventions than women, but there are less studies of women than men [14]. Linden et al. [16] showed that programs, which were initiated at least 2 months after the cardiac event, showed stronger effects on the rate of future events than those initiated immediately after. Welton et al. [17] carried out systematic literature searches to update an earlier Cochrane review and classified components of interventions into six types: usual care, educational, behavioral, cognitive, relaxation, and support. Most interventions were a combination of these components. There was some evidence that psychological interventions were effective in reducing total cholesterol and standardized mean anxiety scores, that interventions with behavioral components were effective in reducing the odds of all-cause mortality and nonfatal myocardial infarction, and that interventions with behavioral

and/or cognitive components were associated with reduced standardized mean depression scores. The meta-analysis by Whalley et al. [18] underlined the positive effects of psychological interventions on quality of life, depressive symptoms, and anxiety, as well as an effect on cardiac mortality. Pogosova et al. [2] affirmed that stress management should be offered to patients (on an individual basis or in small groups) and that significant others should be included in the programs. A recent umbrella review and meta-analysis of RCT of psychotherapeutic interventions aimed at patients with ischemic heart disease [19], which consists of 4 systematic reviews and of the meta-analysis of 24 RCTs, showed positive effects on psychological distress conditions, on the management of traditional risk factors, and with respect to some cardiovascular prognostic indices. Furthermore, a Cochrane review [20] highlighted that for people with CHD, psychological treatments reduce the rate of cardiac mortality and symptoms of depression, anxiety, or stress; there is no evidence that psychological treatments influence overall mortality, the risk of revascularization procedures, or the rate of nonfatal AMI. There remain some uncertainties regarding people who would benefit the most from treatment (i.e., people with or without psychological disorders at baseline) and the specific components of successful interventions. Psychological interventions combined with additional pharmacology (when deemed appropriate) seemed to be more specifically effective for people showing depressive symptoms. For anxiety, recruitment interventions for participants with a basic psychological disorder were more effective than those given to non-selected populations.

The most recent systematic review and meta-analysis of randomized controlled trials (RCTs) of psychological interventions in coronary heart disease [21], including RCT with at least 6 months of follow-up, compared the direct effects of psychological interventions to usual care for patients following myocardial infarction or revascularization or diagnosis of angina pectoris or coronary artery disease defined by angiography. Thirty-five studies were included with 10,703 participants (median follow-up of 12 months). In many of the psychological interventions, the reference model is cognitive behavioral therapy (CBT) (Table 1), and many evidence-based techniques developed as management strategies for promoting healthy behaviors and the enhancement of psychosocial well-being are derived by CBT: health counseling, smoking cessation and weight management, self-monitoring, stress management, etc.

Data from the literature on the effectiveness of the psychological interventions and *evidence-based psychotherapy* are mainly based on CBT interventions [14]. Most of the studies with CBT involve individual and/or group interventions; the average duration is about 1 year with weekly

Table 1 Cognitive behavioral therapy model

Cognitive behavioral therapy (CBT)
CBT is a form of psychotherapy oriented toward short-term goals, which aims at a cognitive and behavioral action useful for modifying thoughts, emotions, and problems that are a source of discomfort. CBT is effective, recognized as preferential for most emotional and behavioral disorders by the international scientific community and the WHO.
Behavioral therapy teaches people to react differently to problematic situations. It focuses on changing specific actions using different techniques to decrease or eliminate behaviors that create discomfort and increase or acquire behaviors that promote a better quality of life.
Cognitive therapy helps people learn how thoughts and beliefs often contribute to creating a distorted view of what is happening in our lives making us feel anxious, depressed, and angry. Awareness of the role of these thoughts, combined with other behavioral techniques, helps the person to compete and confront the dreaded situations and their own fears.
The evolution of CBT could be briefly summarized as follow:
"First wave": in the first period [up to 50–60 years] the emphasis was on behavior and learning.
"Second wave": the focus is on the link between thoughts, emotions, and behaviors and on the role of conscious thought in the psychotherapeutic field.
"Third wave": puts more emphasis on the ability to react differently to one's own thoughts, without questioning them or trying to rediscover them.

sessions in the early stages, followed by monthly sessions in the second part [9].

In the literature there are few reports of psychotherapeutic interventions with a non-cognitive behavioral orientation. A randomized clinical trial conducted in 2013 by Roncella et al. [22, 23] shows the efficacy of a short-term psychotherapy (group and individual) on cardiac symptoms, quality of life, and psychological/medical outcomes at 1-year follow-up. This short-term intervention model, however, is awaiting replication studies that could confirm the strength of the results. Finally, Lesperance [24] shows the effectiveness of interpersonal psychotherapy on reducing depression in a sample of patients with CHD. However, further studies are required due to the low number of studies and short follow-up duration (1 year).

Chronic Heart Failure (CHF)

CHF is a common chronic disease with poor prognosis and significant quality of life limitations. The European guidelines on heart failure [25] point out that heart failure is a common and chronic disease with an unfavorable prognosis and severe quality of life limits. Patients are required to follow a complex regimen of self-care behaviors, including medication, self-monitoring of symptoms, diet, and exercise. Mental comorbidities such as depressive and anxious disorders are common in patients with CHF. Depressive comorbidities are present in about 20% of patients, anxious comorbidities of up to 40% [26].

Evidence-based *psychological and psychotherapeutic interventions* in heart failure [9] show that it is essential to treat patients in the perspective of a chronic and invasive disease. The patient need to develop cognitive, emotional, and behavioral skills that allow it to live with this disease, adhere to complex therapeutic regimens, and maintain a reasonable level of quality of life. Specific counseling or psychotherapeutic interventions (cognitive therapy and stress management) are often included in the set of non-pharmacological approaches (including physical activity and dietary prescriptions) or included in the global rehabilitative treatment or in multidisciplinary intervention for which it is difficult to document the specific effectiveness. Psychological intervention can be performed on dysfunctional aspects (cognitive, emotional, or behavioral) in the management of the disease, counseling in the optimization of coping, and psychological support during the stabilization phase. Many contributions focus on depression and the provision of emotional support or counseling in order to understand the needs of the patient, manage emotional responses to the disease, improve the quality of life, and optimize the physical outcomes of the therapeutic intervention.

Interventions to optimize the CHF treatment, reduce hospitalizations and mortality, and improve quality of life and management of the disease, carried out during the stay in hospital or at home with telemedicine methods or face-to-face interventions, are linked to two key aspects: [a] self-management and adherence and [b] depression and anxiety [9].

Psychological Support and Psychotherapy: Intervention Models

The Model Developed by the Working Group of Psychologists of GICR-IACPR in the Context of Rehabilitation

Over the past 18 years, psychologists in the context of rehabilitation have started to work more and more in collaboration with cardiology teams, developing tailored interventions to address the needs of both patients and their caregivers [8]. The position paper "Best practice on psychological activities in cardiovascular prevention and rehabilitation" [9] is the update of the "Guidelines for the activities of psychology in rehabilitative and preventive cardiology" [5] and aims to act as a tool for consultation and promotion of best practice in the daily clinical activity of psychological activities in a preventive and rehabilitative cardiology setting directing with clarity the choice of

interventions which are evidence based and which have at least a minimum standard. It contains indications of best practice concerning evaluation and intervention, transversal to various cardiac pathologies (coronary heart disease, heart failure, cardiac surgery, etc.), deduced from the analysis of scientific evidence, as well as from legal and deontological considerations:

- Assess the possible presence of psychopathological aspects in the medical history, and consider referring the patient to local community services.
- Investigate the possible presence of previous cognitive deficits.
- Evaluate the possible presence of depression and anxiety, either reactive or related to the clinical condition.
- Evaluate the presence/absence of social support.
- Evaluate the knowledge, awareness, acceptance, and management of the disease.
- Take into account sex, age, and ethnic minorities.
- Evaluate positive, personal, and environmental resources, and construct interventions aimed at reinforcing them.
- Evaluate the level of health literacy of the patient and caregiver in order to personalize the informative, educational, and communication intervention.
- Design psychological interventions of low/high intensity based on the problems detected and the working and organizational resources present.
- Provide counseling to caregivers where problems are detected and/or their need emerges from the patients themselves, the family, and/or the multidisciplinary team.
- Provide counseling on sexuality, where problems arise.
- Structure all of the psychological activity within the multidisciplinary intervention and in synergy with the team.

The literature analysis permitted the authors to define a model of assessment and intervention in the cardiac diseases. CHD and CHF evaluation and intervention suggested in the position paper are reported in Tables 2 and 3.

Table 2 CHD evaluation and psychological intervention

Assessment
Behavioral risk factors
Social factors
Depression
Anxiety and panic
Stress
Posttraumatic stress disorder
Personality factors (type D)
Intervention
Psychological support and psychoeducational sessions (patient and family)
Psychotherapeutic interventions
Cognitive behavioral therapy (depression, anxiety, relaxation, stress management)
Interpersonal psychotherapy on depression
Short-term – psychoanalytic therapy
Mindfulness interventions

Table 3 CHF evaluation and psychological intervention

Assessment
Alcohol and cocaine addiction
Social factors
Depression
Anxiety
Neuropsychological disorders
Sleep disorders
Disease management
Intervention
Psychoeducational and disease management interventions (self-care)
Cognitive behavioral interventions
Telemedicine
Psychological support and psychoeducational interventions in family members
Caregiver burden interventions

Psychoanalytic Psychotherapy

Psychodynamic psychotherapy is another methodology used in the field of cardiac psychology. It is an empirical and speculative discipline that includes a wide range of theoretical models of mind and psychopathology and a wide range of

psychotherapeutic techniques. Since it was first developed, derived from Freud's psychoanalytic theory, it has been contaminated by contributions from various theoretical approaches – such as ethology, the cognitive sciences, and the neurosciences. Despite these important premises and the long-standing tradition of psychoanalytic psychotherapy, the psychodynamic literature within cardiology reveals many gaps, as outlined in systematic review published by Jordan and Barde in 2007 [27]. The authors pointed out some of the methodological limits of prior studies (e.g., small subject samples and high drop-out rates). Furthermore, the studies reviewed by the authors focused on the personality characteristics of patients with cardiovascular disease rather than on their treatment.

Psychological Intervention for Enhancing Cardiac Patient Adherence

In this paragraph, some researches about psychoeducational programs, which aim to improve adherence and to reduce anxiety and depression, will be reviewed. The focus will be on cardiac treatment studies to enhance adherence in CHD, CHF, and diabetes patients.

Noncommunicable diseases (NCDs, also known as chronic diseases, are not passed from person to person. They are of long duration and generally slow progression. The four main types of noncommunicable diseases are cardiovascular diseases (like heart attacks and stroke), cancers, chronic respiratory diseases, (such as chronic obstructed pulmonary disease and asthma), and diabetes. The World Health Organization (WHO) estimated that ≈80% of NCDs could be prevented if four key lifestyle practices were followed: a healthy diet, being physically active, avoidance of tobacco, and alcohol intake in moderation [28]. In the 2003, the WHO defines adherence as "...the extent to which a person's behavior – taking medication, following a diet, and/or executing lifestyle changes – corresponds with the agreed recommendations from a provider" [29]. Furthermore, the WHO's adherence definition emphasizes the importance of active involvement of the patient and good communication with healthcare professionals. Given the magnitude and clinical implications of nonadherence to medication regimens, the WHO has published evidence-based guidelines for clinicians, healthcare managers, and policymakers on strategies to improve medication adherence [29]. More recently, the ABC (Ascertaining Barriers to Compliance) taxonomy defines the overarching concept of "medication adherence" as a process divided into three essential phases: "initiation," "implementation," and "persistence." This process well describes the sequence of events that have to happen for a patient to experience the optimal benefit from the prescribed treatment [30, 31].

In older adults and severe cardiac patients, optimal adherence should be viewed as a means of achieving a satisfactory therapeutic outcome and not as a goal in itself [32]. To achieve this goal, it is advisable to adopt a multidisciplinary approach, in terms of multidisciplinary team [33] and educational/psychoeducational programs [6]. The interest on this topic is based on the idea that a range of specific interplaying factors facilitates the process of developing self-management strategies and regulates emotional/cognitive process. Among these, disease awareness, self-efficacy, self-care, and other metacognitive factors can be generally improved by using appropriate psychological techniques and interventions. In this circular process, the final goal is to enhance cardiac patient adherence to pharmacological and non-pharmacological prescriptions (Fig. 1) [34].

Psychoeducational Interventions to Enhance Cardiac Patient Adherence: Theory, Model, and Specific Studies

Mutual mechanisms link psychosocial factors to increased CVD risk and lower level of adherence: factors that include an unhealthy lifestyle (frequent smoking, poor diet, and poor physical exercise), increased healthcare utilization, financial barriers to healthcare, and low adherence to

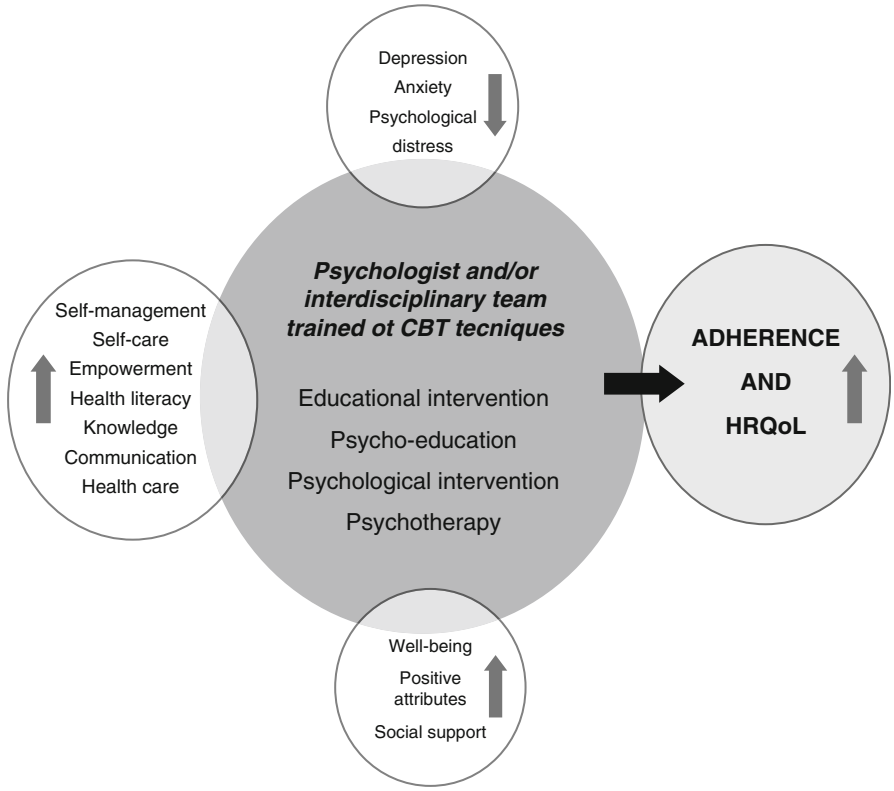

Fig. 1 Psychologist and/or interdisciplinary team trained to CBT techniques

behavior change recommendations or cardiac medications [6]. As discussed before, depression and anxiety are linked to nonadherence and can significantly impair the ability to manage cardiac illness; the odds of medical treatment non-adherence are three times greater among depressed patients compared to non-depressed patients [35, 36]. On the other hand, positive psychological attributes have been linked with improved adherence to a number of behaviors that are important to cardiovascular health. Such behaviors have included healthy eating, sufficient exercise/activity, smoking cessation, and medication adherence. Additional studies have also found links between positive attributes and other health-related behaviors, such as alcohol use and sleep quality [37, 38].

The most important technique used in the psychoeducational interventions is motivational counseling (MC) or motivational interviewing (MI) and cognitive behavioral therapy (CBT) [9, 39, 40]. During the process of self-redefinition, the psychologists motivate the patient to correct health risk factors (e.g., smoking, poor dietary habits, a sedentary lifestyle, high stress, etc.) and to reinforce the patient's adaptive behaviors toward self-care and management adherence. These issues are typical components of CBT in a rehabilitative setting for cardiac patients, with a constant focus not only on limitations but also on resources, according to the biopsychosocial model of illness and the International Classification of Functionality (ICF) [41, 42].

Intervention on anxiety and depression should never be neglected since two objectives could be reached: first to improve the patient's emotional status and secondly to indirectly intervene on adherence self-management. Psychological interventions could be implemented in those

single-case situations where the presence of psychological difficulties could interfere with disease self-management, cardiac rehabilitation adherence, and outcome. These interventions include individual or group counseling on psychosocial risk factors and coping with illness, stress management programs, meditation, autogenic training, biofeedback, breathing, yoga, and/or muscular relaxation [8, 9].

The caregiver-patient team interaction should follow the principles of patient-centered care, which refers to taking a whole person perspective, in contrast to the traditional medical model, and is based on respect for patients' values, needs, and preferences. Empathic and patient-centered communication helps to establish and maintain a trustful relationship and is a powerful source of emotional support and professional guidance in coping with psychosocial stressors, depression, anxiety, and lifestyle risk factors. Combining the knowledge and skills of caregivers into multimodal behavioral interventions can optimize preventive efforts. They enhance coping with illness and improve adherence [4, 6, 9].

Eight out of ten studies of a meta-analysis demonstrated an increased uptake of cardiac rehabilitation. Three out of eight studies demonstrated improvement in adherence to cardiac rehabilitation. Successful interventions included self-monitoring of activity, action planning, and tailored counseling by cardiac rehabilitation staff [18]. On the other hand, randomized controlled trials of positive affect interventions – combined with patient education – have shown clinically significant increases in physical activity among patients after percutaneous coronary intervention and improvements in medication adherence among hypertensive patients, compared with education intervention alone. More work is needed to understand the role of positive psychological factors in the processes of health behavior maintenance and change. It is becoming increasingly clear that psychoeducational programs for CHD patients do not increase event-free survival, but the intervention can improve depression, social isolation, adherence to therapy, health-related quality of life (HRQoL), and overall prognosis [38, 43, 44].

We take into account other studies, not included in the previous meta-analysis, and we summarize them in Table 4 [45–50].

In Table 4 we refer to cognitive behavioral therapy for adherence and depression (CBT-AD) that integrates CBT for depression with another program to promote medical adherence. The treatment, originally developed for patients with HIV, is divided into modules where core CBT skills can be learned, followed by focused work on specific individual problems. In the first session of CBT-AD, beliefs about illness and treatment are elicited from patients, and special attention is paid to cognitions related to the specific treatment regimen of each patient. The CBT-AD has proven to be a good treatment for improving depressive symptoms and medication adherence in the context of various chronic health conditions, including diabetes [49, 50]. Further investigations are needed to strengthen these results and to implement more and more specific interventions to enhance pharmacological and non-pharmacological adherence in cardiac patients.

Tailored Interventions for Older Cardiac Patients and Their Caregivers

When handling the older patient, it is necessary to enact different strategies in order to guarantee adherence to treatment, because the possible presence of cognitive deterioration, visual and auditory deficits, cultural resources, and social status influence communication with these patients on various levels (attention, comprehension, planning, and memory). Therefore, sometimes, it will be necessary to utilize another type of language and a different modality of interaction, which will eventually involve a caregiver. This problem results in being widely underestimated by the health professionals, whose prescriptions are often not adequate to the objectives, the real capacity of understanding, and to the preference of the patient. The findings of a recent review highlight the importance of working to improve healthcare strategies for older adults with low health literacy and the need for a standardized

Table 4 Psychoeducational interventions for improving adherence and psychological well-being in cardiac, high CHD risk, and diabetes patients

Study	Design	Setting	Diagnosis	Patients	Mean age (years)	Follow-up (months)	Intervention	Results
Murphy et al. 2013 [43]	RCT	Multicenter	Acute myocardial infarction, coronary artery bypass graft surgery, or percutaneous coronary intervention patients	275 (238 males, 37 females; 139 intervention; and 136 controls)	59	24	"Beating Heart Problems" program in which CBT and MI are used vs. usual care	Compared to the control group, there was a tendency toward a greater reduction of a 2-year risk score of recurrent cardiac event during both 4- and 12-month follow-ups and a significant benefit related to dietary fat intake and functional capacity
Glozier et al. 2013 [44]	RCT	Multicenter	Depressed and high CHD risk patients	562 (345 females, 217 males; 280 E-couch, intervention; and 182 HealthWatch, control)	58	3	12-week Internet-delivered therapy comparing a cognitive behavioral therapy (iCBT) program (E-couch) with an Internet-delivered attention control health information package (HealthWatch)	Small, but robust, improvement of depressive symptoms, adherence, and some health behaviors in the iCBT participants but no effect upon disability or walking time/day
Mejía et al. 2014 [45]	RCT	Multicenter	Heart failure patients	260 (188 males, 72 females; 95 self-management; and 165 usual care)	70	12	Nurse-facilitated cognitive behavioral self-management program compared with usual care	There is little evidence that the addition of the intervention had any effect on costs or outcomes. It is not reasonable to make recommendations based on cost-effectiveness alone

Smeulders et al. 2010 [46]	RCT	Multicenter	CHF patients	317 (186 intervention and 131 usual care, control)	67	12	6-week nurse-led self-management group program on psychosocial attributes, self-care behavior, and quality of life compared with usual care. The leaders in the intervention were nurses and peer-to-peer leaders	Significant effects were found directly after the program for congestive symptom management, self-care behavior, and cardiac specific quality of life; however no effects were found at the 6- and 12-month follow-ups
Safren et al. 2014 [47]	RCT	Multicenter	Patients with unipolar depression and uncontrolled type 2 diabetes	87 (44 males, 43 females; 45 intervention CBT-AD; and ETAU vs. 42 ETAU, control)	58 (ETAU) 55 (CBT-AD)	12	Patients treated as usual (ETAU), including medication adherence, self-monitoring of blood glucose (SMBG), and lifestyle counseling vs. patients that also received 9–11 sessions of cognitive behavioral therapy for adherence and depression (CBT-AD)	CBT-AD is an effective intervention for adherence, depression, and glycemic control with enduring and clinically meaningful benefits for diabetes self-management and glycemic control in adults with type 2 diabetes and depression
Esbitt et al. 2015 [48]	Pilot study	One center	Patients with type 1 diabetes and elevated levels of diabetes-related distress or depressive symptoms	8 (4 males, 4 females)	44	4	Group-based cognitive behavioral therapy for adherence and depression (CBT-AD)	Participation in the group was acceptable and associated with reductions in depressive symptoms and diabetes-specific distress by an increased social support.

and validated clinical health literacy screening tool for older adults [51, 52].

In the statement of the American Heart Association on secondary prevention in older cardiac patients, the association between health literacy and clinical condition was underlined. In patients who are over 75, especially if they are fragile, an accurate evaluation of costs and benefits of every single intervention is necessary. Until further evidence from single-intervention strategies becomes available, combinations of educational and behavioral strategies should be used to improve medication adherence in the elderly. The communication with the patients and their caregivers needs to be as efficient as possible, and the information needs to be given with modalities, which are in-line with the level of patients' health literacy. Often when physicians and healthcare providers need to provide information on an elderly patient, they speak with younger family members excluding the patient (and sometimes also their elderly partner) from participating in the healthcare plan and the projects for the future, accentuating the barriers to good adherence amplifying the sense of uselessness linked to an increasing age. It is therefore recommended to give priority to the concept of the dyad of caregiver-patient in every event in which a communication must be given. Changes in unhealthy behaviors, such as smoking, an incorrect diet, and a sedentary lifestyle, can be greatly facilitated if also the partner of the patient modifies his/her lifestyle. In fact, recent data support the possibility of making behavioral prescriptions to the couple especially if it is a stable one, which has been consolidated though many years of living together. Furthermore, it is important to keep in mind that when structuring the motivational intervention, the patients' temporal horizon and severe conditions are to be always considered, adapting to their needs and preferences [38].

We must therefore deal with new challenges in a more holistic healthcare system of the elderly to enable the management of highly complex issues that require the integration of competencies of different social and healthcare professionals. Older people's adherence to clinical plans constitutes an essential part of this trip toward adding quality to life rather than adding years to life [52].

Conclusions

This chapter reports on the results of different psychological/psychotherapeutic interventions performed in addition to medical approaches in chronic coronary heart disease and chronic heart failure. It reviews the current state of the art and extends this to incorporate the most recent approaches, as well as future applications, thereby yielding insights into practical models that integrate psychotherapy with medical care.

We also underline the importance of psychological intervention for enhancing cardiac patient adherence, suggesting tailored interventions for older cardiac patients and their caregivers.

Several issues remain to be clarified in a near future, for example, which psychological interventions are more useful in which patients and at which stage of the disease, what is the optimal timing and duration of interventions, and how can different approaches be combined, including psychopharmacologic tools.

References

1. Zipes DP, Libby P, Bonow OR, Mann LD, Tomaselli GF, Braunwald E. Braunwald's heart disease: a textbook of cardiovascular medicine. Philadelphia: Elsevier; 2018.
2. Pogosova N, Saner H, Pedersen SS, Cupples ME, McGee H, Höfer S, et al. Psychosocial aspects in cardiac rehabilitation: from theory to practice. A position paper from the Cardiac Rehabilitation Section of the European Association of Cardiovascular Prevention and Rehabilitation of the European Society of Cardiology. Eur J Prev Cardiol. 2015;22:1290–306.
3. Rozanski A. Behavioral cardiology: current advances and future directions. J Am Coll Cardiol. 2014;64:100–10. https://doi.org/10.1016/j.jacc.2014.03.047.
4. Ladwig KH, Lederbogen F, Albus C, Angermann C, Borggrefe M, Fischer D, Fritzsche K, Haass M, Jordan J, Jünger J, Kindermann I, Köllner V, Kuhn B, Scherer M, Seyfarth M, Völler H, Waller C, Herrmann-Lingen C. Position paper on the importance of psychosocial factors in cardiology: update 2013. Ger Med Sci.

2014;12:Doc 09. https://doi.org/10.3205/000194. E Collection 2014.
5. Task Force per le Attività di Psicologia in Cardiologia Riabilitativa e Preventiva, Gruppo Italiano di Cardiologia Riabilitativa e Preventiva. Guidelines for psychology activities in cardiologic rehabilitation and prevention. Monaldi Arch Chest Dis 2003;60(3):184–234.
6. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts): Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur J Prev Cardiol. 2016;23(11):NP1–NP96. https://doi.org/10.1177/2047487316653709. Epub 2016 Jun 27.
7. Pikhart H, Pikhartova J. The relationship between psychosocial risk factors and health outcomes of chronic diseases. A review of the evidence for cancer and cardiovascular diseases. Copenhagen: WHO Regional Office for Europe; 2015. (Health Evidence Network (HEN) synthesis report).
8. Pierobon A, Sommaruga M. An integrative model of psychotherapy in medical practice according to GICR-IACPR. In: Roncella A, Pristipino C, editors. Psychotherapy for ischemic heart disease. An evidence-based clinical approach. Cham: Springer; 2016.
9. Sommaruga M, Angelino E, Della Porta P, Abatello M, Baiardo G, Balestroni G, et al. A best practice in psychological activities in cardiovascular prevention and rehabilitation: position paper. Monaldi Arch Chest Dis. 2018;88:966, 47–83. https://doi.org/10.4081/monaldi.2018.966.
10. Pedersen SS, von Känel R, Tully PJ, Denollet J. Psychosocial perspectives in cardiovascular disease. Eur J Prev Cardiol. 2017;24(3_suppl):108–15. https://doi.org/10.1177/2047487317703827. Review.
11. Lichtman JH, Froelicher ES, Blumenthal JA, et al. Depression as a risk factor for poor prognosis among patients with acute coronary syndrome: systematic review and recommendations: a scientific statement from the American Heart Association. Circulation. 2014;129:1350–69.
12. Peters A, McEwen BS. Stress habituation, body shape and cardiovascular mortality. Neurosci Biobehav Rev. 2015;56:139–50.
13. Tully PJ, Cosh SM, Baumeister H. The anxious heart in whose mind? A systematic review and meta-regression of factors associated with anxiety disorder diagnosis, treatment and morbidity risk in coronary heart disease. J Psychosom Res. 2014;77:439–48.
14. Sommaruga M. Cognitive and behavioral psychotherapy in coronary artery disease. In: Roncella A, Pristipino C, editors. Psychotherapy for ischemic heart disease. An evidence-based clinical approach. Cham, Springer; 2016. p. 107–20.
15. Colivicchi F, Di Fusco SA, Santini M. Psycho-educational interventions and cardiac rehabilitation. In: Roncella A, Pristipino C, editors. Psychotherapy for ischemic heart disease. An evidence-based clinical approach. Cham: Springer; 2016. p. 107–20.
16. Linden W, Phillips MJ, Leclerc J. Psychological treatment of cardiac patients a meta-analysis. Eur Heart J. 2007;28(24):2972–84. https://doi.org/10.1093/eurheartj/ehm504.
17. Welton NJ, Caldwell DM, Adamopoulos E, Vedhara K. Mixed treatment comparison meta-analysis of complex interventions psychological interventions in coronary heart disease. Am J Epidemiol. 2009;169(9):1158–65.
18. Whalley B, Thompson DR, Taylor RS. Psychological interventions for coronary heart disease: cochrane systematic review and meta-analysis. Int J Behav Med. 2014;21(1):109–21. https://doi.org/10.1007/s12529-012-9282-x. Review.
19. Biondi-Zoccai G, Mazza M, Roever L, et al. Evidence-based psychotherapy in ischemic heart disease: Umbrella review and updated meta-analysis. In: Roncella A, Pristipino C, editors. Psychotherapy for ischemic heart disease. An evidence-based clinical approach. Cham: Springer; 2016. p. 131–58.
20. Richards SH, Anderson L, Jenkinson CE, et al. Psychological interventions for coronary heart disease. Cochrane Database Syst Rev. 2017;4:CD002902.
21. Richards SH, Anderson L, Jenkinson CE, Whalley B, Rees K, Davies P, et al. Psychological interventions for coronary heart disease: Cochrane systematic review and meta-analysis. Eur J Prev Cardiol. 2018;25(3):247–59. https://doi.org/10.1177/2047487317739978. Epub 2017 Dec 7.
22. Lespérance F, Frasure-Smith N, Koszycki D, et al. Effects of citalopram and interpersonal psychotherapy on depression in patients with coronary artery disease the Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) trial. JAMA. 2007;297:367–79.
23. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Authors/Task Force Members; Document Reviewers, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2016;18(8):891–975. https://doi.org/10.1002/ejhf.592. Epub 2016 May 20.
24. Sokoreli I, de Vries JJ, Pauws SC, Steyerberg EW. Depression and anxiety as predictors of mortality among heart failure patients: systematic review and meta-analysis. Heart Fail Rev. 2016;21(1):49–63. https://doi.org/10.1007/s10741-015-9517-4.

25. Jordan J, Bardè B. Psychodynamic hypotheses on the etiology, course, and psychotherapy of coronary heart disease: 100 years of psychoanalytic research. In: Jordan J, Bardé B, Zeiher AM, editors. Contributions toward evidence-based psychocardiology. A systematic review of the literature. Washington, DC: American Psychological Association; 2007.
26. WHO. Noncommunicable diseases and mental health. In: WDP Services, editor. Global action plan for the prevention and control of NCDs 2013–2020. Geneva: WHO Press; 2013.
27. WHO. Adherence to long-term therapies: evidence for action. Geneva: WHO Press; 2013.
28. Vrijens B, De Geest S, Hughes DA, Przemyslaw K, Demonceau J, Ruppar T, ABC Project Team, et al. A new taxonomy for describing and defining adherence to medications. Br J Clin Pharmacol. 2012;73:691–705. https://doi.org/10.1111/j.1365-2125.2012.04167.x.
29. Vrijens B, Kardas B. The ABCS of medication adherence. In: Costa E, Giardini A, Monaco A, editors. Adherence to medical plans for active and healthy ageing. New York: NOVA Science Publishers; 2017. p. 1–11.
30. Bradley MC, Hughes CM. Isuues in aging, adherence, and health-behavior change. In: Martin LR, DiMatteo MR, editors. The Oxford handbook of health communication, behavior change, and treatment adherence. New York: Oxford University Press; 2014. p. 432–53.
31. Bettinardi O, da Vico L, Pierobon A, Iannucci M, Maffezzoni B, Borghi S, et al. First definition of minimal care model: the role of nurses, physiotherapists, dietitians and psychologists in preventive and rehabilitative cardiology. Monaldi Arch Chest Dis. 2014;82(3):122–52. https://doi.org/10.4081/monaldi.2014.55.
32. Pierobon A, Covini E, Callus E. Enhancing patient adherence through integrated educational programs based on psychological techniques and practices. In: Costa E, Giardini A, Monaco A, editors. Adherence to medical plans for active and healthy ageing. New York: NOVA Science Publishers; 2017. p. 129–47.
33. Safren SA, Gonzalez J, Soroudi N. CBT for depression and adherence in individuals with chronic illness. New York: Oxford University Press; 2008.
34. DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. Arch Intern Med. 2000;160:2101–7.
35. Dubois CM, Beach SR, Kashdan TB, Nyer MB, Park ER, Celano CM, et al. Positive psychological attributes and cardiac outcomes: associations, mechanisms, and interventions. Psychosomatics. 2012;53(4):303–18. https://doi.org/10.1016/j.psym.2012.04.004.
36. DuBois CM, Lopez OV, Beale EE, Healy BC, Boehm JK, Huffman JC. Relationships between positive psychological constructs and health outcomes in patients with cardiovascular disease: a systematic review. Int J Cardiol. 2015;195:265–80. https://doi.org/10.1016/j.ijcard.2015.05.121.
37. Martin LR, DiMatteo MR. The Oxford handbook of health communication, behaviour change, and treatment adherence. New York: Oxford University Press; 2013.
38. Spoelstra SL, Schueller M, Hilton M, Ridenour K. Interventions combining motivational interviewing and cognitive behaviour to promote medication adherence: a literature review. J Clin Nurs. 2015;24:1163–73. https://doi.org/10.1111/jocn.12738.
39. WHO. International classification of impairments, disabilities and handicaps. Geneva: WHO Press; 1980.
40. Pierobon A, Giardini A, Callegari S, Majani G. Psychological adjustment to a chronic illness: the contribution from cognitive behavioural treatment in a rehabilitation setting. G Ital Med Lav Ergon. 2011;33(Suppl A):11–8.
41. Sin NL, Moskowitz JT, Whooley MA. Positive affect and health behaviors across 5 years in patients with coronary heart disease: the heart and soul study. Psychosom Med. 2015;77:1058–66.
42. Pristipino C. Psychological stress, inflammation, immunity, and coagulation in ischemic heart disease. In: Roncella A, Pristipino C, editors. Psychotherapy for ischemic heart disease. An evidence-based clinical approach. Cham, Springer; 2016. p. 45–58.
43. Murphy BM, Worcester MU, Higgins RO, Elliott PC, Le Grande MR, Mitchell F, et al. Reduction in 2-year recurrent risk score and improved behavioral outcomes after participation in the "Beating Heart Problems" self-management program: results of a randomized controlled trial. J Cardiopulm Rehabil Prev. 2013;33:220–8. https://doi.org/10.1097/HCR.0b013e31828c7812.
44. Glozier N, Christensen H, Naismith S, Cockayne N, Donkin L, Neal B, et al. Internet-delivered cognitive behavioural therapy for adults with mild to moderate depression and high cardiovascular disease risks: a randomised attention-controlled trial. PLoS One. 2013;8:e59139. https://doi.org/10.1371/journal.pone.0059139.
45. Mejía A, Richardson G, Pattenden J, Cockayne S, Lewin R. Cost-effectiveness of a nurse facilitated, cognitive behavioural self-management programme compared with usual care using a CBT manual alone for patients with heart failure: secondary analysis of data from the SEMAPHFOR trial. Int J Nurs Stud. 2014;51:1214–20. https://doi.org/10.1016/j.ijnurstu.2014.01.009.
46. Smeulders ES, van Haastregt JC, Ambergen T, Uszko-Lencer NH, Janssen-Boyne JJ, Gorgels AP, et al. Nurse-led self-management group programme for patients with congestive heart failure: randomized controlled trial. J Adv Nurs. 2010;66:1487–99. https://doi.org/10.1111/j.1365-2648.2010.05318.x.
47. Safren SA, Gonzalez JS, Wexler DJ, Psaros C, Delahanty LM, Blashill AJ, et al. A randomized

controlled trial of cognitive behavioural therapy for adherence and depression (CBT-AD) in patients with uncontrolled type2 diabetes. Diabetes Care. 2014;37:625–33. https://doi.org/10.2337/dc13-0816.

48. Esbitt SA, Batchelder AW, Tanenbaum ML, Shreck E, Gonzalez JS. "Knowing that you're not the only one": perspectives on group-based cognitive-behavioral therapy for adherence and depression (CBT-AD) in adults with type 1 diabetes. Cogn Behav Pract. 2015;22(3):393–406. https://doi.org/10.1016/j.cbpra.2014.02.006.
49. Fattirolli F, Pratesi A. Cardiovascular prevention and rehabilitation in the elderly: evidence for cardiac rehabilitation after myocardial infarction or chronic heart failure. Monaldi Arch Chest Dis. 2016;84(1–2):731. https://doi.org/10.4081/monaldi.2015.731.
50. Chesser AK, Keene Woods N, Smothers K, Rogers N. Health literacy and older adults: a systematic review. Gerontol Geriatr Med. 2016;2:2333721416630492. https://doi.org/10.1177/2333721416630492.
51. Forman D, Wenger NK. What do the recent American Heart Association/American College of Cardiology Foundation Clinical Practice Guidelines tell us about the evolving management of coronary heart disease in older adults? J Geriatr Cardiol. 2013;10:123–8. https://doi.org/10.3969/j.issn.1671-5411.2013.02.012.
52. Giardini A, Maffoni M, Kardas P, Costa E. A cornerstone of healthy aging: do we need to rethink the concept of adherence in the elderly? Patient Prefer Adherence. 2018;12:1003–5. https://doi.org/10.2147/PPA.S164686.

Part V

Neurological Diseases and How They May Influence Cardiovascular Activity, Disease Onset, Outcomes, and Quality of Life

Heart Activity and Cognition

25

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Contents

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*,
https://doi.org/10.1007/978-3-030-28008-6_12

Abstract

Brain function and heart function deeply influence each other in both evident and more subtle ways. This is a reciprocal phenomenon that can

happen at many levels. The following chapter will primarily focus on this bidirectional influence. We have decided to describe five physiopathological and psychopathological conditions in which a primary cardiovascular impairment causes a secondary dysfunction of cerebral cognitive activity or the opposite.

First, the consequences on brain cognition of two major heart dysfunctions, cardiac arrest and heart transplantation, have been analyzed. Second, we discussed how three severe and impairing psychopathological conditions, namely, autism spectrum disorders (ASD), intellectual disability (ID), and dementia, may have an extensive impact on the cardiac activity.

The co-occurrence of this double impairment, both on heart and cognition, has been explored from a biopsychosocial point of view. The biopsychosocial model helps to understand the complexity of the patient as an individual, considering him as a unique system rather than focusing on single diseases, in line with the idea that such systems are interdependent and not separated entities.

Keywords

Cognition · Cardiovascular activity · Cardiac arrest · Heart transplantation · Autism spectrum disorders · Autonomous nervous system · Dementia · Heart rate

Introduction

In 1977 George L. Engel firstly proposed a new theoretical and practical model of medicine, the "biopsychosocial model." From the assumption that "nothing exists in isolation," Engel underlined that physicians should not focus on patients with a mere biomedical approach, which he defined reductionist. They, indeed, should see the patient as a person, a whole system, from a psychological perspective too. The person-system is, in turn, included in a wider system that ultimately is represented by the social and cultural context he lives in.

In a paper published in 1980 [1], Engel illustrated a clinical example of his revolutionary biopsychosocial model. In doing this, he purposely avoided to describe a psychiatric clinical case. Instead, the author exposed the case of "Mr. Glover" in the event of a coronary artery occlusion. This shows how even a cardiac accident can be approached by a wide perspective, including social and psychological consequences, not alone the strictly biomedical factors.

Engel's biopsychosocial model and Mr. Glover's example form a conceptual and historical basis of how cardiac activity and psychological functions, including cognition, influence each other.

In the following chapter, we will deepen how cognition and heart activity interact. This analysis will be conducted at different levels, or "systems," to use a term of biopsychosocial models.

Consequences of Cardiac Arrest on Cognition

Pathophysiology of Cardiac Arrest

Cardiac arrest (CA) can be defined as the cessation of cardiac mechanical activity; it is usually confirmed by the absence of signs of circulation. This sudden loss of circulation brings the effective cerebral blood flow to zero. Cerebral consumption is estimated from 20% to 25% of cardiac output, and brain tissue is extremely sensitive to ischemia [2]. Neuronal tissue lacks nutrient stores, being highly glucose-dependent, thus neuroglycopenia and metabolic crisis happen in few minutes after an episode of CA. This ultimately brings neurons to cell death. But the threshold for ischemic/hypoxic damage varies between different brain areas, with studies showing that the gray matter have a higher threshold than the white matter [3].

Clinically, the loss of neurological functions is manifested by a decreased level of consciousness after global cerebral ischemia [4]: 10 s are enough to lead to acute decreased level of consciousness after the cessation of cerebral blood flow (CBF) by neck cuff insufflation to 600 mmHg in humans. Clinical findings show that decreased levels of

consciousness after CA occur within 20 s after onset of ventricular fibrillation; neurophysiologically, the loss of neurological function has been demonstrated by isoelectric electroencephalography in observational studies.

Recent findings evaluated isoelectric electroencephalography rhythms within 15 s and 30 s of asystole and ventricular fibrillation, respectively. These evidences in humans are paralleled by animal models. A recent study, about the decapitation of conscious or anesthetized rats, establishes a similar timing (from 10 to 30 s) from cerebral ischemia to isoelectric electroencephalography, assuming that isoelectricity means that the animal as completely unconscious.

Cardiopulmonary resuscitation (CPR) partially restores blood flow, including cerebral blow flow. If an optimally conducted CPR can assure a cardiac output which is between 25% and 40% of pre-cardiac arrest values, almost 30% of it goes to the brain. It is well established that reperfusion can bring further neuronal damage, due to inflammatory and coagulation pathways activation, reactive oxygen species (ROS) creation, endothelial damage, and calcium dysregulation.

Nonetheless early CPR has a crucial role in post-CA prognosis. When talking about cognitive sequelae of CA, CPR seems to be protective regardless of its timing.

Many studies acknowledge hypoxic brain damage as main mechanism of damage and executive functions, memory and attention, as main areas of cognitive impairment. As stated above, neurons feature a different sensibility to hypoxia according to their area in the brain. Hippocampal neurons are markedly prone to hypoxic ischemic damage. Among these neurons, the cornu ammonis 1 (CA1) are the most fragile [5]. The reason may be the lack of a strong blood supply, compared to other brain areas. This weakness accounts for the high frequency of memory impairment in patients with CA. For example, a recent study compared CA patients with myocardial infarction controls, finding significantly worse memory performance in the first population. This evidence is reflected by a significant reduction in hippocampal volume.

Effects on Cognition

If patients have an immediate complete recovery after CPR and return of spontaneous circulation, they may have no residual cognitive impairment or minimal deficits. With a period of coma from 1 to 7 days, the prognosis is uncertain. Part of the patients show important impairment in several cognitive domains, mainly memory and psychomotor functioning, whereas a larger group shows a milder impairment, limited to memory and psychomotor domains. If coma lasts more than a week, patients may have a bad prognosis, in terms of cognitive and, in general, neurological functioning.

A review published in 2009 [6] describes that orientation, attention, memory, perception, executive functioning, apraxia, verbal functioning, language skills, construction, concept formation and reasoning are the main cognitive domains measured by original studies about cognitive sequelae of CA. In spite of the wide range of scales, questionnaires, tests, and interviews, most of the studies included in the review agree that cognitive impairment is a common condition after an episode of CA. Only 2 studies, out of 28, did not agree with this conclusion. The best studies, in terms of quality, recorded cognitive problems in half of the patients. This finding is supported from more recent studies, with percentages of impairment of 54% in one or more cognitive tests [7]. As stated above, memory is the most frequent altered domain, along with attention and executive functioning. Data from the previously mentioned 2009 review (12–100% of CA patients with a memory problem) are in line with more recent findings. For example, Polanowska et al. [8] have reported that 100% of CA cases have memory impairment immediately after the occurrence of CA. This total declines to 57% after 12 months from the CA episode.

Many prospective studies not only focus on the acute brain and functional damage after CA but also try to estimate whether there is some recovery in cognition over time. In 2009 Moulaert et al. underlined that the improvement, if there is some, is limited to the first 3–5 months after the cardiac accident [9]. After that, cognitive function does

not seem to restore. Some long-term studies [10, 11] have stated that a cognitive impairment lasting for 1 year after CA is likely to be permanent and not susceptible to spontaneous recovery. Nedergaard et al. [12] analyzed a series of studies about timely interventions, in the intensive care unit (ICU), to prevent cognitive impairment in critical patients (including a few with CA). They found that none of them seems to prevent cognitive impairment, despite the wide range of interventions and their immediate timing. When speaking of rehabilitation after CA [13], a lower cognitive function represents a disadvantage during the program [14]. Nonetheless, physical exercise, when possible, may be beneficial for cognitive problems [15]. This is true even for memory [15], frequently impaired after CA, suggesting the need of implementing new trials based on physical activity and focused on the rehabilitation of single cognitive domains.

Psychological and Psychiatric Comorbidities

The co-occurrence of psychological distress, such as anxiety, depressive symptoms, and post-traumatic stress disorder (PTSD) in CA survivors is also relevant. This population shows a prevalence of anxious symptoms which ranges from 13% to 61%; depressive symptoms are present in the 14%–45% of this population, and PTSD symptoms range from 19% to 27% [16]. The presence of anxiety and/or depression is often associated with cognitive problems [17]. On one hand, depression can lead to worse cognitive performance (depressive pseudodementia); on the other hand a worse neurological, both physical and cognitive, performance can lead to a significantly lower quality of life (QoL) [18]. A lower perception of QoL is both a cause and consequence of anxious and depressive symptoms.

The precise psychopathological mechanism and the link between psychological distress and brain damage after CA are still not clear. The event of a CA can be shaped as a traumatic event, explaining the high levels of anxiety in this population [19]. This also accounts for the high rate of PTSD in CA survivors and for the presence of this disturbance in CA caregivers too [20].

Some authors suggest a psychological screening in CA patients, along with the routine neurological assessment. However, further studies are needed to establish how to treat this psychological distress in terms of psychopharmacology and psychotherapy.

Heart Transplantation and Cognition

Pathophysiology and Consequences of Heart Failure

Heart transplantation (Htx) is a surgical procedure, first successfully performed in 1967. It is exploited for people with end-stage heart failure (ESHF) and other severe cardiac disturbances shown to be resistant to other treatments. As described in another chapter, heart failure (HF) is associated with multiple organ dysfunctions, involving also the brain. Preexisting conditions of vascular brain damage, as cardiac failure and cerebral vasculopathy share a wide range of risk factors, can be worsened by circulatory impairment from HF. Therefore, Htx candidates are more likely to have a cognitive impairment than the general healthy population, as it happens for patients with heart failure. Htx candidates are, indeed, part of this population with a more severe and untreatable disease.

In 2016, Roman et al. [21] thoroughly evaluated neurological and psychological functioning in Htx candidates. The studied population had severe, end-stage HF, classes III–IV of New York Heart Association (NYHA). Their finding of a significant evidence of cognitive impairment in the analyzed population is remarkable, as this study's patients are younger than the ones from similar studies. While it is established to have a cognitive impairment in older end-stage HF patients [22], Roman and colleagues stated that it may be the norm also in younger ESHF patients. The improvement of surgical and medical techniques also made possible to widen the population of candidates. Nowadays, more subjects with diabetes mellitus, hypertension, and left ventricular assist device undergo Htx process. These

conditions are linked to a higher risk of cognitive problems [23], increasing the cumbersome pathological burden of Htx recipients.

Htx Candidates

Patients with ESHF are a frail-health population who deserve a challenging surgical procedure, a complex posttransplant pharmacotherapy, and a strict follow-up. Therefore, Htx candidates undergo an established evaluation before becoming eligible to the procedure, as stated by the International Society for Heart and Lung Transplantation (ISHLT) Guidelines, updated in 2016. This evaluation includes a dedicated psychosocial analysis. The ability to give an informed consent, the compliance with clinicians' instructions and with drug therapy, and the existence of a social and familiar support system are taken into account. If 2006 ISHLT Guidelines considered mental retardation and dementia as a relative contraindication, 2016 Guidelines state that:

> "Any patient for whom social supports are deemed insufficient to achieve compliant care in the outpatient setting may be regarded as having a relative contraindication to transplant. The benefit of heart transplantation in patients with severe cognitive-behavioral disabilities or dementia (e.g. self-injurious behavior, inability to ever understand and cooperate with medical care) has not been established, has the potential for harm and therefore heart transplantation cannot be recommended for this subgroup of patients."

This caveat makes the neuropsychological evaluation a tricky and fundamental step prior to transplantation. This is harder considering the described high rate of cognitive impairment in this population. ISHLT further recognize that patients with intellectual disability, instead, may be eligible if they have a valid social support and lack of any other contraindication [24].

Brain Function after Transplantation

There is still no clear evidence that cognition is restored after Htx procedure. Even though cardiac functioning improves, this is not clear for cognitive abilities. Some structural brain changes are undoubtedly irreversible and do not recover even with a normal or subnormal cerebral blood flow. Older studies [25] reported improvement in some cognitive measures, but the relevance of this finding is discussed. There may be a group [26] of Htx recipients whose cognitive function does not restore, maybe because of chronical and irreversible brain damage from chronic HF.

Another factor to be taken into account is that Htx patients undergo a strict and challenging pharmacological regime that may have secondary effects on the brain. Organ transplant recipients are due to take immunosuppressive drugs, with various possible regimes. Some immunosuppressants may be neurotoxic, and others may influence cognitive outcomes too, while not clearly being neurotoxic. Calcineurin inhibitors (CNI), such as cyclosporine, have an established neurotoxicity. Nonetheless, it is not clear whether they have a negative or positive effect on cognition after Htx. Burker [23] and colleagues recently compared two populations of Htx recipients, one cohort on CNI therapy and one on everolimus therapy. This immunosuppressive drug is part of a class called mTor (mammalian target of rapamycin) inhibitors. Results showed no significant difference between two groups in terms of the impact on cognitive impairment. Lang et al. [27], instead, found that a CNI-free immunosuppressive therapy in Htx follow-up is associated with significant improvements in several neuropsychiatric domains. Patients on everolimus (another mTor inhibitor) saw an improvement in memory and concentration and a decrease of psychiatric symptoms.

Psychological and Psychiatric Comorbidities

A strict follow-up, risks of rejection, infection care, and the complex pharmacotherapy and its possible side effects can be distressing factors after solid organ transplantation. Patients, also, need to actively change their lifestyle and their diet and follow clinicians' advices. So, quality of life (QoL) has become a relevant outcome to be evaluated during follow-up. Nowadays, we have

several studies focused on this issue, some of them with long-term follow-up. Politi et al. [28] studied QoL ten years after Htx, finding that physical quality of life was significantly lower than the general population, while mental quality of life was comparable to that of the general population. More recently, Grady et al. [29] studied QoL, in terms of physical and occupational function, psychological state, social interaction, and somatic sensation, with a 5–10 years follow-up. They found overall good levels of QoL 5–10 years after transplantation. Even though these high level results, they identified some biopsychosocial factors negatively influencing QoL even after years from the surgical procedure. Depression, surely the most common psychiatric comorbid after Htx, deeply influences quality of life with depressive, anxious, and somatic symptoms. Poor sleep is one of them and it is linked to lower QoL scores. Also, cardiopulmonary distress symptoms and difficulty in moving can affect this result even after 10 years. One out of four Htx recipients can have depression at 1 year follow-up [30]. Depression is also associated with poorer outcomes and lower compliance [31].

Autism Spectrum Disorders and the Autonomic Nervous System

The term autism spectrum disorders (ASD) includes a variety of chronic neurodevelopmental conditions. Impairment in reciprocal social interactions and restricted, repetitive, and stereotyped behaviors or interests characterize this condition. As stressed by the mentioning of a spectrum, there is a high variability in severity of autistic disorder itself. These patients are often affected by several other psychiatric and medical co-occurrent diseases. Some of them are nowadays clearly more frequent in ASD population than in the general population, namely, epileptic disorders, gastrointestinal dysfunctions, sleep disturbances, and intellectual disability [32].

Even though ASD were firstly regarded as rare conditions, ASD prevalence and incidence numbers are rising. In the USA, the Center for Disease Control (CDC) estimates that ASD affects 1 child out of 59 [33]. The prevalence rates of ASD have been rising worldwide, both in developed and in developing countries. Worldwide, there are more than 52 millions of people with ASD [34]. ASD is also characterized by a typical male-to-female ratio of 4:1 [35]. This rate changes if cognitive abilities and IQ are taken into account. A population of high-functioning ASD individuals may have a higher male-to-female ratio, such as 10:1. If both ASD and ID are present, male-to-female ratio may be markedly lower, 1.8:1.

Cognitive Models of ASD

Several theoretical models of cognition in ASD have been proposed from the discovery of this condition. Many of them aim to explain the so-called core symptoms of ASD, namely, the impairment in social interaction and communication and restricted/repetitive behaviors.

The first model claims that individuals with ASD may have impairment of theory of mind (ToM). ToM can be defined as the ability to infer other people's state of mind. ASD individuals may be unable to predict others' behaviors, intentions, sense of humor, and, ultimately, language. This deficit can explain the social and communication impairment of ASD, but it does not ground for stereotypical behaviors and repetitive interests, as well as for other non-core symptoms. So, the ASD population have significantly lower scores in tasks that measure ToM, when compared to neurotypical individuals [36].

The second model, the "weak central coherence" theory [37], clarifies the core symptoms of restricted interests in ASD individuals. Central coherence can be defined as the ability to give coherence from a wide array of stimuli, thus putting them in a context with a general meaning. This is an adaptive skill to "make sense" and have priorities out of an overwhelming, even apparently chaotic and meaningless, group of information. According to this model, people with ASD may perceive these stimuli as detached, being unable to integrate them into a meaningful entirety. This also means that they have a cognitive and attentive profile focused on detailed and

localized information rather than on extracting the global meaning. More recently, other authors emphasized the inability of people with ASD to use the general context to bestow a meaning to stimuli. This deficit has been called context blindness [38].

The third model states that people with ASD may have impairment in executive functions (EF). These comprise a set of high-order cognitive abilities and cognitive control processes. There are three [39] "core" executive functions, namely, inhibition, working memory, and cognitive flexibility. Making plans, putting actions in order, and dealing with novel situations are more complex, high-order functions that start from core EF [40]. Many studies underline a series of deficits in EF, such as planning, cognitive flexibility, working memory, and attention [41]. A recent meta-analysis by Geurts and colleagues [42] confirmed that ASD people have problems with inhibition (a prepotent response inhibition) and interference control (i.e., the ability to resist distractor stimuli).

Impairment in cognitive flexibility can lead to pervasive errors that some authors found in the ASD population. Leung et al. [43] quantitatively meta-analyzed the magnitude of cognitive flexibility impairment in ASD. This disparity between typically developing (TD) and ASD people relates with the restricted interests, the opposition to changes, and the inability to switch to different tasks. According to another recent meta-analysis, working memory too seems to be impaired in ASD. Notably, visuospatial working memory is more impaired than verbal working memory [44].

Autonomic Dysfunctions in ASD

There is currently an increasing evidence that people with ASD may have abnormalities in autonomic nervous system (ANS) [45]. Among the multiple pathophysiological effects of ANS activation, ANS function and/or dysfunction may be involved in behavioral responses and irregularities.

ANS (also called "involuntary nervous system" or "vegetative nervous system") functions are beyond conscious control. It mainly targets glands and muscle tissues of internal organs. Several structures of the central nervous system (CNS), such as pons, medulla, limbic area, hypothalamus and thalamus monitor it and CNS is, in turn, influenced by ANS. This is divided into two branches, sympathetic (SNS) and parasympathetic (PSN), both have opposite functions and are physiologically balanced. The PNS is associated with functions that we exert at rest. It favors digestion, decreases heart rate (HR), dilates blood vessels, and relaxes muscles in the gastrointestinal tract. This is the so-called "rest and digest" response. The sympathetic nervous system increases heart rate and breathing rate and narrows blood vessels, thus increasing blood pressure. This is the so-called "fight or flight" response.

The polyvagal theory by Porges [46, 47] is a model of how ANS may influence behavioral states and responses. According to this theory, there are three distinct autonomic subsystems, each of which is of phylogenetic origin. The immobilization system, the most primitive one, deals with vasovagal syncope, behavioral shutdowns, and apparent death states. It depends on the unmyelinated vagus. The mobilization system, dependent on SNS, starts the fight-or-flight reactions. The social communication system, phylogenetically complex and dependent on myelinated vagus (present only in mammals), controls our social functions, such as facial expressions, vocalization, and listening. The polyvagal theory has been considered as a theoretical model that may explain some social-behavioral impairments in ASD. A dysfunctional ANS would lead to dysfunctional social interactions and behavioral response. According to this theory, an altered ANS-mediated response to environmental stimuli may favor emotional and behavioral dysregulation. So a stressful and overstimulating task, which the person with ASD is not able to restrain, leads to behavioral disturbances (self-injury, aggression, tantrums) [48]. A state of hyper-arousal may favor this kind of response. Some authors [49] claim that ANS-mediated hyper-arousal may be related to sympathetic hyperactivity, parasympathetic undertone, or an imbalance between the two systems. According to a recent review [45], there is no evidence for

autonomic imbalance during resting parasympathetic activity in children with ASD, and their pattern of autonomic response to a multitude of tasks is different than TD children.

Heart Rate

Heart rate (HR), i.e., the number of heartbeats (contractions) per minute, is one of the simplest measures of cardiovascular activity. In humans, it reflects the action of both SNS and PNS. The first one increases HR, while the second one decreases it. Speaking of baseline HR, there is some evidence of higher HR in the ASD population at rest. There are some findings, too, of elevated HR during sleep. Other studies focused on how HR changes when ASD individuals are exposed to different kinds of external stimuli. Their findings are consistent with a blunted HR response to stimuli. For example, Pace and colleagues [50] recently found that people with ASD have a decreased adaptive HR response to physical exercise (a standardized set of physical fitness tests), when compared to TD controls. Kushki et al. [51] exposed ASD people to tasks stimulating their social anxiety (a 3-min public speaking task). From data analysis, they found a specifically blunted HR reactivity to psychosocial stimuli. A basal hyper-aroused state, with SNS hyperactivity, may be the explanation of this low HR increase, with a saturation of SNS response. In this sense, HR change and anxiety scores were negatively associated. These altered responses to different kinds of stimuli, namely, physical stress and social anxiety, sustain the evidence of a dysautonomia. Recently, Harder et al. [52] studied basal HR during sleep. This period offers the opportunity to study ANS activity in ASD without social stress factor that may elicit the hyperarousal state during daytime. They recorded higher HR during sleep, both in non-REM and REM phases. When falling asleep, both groups had lower levels than when awake. Both showed the trough during N2 (non-REM phase 2) and higher levels during REM phase. People with ASD had significantly higher HR values than TD in each phase of sleep. This support the hypothesis of ANS in ASD, even during sleep. An absolute higher HR in ASD than TD during sleep may be due to a less effective vagal modulation. Also, an abnormal SNS activity may be a factor.

Respiratory Sinus Arrhythmia

Respiratory sinus arrhythmia (RSA) is a physiological phenomenon, occurring during respiratory cycle. In depth, HR increases during inspiration and decreases during expiration. PNS exerts its influence on HR reducing it. So, a PNS activity decrease determines a HR increase during the inspiratory phase. While both SNS and PNS impact HR, a variation in RSA reflects the reduced or valid influence of PNS, thus excluding the ANS. Ellenbroek [53], in a recent review, states that most studies recorded a reduction of RSA in ASD population. Following the polyvagal theory, the reason may be a chronically reduced parasympathetic tone. In this sense, a reduction in RSA is measured in ASD at baseline condition [54]. According to Condy et al. [55], a reduced vagal tone, measured as blunted RSA, predicts the presence and the severity of repetitive and/or restricted behaviors in people with ASD. Patriquin et al. [56] confirmed a positive correlation between social functioning and RSA amplitude in people with ASD, as it is established in the general population.

Preejection Period

Preejection period (PEP) is a noninvasive measure of the latency between the onset of left ventricular depolarization. It is measured by the Q-wave onset on the electrocardiogram (ECG), and by the opening of the aortic valve, recorded as the B-point by the thoracic impedance cardiogram (ICG). PEP [57] is an established index of SNS and beta-adrenergic activity, as it is influenced by myocardial contractility. An increase in contractility, as of SNS activity or beta-adrenergic drugs, leads to a higher HR and to a lower PEP. This is a pure SNS index, as ANS

does not interfere with its length. Edmiston et al. [58] studied changes in PEP in people with ASD, compared to TD people, when exposed to a social threat. ASD individuals showed a reduced SNS reactivity. This parallels the lower HR response in the ASD population, accounting for a SNS saturation and a hyper-arousal baseline state. In another trial by Schaaf et al. [59], PEP response did not differ between TD and ASD people during sensory stimulation.

Intellectual Disability and Cardiovascular Risk

Definition of Intellectual Disability

Intellectual disability (ID) is defined as a condition of significant deficits in cognition and functional and adaptive abilities. The expression "intellectual disability" officially replaced "mental retardation" in the last edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) [60]. This long awaited change [61] aligns the American Psychiatric Association manual with International Classification of Diseases by World Health Organization and other associations of professionals.

Historically, the standardized threshold for IF has been an intelligence quotient (IQ) below 70 (approximately, 2 standard deviations or more below the mean of 100 in general population). The IQ scoring has now been removed from diagnostic criteria, but it is retained in disease description. According to DSM-5 authors, this allows to de-emphasize test scoring as a sole criterion and forces to clinically measure the level of functioning.

Three criteria need to be fulfilled to have a DSM-5 diagnosis of ID. They are:

A. Deficits in intellectual functions (reasoning, problem-solving, planning, abstract thinking, judgment, academic learning, learning from experience), confirmed by clinical assessment and individualized standard IQ testing.
B. Deficits in adaptive functioning that significantly hamper conforming to developmental and sociocultural standards for the individual's independence and ability to meet their social responsibility.
C. The onset of these deficits during childhood.

ID Population and Cardiovascular Risk Factors

ID prevalence is around 1% in the general population, even though a precise number is disputed. A recent review by McKenzie and colleagues [62] estimated that this rate may be lower than expected. Maulik [63] and other authors underlined how the social and economic environment, the place of birth, the ethnic origin, and the mean age of study population can interfere with the evaluation of ID prevalence.

Nowadays, individuals with ID still have a lower life expectancy, compared to the general population [64]. Even though lifespan increased in both populations, there is still a gap of years between ID and non-ID individuals. On one hand, some syndromes that present with some degree of ID can show severe medical conditions, too, thus lowering the mean age of survival [65]. On the other hand, behavioral consequences of ID may lead to a less healthy lifestyle, with a higher exposure to risk factors for various diseases. Furthermore, some authors [66] underlined that the ID population may have more difficulty in accessing health services. They are more exposed to social risk factors, such as poverty and unemployment, communication difficulties, a less healthy lifestyle, and genetic and environmental risk factors. It is clear that ID individuals are more fragile and exposed when compared to the general population. In addition, they exhibit sedentary habits and unbalanced diets, leading to dyslipidemia. For the same reason, obesity is also more frequent in this population than in the general population, along with diabetes mellitus (DM) type 2 [67]. Speaking of DM type 1, the same genetic factors that cause ID may predispose to it [68]. Glucose and lipid imbalance is favored, in addition, by the wide use of antipsychotic medication for MR. This is particularly true for the second-generation antipsychotics that are known to have worse metabolic adverse effects and are often prescribed in this

population. De Kuijper et al. [69] found that one out of three persons with ID receives an antipsychotic prescription. Outspoken psychotic symptoms are rarely the reason for the use of this class of drugs in ID. The main use of antipsychotics may be their sedative effect and their assumptive control on problem behaviors. Conversely, some authors state that antipsychotics, regardless of the generation, are not proven to be effective and suggest not to prescribe these drugs in individuals with ID, thus avoiding adverse effects. Other authors suggest to use them only if the problematic behavior is severe, persistent, and not otherwise solvable [70]. For example, Trollor et al. [71] suggest to use antipsychotic in ID with the same guidelines as for the general population. Cardiovascular risk in ID can be worsened [72] by the above cited seldom unnecessary and excessive antipsychotic usage. In general, polypharmacy is an issue of public health in this specific population (Schoufour) [73]. Even more so, higher prevalence of hypertension is reported in ID individuals [74].

All the above factors configure metabolic syndrome (syndrome X) and increase cardiovascular risk. Cardiovascular events are a leading cause of death in both developed and developing countries, where the prevalence of ID is higher. In recent times, the number of cardiovascular (CV) deaths decreased in the general population. Some authors [75], indeed, did not find this decrease in the ID population. In this sense, the increasing lifespan of ID individuals may predispose to a higher risk of CV events. Nowadays, we have more ID elderly, whose CV risk is burdened both by age and intellectual disability. Furthermore, many of them have been deinstitutionalized with the chance of a more independent daily living. But this means, too, fewer chances of controlling their health. For example, people with a moderate ID, able to live almost independently, may be more at risk to adopt unhealthy habits. This may explain the high CV risk state that they have, confirmed by studies with comparison both to people without ID and people with a more severe ID. A recent review [76] showed a 16% prevalence of tobacco use in this population. Even though the authors underline that this number may not be conclusive (due to inhomogeneous cohorts), a 16% prevalence is higher than in the general population. This issue needs further studies. Smoking is a proven CV risk factor, and it is more prevalent in socially and economically disadvantaged classes. It is even increasing in elderly with ID [77].

A recent meta-analysis by Correll et al. [78] estimated prevalence, incidence, and mortality by CV disease in people with severe mental illness (schizophrenia, bipolar disorder, major depressive disorder, and their related spectrum disorders), who, generally speaking, have a higher mortality than the general population [79]. They feature an estimated higher risk, too, of cardiovascular death, coronary heart disease, and cerebrovascular disease. So, CV events may be a leading cause of decreased lifespan in people with severe mental illness. There is a need to evaluate whether it is true for intellectual disability with a definitive meta-analysis. This would help too to target public health intervention for this specific population. Individuals with ID are less frequently targeted by preventive medicine and screening interventions [80].

Health-promoting interventions should be specifically tailored for ID adults, with an eye to long-term adherence [81]. Otherwise, they may be ineffective and wasteful, as underlined by a recent meta-analysis [82].

The link between cardiovascular risk and ID, in sum, needs to be further investigated from an epidemiologic and etiologic point of view, with specific attention to health-promoting prophylaxis interventions. The main issue is still their reduced quality of life and life expectancy, along with the new issues arising from the aging of ID adults.

Dementia, Anti-Dementia Drugs, and Cardiovascular Effects

Dementia is a long-established term for a clinical syndrome centered around cognitive decline. It specifically requires a cognitive impairment that is severe enough to alter previous social and occupational functioning.

DSM-5 Definition

A historical adjustment occurred after the publication of DSM-5 [60, 83]. This renamed dementia as a major neurocognitive disorder (NCD). It recognizes, along with it, a milder state, corresponding to mild cognitive impairment (MCI), called mild NCD, which could benefit from some specific treatment too. These changes are aimed to stress the existence of a continuum from MCI to dementia, naming them both NCD. Also, DSM-5 removed the presence of memory impairment as a compulsory criterion for dementia or NCD. This now requires impairment in any of the cognitive domains, listed in DSM-5, namely, complex attention, executive function, learning and memory, language, perceptual-motor function, and social cognition. The impairment may be modest and not interfering with previous levels of functioning (diagnosis of mild NCD), or it may be severe and interfering with previous state of independence in daily living activities (diagnosis of NCD).

Epidemiology

Dementia has a significantly higher prevalence in the old ages of life. From 70 to 75 years, it is around 2–3%, rising to 20–25% among 80–85 years. Worldwide prevalence is growing, due to the increasing lifespan in developing countries.

In developed countries, almost 80% of cases of dementia is due to Alzheimer's disease (AD). Vascular dementia (VaD) accounts for 15–20% and dementia with Lewy bodies (LBD) for 10–15%. Other causes of dementia, such as frontotemporal dementia and rare causes, and dementia due to a reversible condition are responsible of the remaining 5%.

Pharmacological Treatment

Dementia in AD features two classes of drugs approved for pharmacological treatment [84]. The first one comprises acetylcholinesterase inhibitors (AChEIs), such as donepezil, galantamine, and rivastigmine; the second one is represented by memantine, an antagonist of N-methyl-D-aspartate (NMDA) receptor.

AChEIs selectively target enzyme acetylcholinesterase, by reversibly inhibiting the degradation of acetylcholine. This effectively enhances the presence of acetylcholine in the presynaptic space and its activity to muscarinic Ach receptors. Central muscarinic receptors have a role in cognitive process and in memory. M1 and M2 are mainly responsible for this cognitive effect, out of five subtypes (M1 to M5) [85].

This role of Ach in cognitive and mnestic process fits well into the cholinergic hypothesis of AD. According to this hypothesis [86], the brain of individuals with AD has lowered levels of acetylcholine, due to a reduced production and/or hyperactivity of acetylcholinesterase. Parasympathetic nervous system too may be targeted by these drugs, thus causing some of AChEI side effects. Donepezil, rivastigmine, and galantamine, in sum, are indicated for mild-to-moderate dementia in AD, without being a disease-modifying therapy [87].

The only approved NMDA receptor antagonist is memantine. NMDA receptor are ionic channels, activated by glutamate, the main excitatory CNS neurotransmitter [88, 89]. They wield several actions in the brain, being firstly involved in excitatory signal transmission. Also, synaptic plasticity, formation of new neural pathways, and, thus, learning and memory are under NMDA influence. Conversely, an excessive activation of NMDA receptors leads to excitotoxicity, loss of synaptic function, and cell death. This loss parallels the progressive cognitive and mnestic impairment of AD that can be clinically observed. The memantine-mediated, low-affinity NMDA antagonism may limit the influx of calcium ions, which are the biochemical basis of excitotoxicity. Even though memantine is indicated for moderate-to-severe dementia in AD, it is not a disease-modifying therapy.

Cardiovascular Side Effects of AChEI

Acetylcholine enhancement, mediated by AChEI, selectively happens in the brain. Nonetheless, AChEIs marginally strengthen Ach activity in parasympathetic nervous system. This PSN tone increase, mainly vagal, may be responsible for the side effects of AChEI. Even though the most frequent side effects are at the gastrointestinal level, namely diarrhea, nausea, and vomiting, some studies recorded side effects at the cardiovascular system level [84]. They are rarely reported than gastrointestinal symptoms, but they need to be taken into account, as AD patients are a fragile population.

The occurrence of bradycardia has been reported with an increased risk for hospitalization [90]. Elderly people with AD, taking AChEI, showed higher rates of syncope, with falling-related injuries, such as hip fracture, and the necessity of pacemaker insertion [91]. There are also some reports of QT prolongation after the administration of AChEI [92]. A recent meta-analysis by Isik et al. [93] evaluated the cardiovascular effects of this class of drugs.

A significant finding is that individuals with dementia treated with AChEIs showed a higher risk of bradycardia, as stated above. Notwithstanding, a reduction of HR did not lead to higher rates of hospitalization for the consequences of bradycardia and falling. Also, they found that treatment with AChEIs leads to a significant prolongation in PR interval, but not in the QT/QTc intervals.

Conversely, an AChEI treatment in people with dementia was associated with a reduced risk of cardiovascular events. The authors evoked the PNS effects of AChEI with a cholinergic protective action of myocardiocytes, their thrombomodulin modulation, and cognitive profile improvement as possible explanation of this risk reduction. This finding is in line with a recent cohort study by Nordstrom and colleagues [94]. They underlined the association of AChEI treatment with a reduced risk of myocardial infarction that was stronger with higher AChEI doses.

Cardiovascular Side Effects of Memantine

Even though memantine do not show the vagotonic effect of AChEI, there are some studies and reports suggestive of possible cardiovascular consequences of this drug. A recent retrospective study [89] found that memantine was associated with higher risk of myocardial infarction (fatal or nonfatal) and cardiac death, when compared to donepezil. As the association is not clear, the authors suggested that it may be due to differences from patients taking memantine with patients taking donepezil. In that cohort, memantine-treated individuals had a more severe dementia, so they were more likely to have behavioral abnormalities and, therefore, an antipsychotic medication. All these factors lead to an increased cardiovascular risk. A French pharmacovigilance database (2003–2007) [95] recorded 18 reports of bradycardia and 18 cardiovascular adverse drug reactions (mainly orthostatic hypotension and ECG abnormalities) after memantine administration. The underlying mechanism of CV influence of memantine is unclear and there is still scarce literature about it.

Conclusions

This chapter summarizes five practical examples of connections between cognitive functioning and heart activity and how they influence each other. Severe cardiological diseases, such as end-stage heart failure and cardiac arrest, can deeply affect cognitive function, thus lowering patients' compliance and, ultimately, their life expectancy. On the other hand, major psychiatric illness, including intellectual disability and dementia, may represent risk factor for cardiovascular diseases. Antipsychotic and anti-dementia medication may worsen it, even more so a decompensated mental illness. The example of ASD exhibits a connection between heart and brain function through the ancestral autonomous nervous system. These are fascinating lines of research that deserve to be deepened.

References

1. Engel GL. The clinical application of the biopsychosocial model. Am J Psychiatry. 1980;137(5):535–44.
2. Sekhon MS, Ainslie PN, Griesdale DE. Clinical pathophysiology of hypoxic ischemic brain injury after cardiac arrest: a "two-hit" model. Crit Care. 2017;21(1):1–10.
3. Arakawa S, Wright PM, Koga M, Phan TG, Reutens DC, Lim I, et al. Ischemic thresholds for gray and white matter: a diffusion and perfusion magnetic resonance study. Stroke. 2006;37(5):1211–6.
4. Chalkias A, Xanthos T. Post-cardiac arrest brain injury: pathophysiology and treatment. J Neurol Sci [Internet]. 2012;315(1–2):1–8. https://doi.org/10.1016/j.jns.2011.12.007.
5. Bartsch T, Döhring J, Reuter S, Finke C, Rohr A, Brauer H, et al. Selective neuronal vulnerability of human hippocampal CA1 neurons: lesion evolution, temporal course, and pattern of hippocampal damage in diffusion-weighted MR imaging. J Cereb Blood Flow Metab. 2015;35(11):1836–45.
6. Moulaert VRMP, Verbunt JA, van Heugten CM, Wade DT. Cognitive impairments in survivors of out-of-hospital cardiac arrest: a systematic review. Resuscitation. 2009;80(3):297–305.
7. Steinbusch CVM, van Heugten CM, Rasquin SMC, Verbunt JA, Moulaert VRM. Cognitive impairments and subjective cognitive complaints after survival of cardiac arrest: a prospective longitudinal cohort study. Resuscitation [Internet]. 2017;120:132–7. https://doi.org/10.1016/j.resuscitation.2017.08.007.
8. Polanowska KE, Sarzyńska-Długosz IM, Paprot AE, Sikorska Ś, Seniów JB, Karpiński G, et al. Neuropsychological and neurological sequelae of out-of-hospital cardiac arrest and the estimated need for neurorehabilitation: a prospective pilot study. Kardiol Pol. 2014;72(9):814–22.
9. Ørbo M, Aslaksen PM, Larsby K, Schäfer C, Tande PM, Anke A. Alterations in cognitive outcome between 3 and 12 months in survivors of out-of-hospital cardiac arrest. Resuscitation [Internet]. 2016;105:92–9. https://doi.org/10.1016/j.resuscitation.2016.05.017.
10. Torgersen J, Strand K, Bjelland TW, Klepstad P, Kvåle R, SØreide E, et al. Cognitive dysfunction and health-related quality of life after a cardiac arrest and therapeutic hypothermia. Acta Anaesthesiol Scand. 2010;54(6):721–8.
11. Jackson JC, Girard TD, Gordon SM, Thompson JL, Shintani AK, Thomason JWW, et al. Long-term cognitive and psychological outcomes in the awakening and breathing controlled trial. Am J Respir Crit Care Med. 2010;182(2):183–91.
12. Nedergaard HK, Jensen HI, Toft P. Interventions to reduce cognitive impairments following critical illness: a topical systematic review. Acta Anaesthesiol Scand. 2017;61(2):135–48.
13. Boyce LW, Reinders CC, Volker G, Los E, van Exel HJ, Vliet Vlieland TPM, et al. Out-of-hospital cardiac arrest survivors with cognitive impairments have lower exercise capacity. Resuscitation [Internet]. 2017;115:90–5. https://doi.org/10.1016/j.resuscitation.2017.04.010.
14. Eggermont LHP, De Boer K, Muller M, Jaschke AC, Kamp O, Scherder EJA. Cardiac disease and cognitive impairment: a systematic review. Heart. 2012;98(18):1334–40.
15. Nagamatsu LS, Chan A, Davis JC, Beattie BL, Graf P, Voss MW, et al. Physical activity improves verbal and spatial memory in older adults with probable mild cognitive impairment: a 6-month randomized controlled trial. J Aging Res. 2013;2013(Mci):861893.
16. Wilder Schaaf KP, Artman LK, Peberdy MA, Walker WC, Ornato JP, Gossip MR, et al. Anxiety, depression, and PTSD following cardiac arrest: a systematic review of the literature. Resuscitation [Internet]. 2013;84(7):873–7. https://doi.org/10.1016/j.resuscitation.2012.11.021.
17. Lilja G, Nilsson G, Nielsen N, Friberg H, Hassager C, Koopmans M, et al. Anxiety and depression among out-of-hospital cardiac arrest survivors. Resuscitation [Internet]. 2015;97:68–75. https://doi.org/10.1016/j.resuscitation.2015.09.389.
18. Verberne D, Moulaert V, Verbunt J, van Heugten C. Factors predicting quality of life and societal participation after survival of a cardiac arrest: a prognostic longitudinal cohort study. Resuscitation [Internet]. 2018;123:51–7. https://doi.org/10.1016/j.resuscitation.2017.11.069.
19. Davies SE, Rhys M, Voss S, Greenwood R, Thomas M, Benger JR. Psychological wellbeing in survivors of cardiac arrest, and its relationship to neurocognitive function. Resuscitation [Internet]. 2017;111:22–5. https://doi.org/10.1016/j.resuscitation.2016.11.004.
20. Wachelder EM, Moulaert VRMP, van Heugten C, Verbunt JA, Bekkers SCAM, Wade DT. Life after survival: long-term daily functioning and quality of life after an out-of-hospital cardiac arrest. Resuscitation. 2009;80(5):517–22.
21. Roman DD, Holker EG, Missov E, Colvin MM, Menk J. Neuropsychological functioning in heart transplant candidates. Clin Neuropsychol [Internet]. 2017;31(1):118–37. https://doi.org/10.1080/13854046.2016.1212096.
22. Hjelm C, Dahl A, Broström A, Mårtensson J, Johansson B, Strömberg A. The influence of heart failure on longitudinal changes in cognition among individuals 80years of age and older. J Clin Nurs. 2012;21(7–8):994–1003.
23. Bürker BS, Gullestad L, Gude E, Relbo Authen A, Grov I, Hol PK, et al. Cognitive function after heart transplantation: comparing everolimus-based and calcineurin inhibitor-based regimens. Clin Transplant. 2017;31(4)

24. Samelson-Jones E, Mancini DM, Shapiro PA. Cardiac transplantation in adult patients with mental retardation: do outcomes support consensus guidelines? Psychosomatics [Internet]. 2012;53(2):133–8. https://doi.org/10.1016/j.psym.2011.12.011.
25. Bornstein RA, Starling RC, Myerowitz PD, Haas GJ. Neuropsychological function in patients with end-stage heart failure before and after cardiac transplantation. Acta Neurol Scand. 1995;91(4):260–5.
26. Cupples SA, Stilley CS. Cognitive function in adult cardiothoracic transplant candidates and recipients. J Cardiovasc Nurs. 2005;20(5 Suppl):S74.
27. Lang UE, Heger J, Willbring M, Domula M, Matschke K, Tugtekin SM. Immunosuppression using the mammalian target of rapamycin (mTOR) inhibitor Everolimus: pilot Study shows significant cognitive and affective improvement. Transplant Proc [Internet]. 2009;41(10):4285–8. https://doi.org/10.1016/j.transproceed.2009.08.050.
28. Politi P, Piccinelli M, Poli PF, Klersy C, Campana C, Goggi C, et al. Ten years of "extended" life: quality of life among heart transplantation survivors. Transplantation. 2004;78(2):257–63.
29. Grady KL, Naftel DC, Kobashigawa J, Chait J, Young JB, Pelegrin D, et al. Patterns and predictors of quality of life at 5 to 10 years after heart transplantation. J Hear Lung Transplant. 2007;26(5):535–43.
30. Okwuosa I, Pumphrey D, Puthumana J, Brown RM, Cotts W. Impact of identification and treatment of depression in heart transplant patients. Cardiovasc Psychiatry Neurol. 2014;2014:1.
31. Havik OE, Sivertsen B, Relbo A, Hellesvik M, Grov I, Geiran O, et al. Depressive symptoms and all-cause mortality after heart transplantation. Transplantation. 2007;84(1):97–103.
32. Sappok T, Diefenbacher A, Budczies J, Schade C, Grubich C, Bergmann T, et al. Diagnosing autism in a clinical sample of adults with intellectual disabilities: how useful are the ADOS and the ADI-R? Res Dev Disabil [Internet]. 2013 [cited 2015 Jul 18];34(5):1642–55. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23475013
33. Baio J, Wiggins L, Christensen DL, Maenner MJ, Daniels J, Warren Z, et al. Prevalence of autism spectrum disorder among children aged 8 Years – Autism and developmental disabilities monitoring network, 11 Sites, United States, 2014. MMWR Surveill Summ. 2018;67(6)
34. Baxter AJ, Brugha TS, Erskine HE, Scheurer RW, Vos T, Scott JG. The epidemiology and global burden of autism spectrum disorders. Psychol Med [Internet]. 2014 [cited 2015 Jun 20];45(03):1–13. Available from: http://journals.cambridge.org/abstract_S0033291714001720X
35. Fombonne E. The epidemiology of autism: a review. Psychol Med [Internet]. 1999 [cited 2015 Jul 7];29(4):769–86. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10473304.
36. Mathersul D, McDonald S, Rushby JA. Understanding advanced theory of mind and empathy in high-functioning adults with autism spectrum disorder. J Clin Exp Neuropsychol. 2013;35(6):655–68.
37. Aljunied M, Frederickson N. Does central coherence relate to the cognitive performance of children with autism in dynamic assessments? Autism. 2013;17(2):172–83.
38. Vermeulen P. Context blindness in autism Spectrum disorder: not using the Forest to see the trees as trees. Focus Autism Other Dev Disabl. 2015;30(3):182–92.
39. Diamond A. Executive functions. Annu Rev Psychol. 2013;64:135–68.
40. Demetriou EA, Lampit A, Quintana DS, Naismith SL, Song YJC, Pye JE, et al. Autism spectrum disorders: a meta-analysis of executive function. Mol Psychiatry [Internet]. 2018;23(5):1198–204. https://doi.org/10.1038/mp.2017.75.
41. Wallace GL, Kenworthy L, Pugliese CE, Popal HS, White EI, Brodsky E, et al. Real-world executive functions in adults with autism Spectrum disorder: profiles of impairment and associations with adaptive functioning and co-morbid anxiety and depression. J Autism Dev Disord. 2016;46(3):1071–83.
42. Geurts HM, van den Bergh SFWM, Ruzzano L. Prepotent response inhibition and interference control in autism spectrum disorders: two meta-analyses. Autism Res. 2014;7(4):407–20.
43. Leung RC, Zakzanis KK. Brief report: cognitive flexibility in autism spectrum disorders: a quantitative review. J Autism Dev Disord. 2014;44(10):2628–45.
44. Wang Y, Zhang Y, Liu L, Cui J, Wang J, DHK S, et al. A meta-analysis of working memory impairments in autism Spectrum disorders. Neuropsychol Rev. 2017;27(1):46–61.
45. Benevides TW, Lane SJ. A review of cardiac autonomic measures: considerations for examination of physiological response in children with autism Spectrum disorder. J Autism Dev Disord. 2013;45(2):560–75.
46. Porges SW. The polyvagal theory: phylogenetic substrates of a social nervous system. Int J Psychophysiol. 2001;42(2):123–46.
47. Porges SW. The vagus: a mediator of behavioral and physiologic features associated with autism. In: The neurobiology of autism 2. 2005. p. 65–77.
48. Mazefsky CA, White SW. Emotion regulation. Concepts & Practice in autism Spectrum disorder. Child Adolesc Psychiatr Clin N Am. 2014;23(1):15–24.
49. Panju S, Brian J, Dupuis A, Anagnostou E, Kushki A. Atypical sympathetic arousal in children with autism spectrum disorder and its association with anxiety symptomatology. Mol Autism [Internet]. 2015;6(1):1–10. https://doi.org/10.1186/s13229-015-0057-5.
50. Pace M, Bricout VA. Low heart rate response of children with autism spectrum disorders in comparison to controls during physical exercise. Physiol Behav [Internet]. 2015;141:63–8. https://doi.org/10.1016/j.physbeh.2015.01.011.

51. Kushki A, Brian J, Dupuis A, Anagnostou E. Functional autonomic nervous system profile in children with autism spectrum disorder. Mol Autism. 2014;5(1):1–10.
52. Harder R, Malow BA, Goodpaster RL, Iqbal F, Halbower A, Goldman SE, et al. Heart rate variability during sleep in children with autism spectrum disorder. Clin Auton Res [Internet]. 2016;26(6):423–32. Available from: https://pubmed.ncbi.nlm.nih.gov/27491489
53. Ellenbroek BA, Sengul HK. Autism spectrum disorders: autonomic alterations with a special focus on the heart. Hear Mind. 2017;1(2):78.
54. Neuhaus E, Bernier RA, Beauchaine TP. Children with autism show altered autonomic adaptation to novel and familiar social partners. Autism Res. 2016;9(5):579–91.
55. Condy EE, Scarpa A, Friedman BH. Respiratory sinus arrhythmia predicts restricted repetitive behavior severity. J Autism Dev Disord. 2017;47(9):2795–804.
56. Patriquin MA, Scarpa A, Friedman BH, Porges SW. Respiratory sinus arrhythmia: a marker for positive social functioning and receptive language skills in children with autism spectrum disorders. Dev Psychobiol. 2013;55(2):101–12.
57. Newlin DB, Levenson RW. Pre-ejection period: measuring Beta-adrenergic influences upon the heart. Psychophysiology. 1979;16(6):546–52.
58. Edmiston EK, Muscatello RA, Corbett BA. Threat in Adolescents with autism spectrum disorder. 2018;57–65.
59. Schaaf RC, Benevides TW, Leiby BE, Sendecki JA. Autonomic dysregulation during sensory stimulation in children with autism spectrum disorder. J Autism Dev Disord. 2013;45(2):461–72.
60. Association AP. Diagnostic and statistical manual of mental disorders (DSM-5®). American Psychiatric Pub; 2013.
61. Salvador-Carulla L, Bertelli M. 'Mental retardation' or 'intellectual disability': time for a conceptual change. Psychopathology [Internet]. 2008;41(1):10–6. https://doi.org/10.1159/000109950.
62. McKenzie K, Milton M, Smith G, Ouellette-Kuntz H. Systematic review of the prevalence and incidence of intellectual disabilities: current trends and issues. Curr Dev Disord Reports [Internet]. 2016;3(2):104–15. https://doi.org/10.1007/s40474-016-0085-7.
63. Maulik PK, Mascarenhas MN, Mathers CD, Dua T, Saxena S. Prevalence of intellectual disability: a meta-analysis of population-based studies. Res Dev Disabil. 2011;32(2):419–36.
64. Dieckmann F, Giovis C, Offergeld J. The life expectancy of people with intellectual disabilities in Germany. J Appl Res Intellect Disabil. 2015;28(5):373–82.
65. Coppus AMW. People with intellectual disability: what do we know about adulthood and life expectancy? Dev Disabil Res Rev. 2013;18(1):6–16.
66. Emerson E. Health status and health risks of the "hidden majority" of adults with intellectual disability. Intellect Dev Disabil. 2011;49(3):155–65.
67. Rimmer JH, Yamaki K, Lowry BMD, Wang E, Vogel LC. Obesity and obesity-related secondary conditions in adolescents with intellectual/developmental disabilities. J Intellect Disabil Res. 2010;54(9):787–94.
68. Huang CJ, Wang SY, Lee MH, Chiu HC. Prevalence and incidence of mental illness in diabetes: a national population-based cohort study. Diabetes Res Clin Pract [Internet]. 2011;93(1):106–14. https://doi.org/10.1016/j.diabres.2011.03.032.
69. de Kuijper G, Hoekstra P, Visser F, Scholte FA, Penning C, Evenhuis H. Use of antipsychotic drugs in individuals with intellectual disability (ID) in the Netherlands: prevalence and reasons for prescription. J Intellect Disabil Res. 2010;54(7):659–67.
70. Deb S, Kwok H, Bertelli M, Salvador-Carulla L, Bradley E, Torr J, et al. International guide to prescribing psychotropic medication for the management of problem behaviours in adults with intellectual disabilities. World Psychiatry. 2009;8(3):181–6.
71. Trollor JN, Salomon C, Franklin C. Prescribing psychotropic drugs to adults with an intellectual disability. Aust Prescr. 2016;39(4):126–30.
72. McKee JR, Bodfish JW, Mahorney SL, Heeth WL, Ball MP. Metabolic effects associated with atypical antipsychotic treatment in the developmentally disabled. J Clin Psychiatry. 2005;66(9):1161–8.
73. Schoufour JD, Oppewal A, Van Der Maarl HJK, Hermans H, Evenhuis HM, Hilgenkamp TIM, et al. Multimorbidity and polypharmacy are independently associated with mortality in older people with intellectual disabilities: a 5-year follow-up from the HA-ID study. Am J Intellect Dev Disabil. 2018;123(1):72–82.
74. Sarı HY, Yılmaz M, Serin E, Kısa SS, Yesiltepe Ö, Tokem Y, et al. Obesidade e hipertensão em adolescentes e adultos com deficiência intelectual. Acta Paul Enferm. 2016;29(2):169–77.
75. Draheim CC. Cardiovascular disease prevalence and risk factors of persons with mental retardation. Ment Retard Dev Disabil Res Rev. 2006;12(1):3–12.
76. Huxley A, Dalton M, Tsui YYY, Hayhurst KP. Prevalence of alcohol, smoking, and illicit drug use amongst people with intellectual disabilities: review. Drugs Educ Prev Policy [Internet]. 2019;26(5):365–84. https://doi.org/10.1080/09687637.2018.1488949.
77. Hiscock R, Bauld L, Amos A, Fidler JA, Munafò M. Socioeconomic status and smoking: a review. Ann N Y Acad Sci. 2012;1248(1):107–23.
78. Correll CU, Solmi M, Veronese N, Bortolato B, Rosson S, Santonastaso P, et al. Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: a large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls. World Psychiatry. 2017;16(2):163–80.
79. Walker ER, McGee RE, Druss BG. Mortality in mental disorders and global disease burden implications a

systematic review and meta-analysis. JAMA Psychiat. 2015;72(4):334–41.
80. Hanlon P, MacDonald S, Wood K, Allan L, Cooper S-A. Long-term condition management in adults with intellectual disability in primary care: a systematic review. BJGP Open. 2018;2(1):bjgpopen 18X101445.
81. Hithersay R, Strydom A, Moulster G, Buszewicz M. Carer-led health interventions to monitor, promote and improve the health of adults with intellectual disabilities in the community: a systematic review. Res Dev Disabil. 2014;35(4):887–907.
82. Willems M, Waninge A, Hilgenkamp TIM, van Empelen P, Krijnen WP, van der Schans CP, et al. Effects of lifestyle change interventions for people with intellectual disabilities: systematic review and meta-analysis of randomized controlled trials. J Appl Res Intellect Disabil. 2018;31(6):949–61.
83. Tay L, Lim WS, Chan M, Ali N, Mahanum S, Chew P, et al. New DSM-V neurocognitive disorders criteria and their impact on diagnostic classifications of mild cognitive impairment and dementia in a memory clinic setting. Am J Geriatr Psychiatry [Internet]. 2015;23(8):768–79. https://doi.org/10.1016/j.jagp.2015.01.004.
84. Howes MJR, Perry E. The role of phytochemicals in the treatment and prevention of dementia. Drugs Aging. 2011;28(6):439–68.
85. Saternos HC, Almarghalani DA, Gibson HM, Meqdad MA, Antypas RB, Lingireddy A, et al. Distribution and function of the muscarinic receptor subtypes in the cardiovascular system. Physiol Genomics. 2018;50(1):1–9.
86. Singh M, Kaur M, Kukreja H, Chugh R, Silakari O, Singh D. Acetylcholinesterase inhibitors as Alzheimer therapy: from nerve toxins to neuroprotection. Eur J Med Chem [Internet]. 2013;70:165–88. https://doi.org/10.1016/j.ejmech.2013.09.050.
87. Galimberti D, Scarpini E. Disease-modifying treatments for Alzheimer's disease. Ther Adv Neurol Disord. 2011;4(4):203–16.
88. Wang R, Reddy H. Role of glutamate and NMDA in Alzheimer's desease. J Alzheimer's Desese. 2017;57(4):1041–8.
89. Fosbøl EL, Peterson ED, Holm E, Gislason GH, Zhang Y, Curtis LH, et al. Comparative cardiovascular safety of dementia medications: a cross-national study. J Am Geriatr Soc. 2012;60(12):2283–9.
90. Park-Wyllie LY, Mamdani MM, Li P, Gill SS, Laupacis A, Juurlink DN. Cholinesterase inhibitors and hospitalization for bradycardia: a population-based study. PLOS Med [Internet]. 2009;6(9):e1000157. https://doi.org/10.1371/journal.pmed.1000157.
91. Gill SS, Anderson GM, Fischer HD, Bell CM, Li P, Normand SLT, et al. Syncope and its consequences in patients with dementia receiving cholinesterase inhibitors: a population-based cohort study. Arch Intern Med. 2009;169(9):867–73.
92. Malik BH, Hamid P, Khan S, Gupta D, Islam M. Correlation between donepezil and QTc prolongation and torsades de Pointes: a very rare phenomenon. Cureus. 2019;11(12)
93. Isik AT, Soysal P, Stubbs B, Solmi M, Basso C, Maggi S, et al. Cardiovascular outcomes of cholinesterase Inhibitors in individuals with dementia: a meta-analysis and systematic review. J Am Geriatr Soc. 2018;66 (9):1805–11.
94. Nordström P, Religa D, Wimo A, Winblad B, Eriksdotter M. The use of cholinesterase inhibitors and the risk of myocardial infarction and death: a nationwide cohort study in subjects with Alzheimer's disease. Eur Heart J. 2013;34(33):2585–91.
95. Gallini A, Sommet A, Montastruc J. Does memantine induce bradycardia? A study in the French PharmacoVigilance database. Pharmacoepidemiol Drug Saf. 2008;17(9):877–81.

Dementia and Cerebrovascular Disease

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*,
https://doi.org/10.1007/978-3-030-28008-6_29

Abstract

The prevalence of dementia is continuously increasing worldwide in aging population. Although neurodegenerative changes account for the majority of dementias, one common etiology shared among all forms is cerebrovascular dysfunction at some point during the disease process. The main aim of this chapter is to summarize the current findings in the field and address the mechanisms of vascular brain damage and its contribution to cognitive impairment in these conditions. We review the historical steps of research, the main issues regarding terminology, and the epidemiological aspects of vascular dementia. We then focus on the role of classical and novel risk factors, and that of chronic inflammation, and describe the various subtypes of vascular dementia with the underlying pathological correlates. The role of hypoxia, oxidative stress, endothelial dysfunction, and blood–brain barrier permeability in disease etiology and progression is also discussed. Finally, the issue of mixed dementia (or, as it is now proposed, *mixed Alzheimer's disease*), often encountered in clinical practice, is also reported, along with the various clinical pictures of amyloid angiopathies.

Keywords

Vascular dementia · Cerebrovascular disease · Small vessel disease · Blood-brain barrier · Endothelial dysfunction · Cerebral hypoperfusion · Lacunes · White matter lesions · Cerebral amyloid angiopathy

Introduction

The term vascular dementia (VaD) includes a number of heterogeneous dementing disorders due to cerebrovascular disease (CVD). CVD refers to diseases involving the brain blood vessels and the cerebral circulation, mainly identified with stroke. VaD is another consequence of CVD and it is now recognized to extend beyond the traditional multi-infarct form. In Europe, dementia is more common than stroke, both in terms of incidence and prevalence [1]. VaD is widely regarded as the second most common type of dementia, causing around 15% of cases, after Alzheimer's disease (AD), which predominantly results from neurodegenerative changes [2]. However, unselected community-based studies show that brains of demented subjects often exhibit more than one type of pathology. Moreover, vascular lesions are frequently found to coexist with AD-type lesions in healthy older subjects [3]. The relationship between CVD and cognitive decline is currently a topic of particular interest and it is indeed very complex. This complexity has led over the years to radical views and strong debates, sometimes with opposite conclusions. It is now thought that AD and VaD, in addition to simple coexistence, are closely associated, on both clinical and pathophysiological levels. First of all, they share several vascular risk factors (e.g., arterial hypertension) and vascular pathology in the brain (e.g., lacunae, white-matter lesions) [4]. Although a bidirectional relationship is now well established, the exact link between the two is not yet fully understood [5].

When examining the role of CVD in terms of cognitive decline, interpretations and relative conclusions may be different depending on whether a clinical, neuroimaging, or pathological approach is used [6]:

- From a clinical standpoint, cognitive deficits in CVD are much more variable when compared to other disorders such as AD (which is characterized by a typical amnestic syndrome), and therefore standard neuropsychological testing may lack in specificity.

- The recent increase of neuroimaging availability, particularly magnetic resonance imaging (MRI), has been responsible of the widening of VaD spectrum. Since vascular changes are easier to spot than degenerative ones, even patients with minimal vascular signs on MRI may be classified as affected by VaD rather than degenerative dementia.
- Although diagnosis of definite VaD can be confirmed only by neuropathological analysis, the definition of many vascular lesions is variable, potentially determining heterogeneity in the interpretation of the vascular origin. Currently, pathological consensus criteria for diagnosing and staging of VaD are still lacking.

With the aim of assessing the contribution of AD pathology, the availability of in vivo imaging and cerebrospinal fluid (CSF) markers of both amyloid and tau may provide a substantial contribution. Biomarkers of vascular dementia, apart from imaging changes, are less developed than those for AD. Since endothelial dysfunction (ED) has been identified as a key mechanism in the pathophysiology of VaD, markers of endothelial function are potential candidates, including albumen, metalloproteinases, and inflammatory markers, but they need further validation [5].

Historical Aspects and Terminology

Until the 1960s, the so-called senile dementia was attributed to cerebral arteriosclerosis; the vascular etiology was then challenged by the neuropathological studies of Blessed, Tomlinson and Roth [7], who defined AD, and not CVD, as the main cause of dementia in the elderly. Nevertheless, they identified a certain proportion of patients with AD with mixed cerebrovascular lesions, ranging between 8% and 18%. In the 1980s and 1990s, these two forms of dementia were therefore considered as separate entities. Hachinski and Iadecola [8], in the early 2000s, focused attention on mixed forms; because vascular risk factors are treatable, it appeared possible to prevent cognitive decline in CVD as well as mitigate the vascular exacerbation of AD. Subsequently, the concept of a *continuum* also on a pathophysiological level appeared plausible.

Originally, it was thought that CVD produced dementia only in the case of multiple extensive cortical infarcts, and international classifications (DSM-IV and ICD-10) were largely based on this concept. Subsequently, it became increasingly evident that vascular dementias extend beyond traditional multi-infarct types. Pathological studies from large cohorts showed that subcortical vessel disease, rather than large cortical infarcts, accounted for most cases of VaD. While new criteria for VaD, including those specific for some subgroups such as subcortical ischemic vascular dementia, were needed, the main challenge was the absence of a clear consensus on pathological criteria for VaD [5]. In 1993 the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences proposed the NINDS-AIREN criteria [9] (Table 1). These have been used in the most relevant studies thus far, because of their high specificity compared to ICD-10 and DSM-IV criteria [10]. The criteria for the diagnosis of *probable VaD* include a temporal relationship between the onset of dementia (defined as impairment of memory and two or more cognitive domains including executive function, interfering with activities of daily living and not resulting from effects of stroke alone) and neuroradiological signs of cerebrovascular disease. The relationship between the above two disorders could manifest with either onset of dementia within 3 months after a recognized stroke, or abrupt deterioration in cognitive functions, or fluctuating, stepwise progression of cognitive deficits. In addition, clinical features consistent with the diagnosis of probable VaD include early presence of gait disturbances, history of unsteadiness and frequent unprovoked falls, early urinary frequency or urgency or other urinary symptoms not explained by urologic disease, pseudobulbar palsy and personality and mood changes, abulia, depression, emotional incontinence, or other subcortical deficits including psychomotor retardation and abnormal executive function. Criteria for diagnosis of *definite VaD* require clinical criteria for probable VaD,

Table 1 NINDS-AIREN diagnostic criteria for vascular dementia [9]

I. the criteria for the diagnosis of probable VaD include all of the following:
1. *Dementia*: Impairment of memory and two or more cognitive domains (including executive function), interfering with ADLs and not resulting from effects of stroke alone. Exclusion criteria: Alterations of consciousness, delirium, psychoses, severe aphasia or deficits precluding testing, systemic disorders, Alzheimer's disease, or other forms of dementia 2. *Cerebrovascular disease*: Focal signs on neurological examination (hemiparesis, lower facial weakness, Babinski sign, sensory deficit, hemianopia, dysarthria) consistent with stroke (with or without history of stroke, and evidence of relevant CVD by brain CT or MRI including multiple large-vessel infarcts or a single strategically placed infarct (angular gyrus, thalamus, basal forebrain, or PCA or ACA territories), as well as multiple basal ganglia and white-matter lacunes or extensive periventricular white-matter lesions, or combinations thereof Exclusion criteria: Absence of cerebrovascular lesions on CT or MRI 3. *A relationship between the above two disorders*: Manifested or inferred by the presence of one or more of the following: a. Onset of dementia within 3 months after a recognized stroke b. Abrupt deterioration in cognitive functions; or fluctuating, stepwise progression of cognitive deficits
II. Clinical features consistent with the diagnosis of probable VaD include the following:
1. Early presence of gait disturbances (small step gait or Marche à petits pas, or magnetic, apraxic-ataxic, or parkinsonian gait) 2. History of unsteadiness and frequent, unprovoked falls 3. Early urinary frequency, urgency, and other urinary symptoms not explained by urologic disease 4. Pseudobulbar palsy 5. Personality and mood changes, abulia, depression, emotional incontinence, or other deficits, including psychomotor retardation and abnormal executive function
III. Features that make the diagnosis of VaD uncertain or unlikely include:
1. Early onset of memory deficit and progressive worsening of memory and other cognitive functions, such as language (transcortical sensory aphasia), motor skills (apraxia), and perception (agnosia), in the absence of corresponding focal lesions on brain imaging 2. Absence of focal neurological signs, other than cognitive disturbances 3. Absence of CVD on CT or MRI

histopathologic evidence of CVD obtained from biopsy or autopsy, absence of neurofibrillary tangles and neuritic plaques exceeding those expected for age, and absence of other clinical or pathological disorder capable of producing dementia [9].

On a neuropsychological level, the term vascular dementia was questioned mainly because definitions of dementia were based on the concept of AD and thus included as core criterion deficits in memory domain. In 1994 Hachinski proposed the introduction of the term vascular cognitive impairment (VCI) to include all forms of cognitive impairment due to cerebrovascular disease, from mild cognitive impairment (MCI) to definite dementia [11]. In addition, the term vascular cognitive disorders (VCD) designates a global diagnostic category for cognitive impairment of vascular origin, ranging from VCI to VaD, which explicitly rules out isolated cognitive dysfunctions [12]. Only very recently, classification systems such as DSM-V have removed the necessity for memory impairment to be one of the criteria for dementia, which is currently defined as major neurocognitive disorder.

Epidemiological Aspects

Studies on VaD report that it is the second most common cause of dementia after AD. Poststroke dementia develops in around 15–30% of subjects 3 months after a stroke and in around 20–25% of subjects in the long term [5]. VaD may yet develop also in the absence of stroke or in coexistence with AD. The fact that the brain accounts for only 2% of the body weight but consumes a critical 20% of the body's oxygen and other nutrients supplied via the vascular system highlights the importance of the integrity of the vasculature for the optimal functioning of the brain. In addition to the cardiovascular system, brain vascular control mechanisms are vital for the maintenance of the neurovascular milieu, created by nerve terminals, astrocytic endfeet, and the microvasculature [3]. The "Rotterdam Study" has been a fundamental

longitudinal study carried out in the 1990s to investigate the distribution of cognitive function in elderly people and to assess the impact of clinical manifestations of atherosclerotic disease on this distribution. The study evidenced that a nonmodifiable risk factor for VaD is age, whereas gender has almost no effect, in particular when adjusted for education. Other risk factors included low education, presence of strokes, and atherosclerosis [13]. There is now increasingly awareness that AD and VaD share common traditional risk factors for stroke and cardiovascular disease (e.g., hypertension, diabetes, dyslipidemia), with salt intake, chronic inflammation, and gut infection emerging as additional risk factors. Notably, controlling vascular risk factors does not prevent AD but rather raises the threshold for the clinical manifestation of AD [14].

Strokes, Silent Infarction, White Matter Hyperintensities

In the elderly, strokes or transient ischemic attacks (TIAs) increase the risk of AD up to threefold. Cerebral infarcts appear to accelerate AD progression and account for a large proportion of mixed cases in older age groups. Silent brain infarctions (without overt neurological sequelae) occur with high prevalence in the healthy elderly, around 5% of individuals over 60 years of age in both genders. Almost 90% of these lesions occur subcortically, mainly as lacunae in basal ganglia. Silent infarcts double the risk of dementia, cause steeper cognitive decline, and impact on memory and executive functions [3]. The "Nun Study" emphasized clinical importance of the combined neurodegenerative and vascular pathologies. In this prospectively assessed cohort, with similar environmental influences and general lifestyles, it was estimated that an eightfold greater burden of neocortical neurofibrillary tangles would be necessary to develop dementia in the absence of strategic cerebral infarction [15].

Progressive age-related changes in intracerebral vessels or presence of infarcts may result in white matter abnormalities in as many as 96% of those over 65 years of age. Previous studies have investigated possible correlations between the degree of white matter hyperintensities (WMH) on MRI and cognitive function or disability in the elderly. It appears that total WMH volume may be a critical measure and it is associated with decline in frontal lobe functions which include executive tasks, attention, motor, and processing speed rather than in memory per se. In the LADIS cohort, executive dysfunction was attributed to white matter lesion (WML) severity in the non-disabled elderly [16]. Furthermore, volume of periventricular WMH rather than deep WMH at baseline and progression was found to be longitudinally associated with decline in processing speed.

Cerebral amyloid angiopathy (CAA), another form of CVD, is found in almost all AD patients and more than 50% of the elderly over 90 years [17]. CAA mostly results in lobar hemorrhages, white matter damage, and cortical microinfarcts. Moderate-to-severe CAA is also considered as an independent risk factor for dementia [18].

Vascular Risk Factors and Dementia

Several modifiable risk factors such as hypertension, dyslipidemia, diabetes mellitus, and obesity enhance the rate of both VaD and AD. The link between hypertension and VaD, through the well-established relationship between hypertension and stroke, is evident. In many cases of VaD, in the absence of a clear history of stroke, long-standing elevation of blood pressure may increase the risk for dementia by inducing small-vessel disease (SVD), white matter changes, and cerebral hypoperfusion by disrupting vasoregulatory functions. Hypertension represents a good example of the complex link between vascular and neurodegenerative diseases. On one side, a relationship between hypertension and amyloid plaques, neurofibrillary tangles and brain atrophy is well documented. However, disentangling the pathophysiological link is complex, because vascular

risk factors like hypertension may take years or decades to lead to significant cognitive impairment, and AD pathology is thought to be present years to decades before clinical symptoms appear. Moreover, increased blood pressure apparently precedes AD onset by decades, and later decreases before the start of AD. On the other side, there may also be a reverse association between AD and hypertension. Amyloid β (Aβ) may be able to induce hypertension, possibly through direct systemic vascular effects, without brain parenchymal Aβ deposition and before dementia onset, in the form of CAA. Although CAA may be unrelated to AD, AD patients with CAA may present with stroke and cerebrovascular comorbidity [14].

In comparison to the role of hypertension, the link between hypercholesterolemia and VaD is weaker. While the "Rotterdam study" concluded that carotid atherosclerosis in the elderly is a strong risk factor both for VaD and AD [19], cholesterol levels measured in midlife appear to be associated with higher risk of AD but not VaD. The risk of cognitive impairment is 2–2.5 fold greater among type II diabetics both for AD and (particularly) for VaD, irrespective of age at which diabetes occurs [3]. Neuroimaging evidence suggests an association between diabetes and cerebral atrophy and lacunar infarcts, but the association with WML is less robust [20].

Chronic Inflammation and Gut Infection

Chronic inflammation is also related to CVD pathology, including lacunar stroke, enlarged perivascular spaces, and WMH. Inflammation primarily targets endothelial cells and results in blood–brain barrier (BBB) breakdown probably due to neopterin and cytokines being secreted by activated monocytes/macrophages, and subsequently disrupting the extracellular matrix [21]. Sources of inflammation are salt intake, joint inflammation, C-reactive peptides from the liver (after the ingestion of a carbohydrate-rich meal), serum amyloid P, rheumatoid arthritis, and stroke itself.

Inflammation associated with infection is also considered important both before and after stroke since a plethora of acute and chronic infectious pathogens may affect susceptibility and prognosis of stroke patients. Among pathogens affecting the respiratory system, Chlamydia pneumoniae and influenza increase the risk of stroke. Interestingly, the emerging concept of the brain–gut axis, which proposes that bidirectional signaling between the gastrointestinal tract – or gut microbiota – and the brain is vital for maintaining homeostasis, has gained attention in recent years. For instance, lack of gut microbiota results in reduced anxiety behavior, which can be normalized if microbiota are reconstituted early in life, suggesting a great impact of gastrointestinal environment on brain development. Several studies have reported an association between the brain–gut axis and various disorders including cardiovascular disease and neurodegenerative disorders, through mechanisms of molecular mimicry [22]. Viruses of animal or plant origin may indeed mimic amino acid sequences as well as nucleotide sequences of microRNAs and influence protein expression. More recently, oral microbiota has been hypothesized to affect the brain not only by causing inflammation but also by altering platelet aggregation. Of all the known pathogenic oral bacteria, a few have been linked to CVD. It has been demonstrated that certain strains of *Streptococcus mutans* are potential risk factors for intracerebral hemorrhage [23]. The hemorrhage-causing *S. mutans* strains express collagen-binding proteins on their cell surface, enabling them to attach effectively to exposed collagen fibers on the surface of damaged blood vessels and prevent platelet activation, thereby leading to hemorrhages. Consistent with these data, a strong correlation between cerebral microbleeds and collagen-binding proteins–positive *S. mutans* has been detected [24]. *Porphyromonas gingivalis* is also found in atherosclerotic plaques and has been linked to the increased risk of ischemic stroke [25]. It was reported that *P. gingivalis* infects endothelial cells and increase the expression of endothelial adhesion molecules which promote monocyte/macrophage infiltration; in addition, it produces cysteine proteinase gingipains, which activate protease-activated receptors-1 and -4 on platelets and induce platelet aggregation.

Highlights of Pathophysiology

Endothelial Dysfunction (ED)

Although the mechanisms by which these different factors may impact VaD are currently ill defined, considerable evidence, including that derived from neuroimaging and pathology studies, indicates that ED is a pivotal pathophysiological process [26] [27]. It is proposed that risk factors may alter vascular hemodynamics and impact the endothelial cell function. ED, in turn, can reduce vasomotor reactivity and impair cerebral hemodynamic changes. Endothelium is a monolayer of cells covering the inner surface of blood vessels, with an estimated total area in humans of about 350 m^2. The endothelium is a dynamic organ that serves as a functional and structural barrier between the blood and the vessel wall; it has a wide variety of critical roles in the control of vascular function and, as a consequence of its dysfunction, in many mechanisms underlying vascular disorders. Endothelial cells are the main regulator of vascular homeostasis due to their interaction with both the circulating cells and those present in the vascular wall, mainly the smooth muscle cells. The four main endothelial functions can be summarized as following: (i) regulation of vascular tone which is obtained through the balanced production of vasodilators and vasoconstrictors in response to a variety of stimuli; (ii) regulation of fibrinolysis and coagulation pathways; (iii) participation in inflammation; (iv) blood vessel formation, repair, and remodeling (Fig. 1). The term ED is applied to identify the shift from a normal endothelium to a damaged one that may express with a pro-inflammatory, vasoconstrictive, proliferative, and procoagulation phenotype [27]. Brain microvessels are composed of endothelial cells, pericytes with smooth muscle-like properties that reside adjacent to capillaries, and astroglial processes. It was originally thought that the glial foot processes formed the BBB, but electron-microscopic studies identified the endothelial cell as the principal anatomic site of the BBB. The BBB results indeed from a specialized phenotype of the endothelial cells, which exhibit no fenestrations, extensive tight junctions, and relative lack of vesicular transport [28]. This barrier allows a strict control of exchange of solutes and circulating cells between the plasma and the interstitial space. Cerebral endothelial cells in most brain regions are connected by tight junctions that function as a "physical barrier" preventing molecular traffic between blood and the brain. BBB also acts as a "transport barrier," given to the presence of specific transport systems regulating the

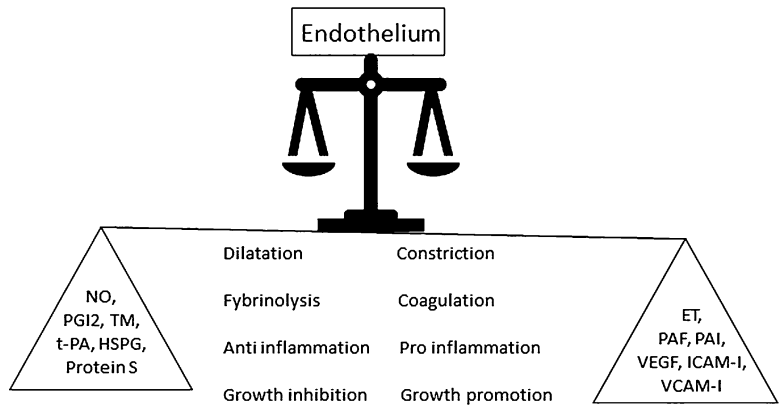

Fig. 1 The main molecules and pathways involved in main endothelial functions. (Modified from [27]). NO, Nitric Oxide; PGI2, Prostacyclin; TM, Thrombomodulin; t-PA, tissue Plasminogen Activator; HSPG, Heparan Sulfate Proteoglycan; ET, Endothelin; PAF, Platelet-Activating Factor; PAI, Plasminogen Activator Inhibitor; VEGF, Vascular Endothelial Growth Factor; ICAM-I, Intercellular Adhesion Molecules I; VCAM-I, Vascular Cell Adhesion Molecule I

transcellular traffic of small hydrophilic molecules, as well as a "metabolic barrier," given the presence of a combination of intracellular and extracellular enzymes.

Assessment of endothelial function consists of the analysis of endothelial cell responsiveness to vasodilator or vasoconstrictor stimuli. The methods include in vitro analysis, such as culture of endothelial cells, and in vivo analysis, such as flow-mediated dilation, venous occlusion plethysmography, and measurement of serum markers. However, none of these methods have been currently applied in the clinical setting, due to invasiveness, high costs, and difficult standardization of the techniques [29].

Different mechanisms have been hypothesized for ED to contribute to brain parenchyma lesions. Reduced cerebral blood flow and impaired cerebral blood flow autoregulation, secondary to an alteration of nitric oxide pathway, has been demonstrated in patients with SVD. Using endogenous contrast MRI perfusion, brain perfusion is reduced in the white matter and, within the white matter, it is reduced not only within regions of radiologic WMH but also in normal appearing white matter, although to a lesser extent [30]. Decreased vasodilation in response to external stimuli such as hypercapnia or salbutamol in patients with lacunar infarction, compared with controls, has been demonstrated [31]. Interestingly, there is now evidence pointing to a systemic ED in patients with cerebral SVD, as indicated by several studies in which endothelial changes have been measured in other vascular beds other than the brain. This association has been documented in districts like the kidney, the skin, and the sublingual microvasculature. Although WML are frequently interpreted as "ischemic," evidence from pathological studies that they are characterized by the expression of hypoxia-related molecules and endothelial markers such as intracellular adhesion molecule 1 (ICAM-1) supports a role for ED [32]. Finally, increased cerebrospinal fluid/serum albumin ratio [33] and increased permeability in the white matter on contrast-enhanced MRI in patients with lacunar stroke compared with patients with cortical stroke [34] suggest that BBB permeability is increased in these patients, with consequent leakage of plasma components into the vessel wall and surrounding parenchyma.

Chronic Cerebral Hypoperfusion

Cerebral hypoperfusion is emerging as a major contributor to cognitive decline and degenerative processes leading to dementia [35]. Several animal models have been developed to mimic the chronic hypoperfusive state in VaD. First, bilateral common carotid artery occlusion results in a severe reduction in cerebral blood flow (CBF) in rats, whereby cortical blood flow drops by over 70% in the days immediately following surgery, recovering to a 40% reduction in 1 month [36]. Another approach, bilateral common carotid artery stenosis by application of microcoils to reduce luminal diameter to ~50% in mice, results in blood flow decrease of 30–40% immediately following surgery, with a recovery to 15–20% of baseline levels at 1 month [37]. Blood flow measures are normally made using laser speckle or Doppler flowmetry or, more recently, arterial spin labeling MRI. Interestingly, these studies highlight that hypoperfusion is not restricted to the cortical vasculature, but involves both cortical and subcortical regions. Gradual common carotid artery stenosis in rats and mice, using ameroid constrictor devices applied on both common carotid arteries is a novel model recently developed to overcome the acute reduction in CBF [38].

Reduced cerebral perfusion correlates with the severity of cognitive impairment and also predicts which individuals with will progress to dementia [39]. Cross-sectional studies show that low cerebral blood flow is related to the severity of WMH on MRI [40] [41]. Interestingly, white matter is damaged in the absence of overt ischemic neuronal damage. Neuropathological investigations have revealed marked reductions in myelin density in the white matter in AD but particularly VaD patients compared with age-matched controls [42] [32], and there is evidence that this is related to reduced white matter perfusion [43]. Selective disruption of key proteins within the paranodal axon–glial junctions, which are critical to the

stability and function of myelinated axons and white matter function, has also been claimed [44]. Finally, in response to increasing duration of hypoperfusion, microglia gradually increases in parallel with the evolving damage to myelinated axons, particularly in the white matter [44] [45]. Astrogliosis can also be observed, but these changes appear to occur later than microglial alterations.

Clinical Features of Cognitive Dysfunction

A practical problem that frequently confronts the internist is the elderly patient with cognitive and behavioral decline, presenting with abnormal score in the Mini-Mental State Examination (MMSE) and presence of vascular lesions on brain imaging. In clinical practice, the Hachinski Ischemic Score (HIS) is a widely used method to differentiate VaD and mixed dementia from AD, with a specificity and sensitivity of 89% [46]. The last HIS version identifies 7 items, with a binary scoring (0, 1), and suggests a vascular component of cognitive impairment if the total score is 2 or higher. The first 13-item formulation, which still remains the most used one, is shown in Table 2 [47].

Table 2 Hachinski Ischemic Score (HIS). A score of 4 or less suggests dementia is due to Alzheimer's disease, a score of 7 or greater suggests vascular dementia [47]

Hachinski Ischemic Scale	
Feature	Value
Abrupt onset	2
Stepwise deterioration	1
Fluctuating course	2
Nocturnal confusion	1
Relative preservation of personality	1
Depression	1
Somatic complaints	1
Emotional incontinence	1
History or presence of hypertension	1
History of strokes	2
Evidence of atherosclerosis	1
Focal neurological symptoms	2
Focal neurological signs	2

Cognitive changes in VaD are much more variable than in other disorders such as AD and are highly dependent on the particular neural substrates affected by the vascular pathology. However, because subcortical vessel disease, rather than large cortical infarcts, accounts for most cases of VaD, lesions are particularly located in the subcortical areas and mainly cause the disruption of corticostriatal loops subserving the frontal lobes functions. While memory impairment is considered the core cognitive feature of degenerative MCI (d-MCI), predominant deficits in attention, information processing, and executive function are seen in vascular MCI (v-MCI). Other functions such as memory, language, and praxis are much more variably affected [5]. The use of the Montreal Cognitive Assessment (MoCA) over standard screening tests for dementia (such as the MMSE) is advisable in CVD patients, due to its higher sensitivity and specificity [2]. Another useful tool is the Vascular Dementia Assessment Scale (VADAS-cog). Recently, the immediate copy of the Rey–Osterrieth Complex Figure (ROCF), which explores cognitive processes such as planning and organizational strategies related to executive functions, has been proposed to differentiate d-MCI from v-MCI [48].

Behavioral and psychological symptoms of dementia (BPSD) are common in VaD as in other types of dementia and can be particularly distressing both for the patient and their family. Some symptoms, such as depression and apathy, are particularly prominent, while other features such as delusions and hallucinations are less frequent [5]. Patients with multi-infarct dementia are more likely to display "positive" symptoms (e.g., hallucinations, agitation/aggression, irritability, and euphoria), whereas "negative" symptoms (e.g., apathy, decreased appetite, and eating disturbances) are more typical of small vessel dementia [49].

Subtypes of Vascular Dementia

Based on type and location of CVD, it is possible to distinguish different subtypes of vascular dementia (Table 3) [5]. Single or recurrent cortical

Table 3 Subtypes of vascular dementia with associated imaging and pathological changes. (Modified from [5])

Multi-infarct dementia	Multiple, large, complete cortico-subcortical infarcts
Strategic infarct dementia	Single infarct in strategic location (e.g., thalamus)
Small vessel dementia	Lacunes, extensive white matter lesions Pathologically, infarcts, demyelination, and gliosis
Hypoperfusion dementia	Watershed infarcts, white matter lesions Pathologically, incomplete infarcts in white matter
Hemorrhagic dementia	Hemorrhagic deep or lobar changes, may be associated with amyloid angiopathy
Hereditary vascular dementia	Multiple lacunes and white matter lesions, temporal lobe white matter affected
Alzheimer's disease with cardiovascular disease	Combination of vascular changes and atrophy, especially medial temporal lobe Pathologically, mixture of vascular and degenerative (plaque and tangle) pathology

infarcts can lead to strategic infarct dementia or multi-infarct dementia, whereas subcortical infarcts such as lacunes or WMLs can be associated with small vessel dementia or hypoperfusion dementia [50].

Multi-Infarct and Strategic Infarct Dementias

Multi-infarct dementia (Fig. 2) typically arise abruptly, with fluctuating symptoms and "stepped" progression, and manifest with cortical and subcortical focal signs and symptoms which depend on the area affected by acute cerebrovascular disease. Dementia develops in around 15–30% of subjects 3 months after a stroke [5]. Although functional outcome can be moderately predicted at baseline, accurate prediction of cognitive outcome remains more elusive. For functional outcome, age, initial stroke severity, and stroke volume have been identified as important

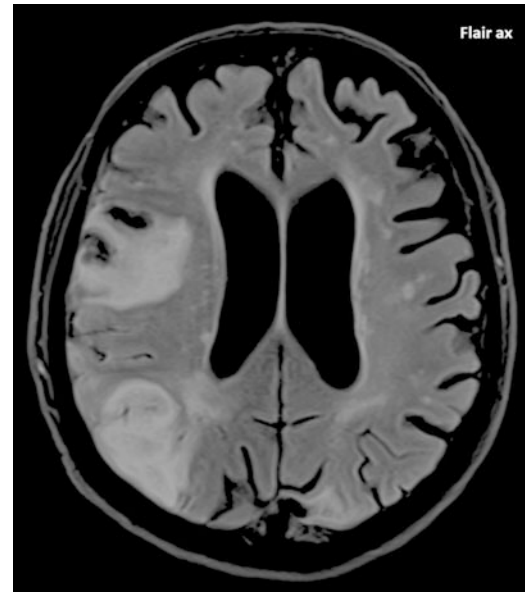

Fig. 2 Multi-infarct dementia. MRI shows ischemic lesions in the territory supplied by the right middle cerebral artery, with hemorrhagic infarction, and another ischemic lesion in the contralateral occipital lobe; in addition, diffuse white matter hyperintensities

predictors. In particular, age and initial severity assessed by the National Institutes of Health Stroke Scale (NIHSS) correctly classify about 70% of the patients with respect to functional recovery [51]. These factors are accepted, even if less predictive, also for cognitive dysfunction. Stroke location is an independent predictor of cognitive outcome: single brain infarct in functionally critical areas of the brain (e.g., angular gyrus, thalamus, basal forebrain, posterior cerebral artery, and anterior cerebral artery territories) can indeed cause dementia itself, in the form of the strategic infarct dementia. Anterior infarcts, cortical locations, and lesions in the left hemisphere are all associated with worse global cognitive scores. The importance of left inferior frontal gyrus and left superior temporal gyrus is recognized for speech production and speech comprehension. Hippocampus, parahippocampal gyrus, and the left middle temporal gyrus are known to be involved in poststroke memory dysfunction. Executive functions are associated not only with prefrontal cortex but also with cingulate cortex, basal ganglia, and thalamus. Furthermore, the

involvement of the left thalamus is associated with a worse global cognitive score, because of its role of relay in several cognitive domains (attention, working memory, visuo-spatial abilities, orientation, long-term memory, and executive functions). All cognitive functions are further integrated by a widely distributed network; therefore, cognitive dysfunction may also be due to deafferentation through white matter fiber damages [52].

Small Vessel Dementia

The term cerebral SVD refers to a group of pathological processes with various etiologies affecting the small arteries, arterioles, venules, and capillaries of the brain. SVD may have various meanings, in pathological rather than clinical and neuroimaging contexts. However, because small vessels cannot be currently visualized in vivo, the term SVD is frequently used to describe the parenchyma lesions visible at CT or MRI scan rather than the underlying small vessel alterations. Lesions on the brain parenchyma, as consequences of SVD, are mainly located in the subcortical structures, such as lacunar infarcts, white matter lesions, large hemorrhages, and microbleeds (Fig. 3). Cerebral arterial small vessels recognize two origins: superficially, they stem from the subarachnoid circulation as the terminal vessels of medium-sized arteries, and deeper, at the base of the brain, they stem directly from the large vessels as perforating arteries. These two systems converge towards each other and, after passing the cortical layers and the deep grey structures, respectively, they tend to merge in the deepest areas of the subcortical white matter where there is a watershed area [17]. In this case, cognitive decline may have an insidious onset and a slow progression, representing an AD mimic. This form is now considered to be the main cause of VaD. From a pathological point of view, the process underlying SVD is mainly included in a systemic small vessel disorder (Table 4). Only in some cases the brain is the main target and the lesions and effects of these diseases might be confined to the brain. The frequency of these

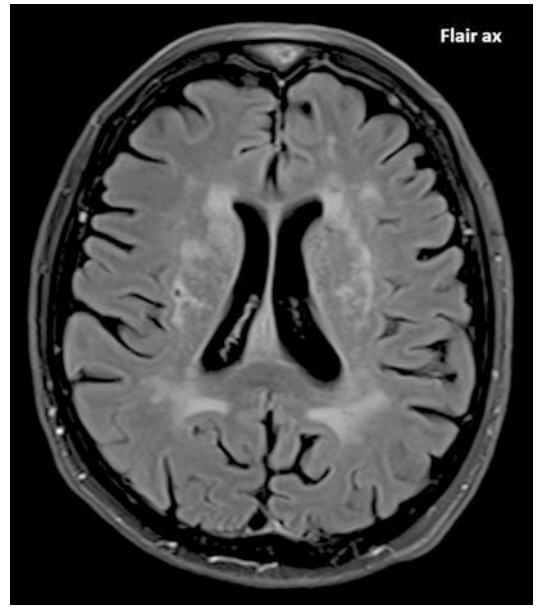

Fig. 3 Small vessel disease dementia. MRI demonstrates prominent periventricular white matter hyperintensities and lacunar infarcts in the corona radiata bilaterally on fluid-attenuated inversion recovery (FLAIR) image

Table 4 Aetiopathogenic classification of cerebral small vessel diseases. (Modified from [17])

Type 1: Arteriolosclerosis
Type 2: Sporadic and hereditary cerebral amyloid angiopathy
Type 3: Inherited or genetic small vessel diseases distinct from cerebral amyloid angiopathy For example, CADASIL, CARASIL, Fabry's disease, cerebroretinal vasculopathies, small vessel diseases caused by COL4A1 mutations, PADMAL, hereditary multi-infarct dementia of the Swedish type, MELAS
Type 4: Inflammatory and immunologically mediated small vessel diseases For example, Wegener's granulomatosis, Churg-Strauss syndrome, microscopic polyangiitis, Henoch- Schönlein purpura, cryoglobulinaemic vasculitis, cutaneous leukocytoclastic angiitis, primary angiitis of the CNS, Sneddon's syndrome, nervous system vasculitis secondary to infections, nervous system vasculitis associated with connective tissue disorders such as systemic lupus erythematosus, Sjögren's syndrome, rheumatoid vasculitis, scleroderma, and dermatomyositis
Type 5: Venous collagenosis
Type 6: Other small vessel diseases For example, post-radiation angiopathy and nonamyloid microvessel degeneration in Alzheimer's disease

forms is very variable, and arteriolosclerosis and sporadic and hereditary cerebral amyloid angiopathy are the most prevalent ones.

Hypoperfusion Dementia

Chronic cerebral hypoperfusion (CCH) is a common consequence of various cerebral vascular disorders and hemodynamic and blood changes and an important cause of both VaD and AD [53]. Three main causes lead to CCH: (i) vascular structural lesions resulting from artery stenosis or occlusion caused by atherosclerosis, arteriovenous malformation, Takayasu arteritis, Moyamoya disease, and cerebral arteriovenous fistula; (ii) cerebral hemodynamic changes, including chronic hypovolemia, prolonged hypotension, and reduced cardiac output due to heart failure; and (iii) changes in blood components of any nature, causing an increase in blood viscosity, such as hyperlipidemia, polycythemia, and hyperhomocysteinemia. The major risk factors of CCH are therefore hypertension, hyperlipidemia, smoking, obesity, age, hyperhomocysteinemia, and obstructive sleep apne/ahypopnea syndrome [54]. As seen above, CCH might promote VaD and neurodegeneration through neuronal energy failure and production of reactive oxygen species and pro-inflammatory cytokines through activated microglial cells that, in turn, damage the neurons and contribute to WMLs. The clinical spectrum of hypoperfusion dementia is broad and depends on the length and extent of hypoperfusion [55]. MRI findings may be unremarkable or show incomplete infarctions with WMHs, hippocampal sclerosis, or scarring. Bilateral globus pallidus lesions (high signal on T2-weighted MRI) may occur. The most vulnerable areas to ischemia appear to be the cortical watershed regions and the basal ganglia. Neurons are particularly susceptible to hypoxic injury in cortical layers 3 and 5, the striatum, the hippocampus, and the Purkinje cells of the cerebellum.

Hemorrhagic Dementia

While intracerebral hemorrhage (ICH) represents only 10–15% of all strokes, it carries a higher risk of morbidity and mortality compared to the more common ischemic forms of stroke. Different underlying pathologies are associated with the specific location of hemorrhage in the brain. Deep ICH results from rupture of small arterioles most commonly in the putamen or thalamus, while lobar ICH results from rupture of small and medium-sized perforating arteries in the cortex and subcortical white matter. While deep perforating vasculopathy, mainly driven by traditional cardiovascular risk factors, appears to underlie deep ICH, CAA, resulting from progressive cerebrovascular Aβ deposition within small cortical and leptomeningeal small vessel walls, accounts for the majority of lobar ICH in the elderly. Effects of ICH on cognition can occur at three different stages during the disease course: before ICH, in the acute stage and in the chronic stage [56]. Cognitive impairment prior to ICH is indeed common. In postmortem studies, SVD was detected in 36% of CAA-related ICH patients versus 75% of non-CAA-related ICH, while AD pathology was found in 68% of CAA-related ICH patients versus 9% of non-CAA-related ICH patients [57]. Therefore, the underlying pathology can cause cognitive changes before symptomatic ICH. In the acute stage, the severity and location of ICH are primarily responsible for the immediately observed cognitive deficits. In the chronic stage, the underlying SVD or neurodegenerative pathology appears to be primarily responsible for the cognitive decline, which presents in a proportion ranging from 5% to 44% of patients. This view also explains why young patients with ICH present overall lower incidence of cognitive impairment. Since a high proportion of these patients had an underlying structural cause of ICH (63%), it is possible that the natural history of these diseases is different from those with primary ICH.

Hereditary Vascular Dementia

There are a small number of familial cerebral microangiopathies caused by mutations in single genes that present with cognitive impairment progressing to dementia [58, 59]. Autosomal Dominant Cerebral Arteriopathy with Subcortical

Infarcts and Leucoencephalopathy (CADASIL) is the most common inherited cause of stroke and VaD in adults with an estimated frequency of 1.5–5.0 per 100,000 in Western Europe. It is caused by dominant mutations in the NOTCH3 gene. It is characterized by five basic symptoms: migraine with aura, subcortical ischemic events, mood disorders, apathy and cognitive impairment, which evolves over the 4th to 7th decades of life. Brain MRI alterations may precede symptoms for up to 10 years; the most frequent anomalies are point hyperintensities in T2 or FLAIR; with the progression of the disease, there are also multiple ischemic lacunes (basal ganglia, thalamus, brainstem), diffuse WMH, and dilated perivascular spaces (Fig. 4). Since the clinical presentation, the profile of neuropsychological deficits and neuroimaging abnormalities are very similar to those of subcortical ischemic VaD, CADASIL has attracted great interest as a possible model for more common forms of small vessel diseases. CARASIL (a cerebral autosomal recessive variant of CADASIL) is a rare disorder found mainly in Asian families, caused by mutations in the HTRA1 gene. Fabry disease is an X-linked disease causing insufficient activity of the enzyme alphagalactosidase A and accumulation of glycosphingolipids especially in vascular endothelium; it is particularly important because of the possibility of enzyme replacement therapy. Cerebroretinal vasculopathies include hereditary endotheliopathy, retinopathy, nephropathy with stroke, and hereditary vascular retinopathy and result from mutations in the TREX1 gene. COL4A1 and COL4A2 are genes coding for type IV collagen, a component of basement membranes in blood vessels. Mutations in these genes are associated with systemic SVD especially affecting eyes, muscles, kidneys, and brain. Pontine autosomal dominant microangiopathy and leukoencephalopathy (PADMAL) is a recently discovered autosomal dominant disease caused by mutation in an untranslated region of COL4A1, leading to upregulated expression of COL4A1. Other familial forms of vascular dementia include an autosomal dominant type of Swedish dementia not linked to CADASIL and mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS).

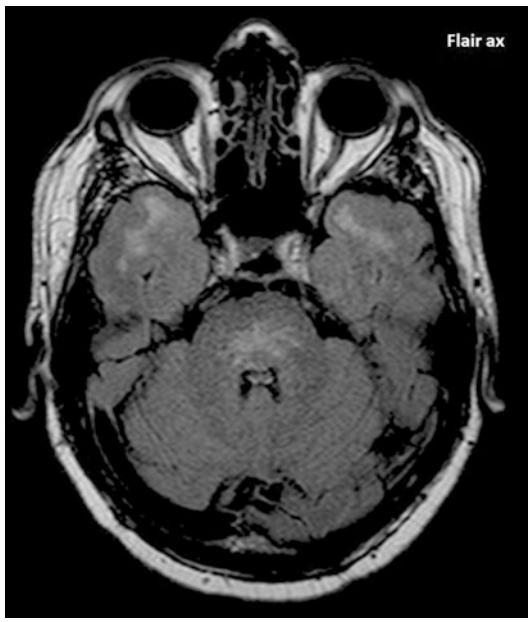

Fig. 4 CADASIL. MRI shows confluent white matter hyperintensities on FLAIR sequence, typically involving the anterior temporal lobes and the pons

Cerebrovascular Pathology and Brain Parenchymal Changes

Although CVD causes pathological damage and impairs cognition, finding the exact contribution of cerebrovascular pathology to cognitive decline and dementia is extremely difficult. The natural history of CVD consists in vessel wall modifications, such as arteriolosclerosis or CAA, which lead to cortical and subcortical infarcts, subinfarct ischaemic lesions (microinfarcts), and cerebral large and small (microbleeds) hemorrhages lesions. In autopsy studies, it is difficult to relate cognitive impairments in life to postmortem pathology, even when using data from prospective studies. Currently, pathological consensus criteria for diagnosing and staging VaD still lack. Different studies therefore use different criteria to report whether individuals have autopsy evidence of substantial CVD, since abnormalities in vascular brain pathology are almost the rule in people aged over 75 years [5].

Lacunes represent small foci of ischemic necrosis resulting from narrowing or occlusion of penetrating arteries branching directly from larger cerebral arteries. Perivascular edema and thickening, inflammation, and disintegration of the arteriolar wall are common, whereas vessel occlusion is rare. Lacunar infarcts are frequently multiple and bilateral and often coexist with other vascular lesions (e.g., large infarcts or diffuse white matter damage) [2]. Lacunar infarcts are a widely accepted sign of SVD. However, isolated lacunar infarcts might be caused also by atheroembolism from atherosclerotic plaques in the carotid arteries or aortic arch and cardioembolism. It may be appropriate to classify patients with lacunar infarcts as having SVD only when the lacunar infarcts are multiple or associated with moderate to severe WMLs. Whether single or multiple, they may be symptomatic or asymptomatic, depending on their location and the volume of normal brain tissue lost; they are typically seen on MRI in locations such as the basal ganglia, internal capsule, thalamus, and pons. Lacunes are defined as hypointense foci on MRI T1-weighted sequences. There is no full consensus on the size of lacunar infarcts; the maximum accepted diameter for the definition of a lacunar infarct is usually 15 mm. On MRI it is sometimes difficult to distinguish these from dilated perivascular spaces. These are enlargements of the spaces around the penetrating vessels in the brain parenchyma (also called Virchow-Robin spaces) and are typically located in some areas (e.g., anterior commissure, vertex) that are different from those of lacunar infarcts; moreover, they are usually smaller than 1×2 mm and have an isointense appearance with the CSF on proton density sequences. Lacunar infarcts and dilated perivascular spaces share the same risk factor profile and it is plausible that dilated perivascular spaces are another expression of SVD [17].

WMLs are considered a form of rarefaction or incomplete infarction where there may be selective damage to some cellular components. Alterations include pallor or swelling of myelin, loss of oligodendrocytes, damage to axons, cavitations with or without presence of macrophages, areas of reactive astrogliosis, and perivenous collagenosis. WMLs are secondary to chronic hypoperfusion with oligodendrocytes particularly vulnerable to hypoxic environment and are associated with chronic pro-thrombotic endothelial dysfunction. WMLs are a hallmark of SVD but also occur most in ~30% of AD and in fact may reflect Wallerian changes secondary to cortical loss of neurons [2]. The previous term to describe the rarefaction of the white matter was leukoaraiosis, which was introduced already more than 20 years ago. WMLs on MRI are seen as more or less confluent areas that are bilaterally and symmetrically sited in the hemispheric white matter and that appear hyperintense on T2-weighted and fluid-attenuated inversion recovery images. Despite the fact that WMLs are typically supratentorial, they do frequently occur in one infratentorial location, the pons [17].

Mixed Dementia, Differential Diagnosis, and the Concept of Mixed AD

AD and VaD together represent the vast majority of dementias. Due to overlapping of their neuropsychological profiles and the possible coexistence of the same brain vascular lesions, differentiating between these two forms of dementia can be difficult. This is a common event in clinical practice, and the label of "mixed dementia" sounds very familial to every neurologist. Interestingly, the most recent proposals of new diagnostic criteria for AD have introduced the term of "*mixed AD*" [60]. This term should refer to patients who fulfill the diagnostic criteria for typical AD, but additionally present with clinical and brain imaging/biological evidence of other comorbid disorders, first of all cerebrovascular disease. The criteria warn that detecting in a patient the co-occurrence of two pathologies that potentially affect cognitive performance does not equate to proof of multiple causation: it is therefore recommended to reserve the "mixed AD" label only for cases in which both clinical features and diagnostic markers point to a mixed etiology. For instance, a typical AD phenotype with

coexistent white matter changes cannot be diagnosed as mixed AD in the absence of motor symptoms or gait disturbances consistent with the distribution of vascular pathology.

The advances in biomarker development (such as CSF tau and beta-amyloid concentrations, brain amyloid PET) now allow biological evidence to be used in support of a diagnosis of mixed AD. With respect to advanced MRI techniques, the identification of quantitative imaging biomarkers specifically sensitive to AD or VaD may facilitate the differential diagnosis. For example, parameters of microstructural abnormalities derived from diffusion tensor imaging (DTI) may be helpful in differentiating between dementias. It has been recently reported that DTI parameters in the parahippocampal tracts are mainly affected in AD, while VaD shows more spread white matter damage associated with thalamic radiations involvement, and that the genu of the corpus callosum is predominantly affected in VaD, while the splenium is mainly involved in AD [61]. Therefore, specific patterns of white matter alterations can help distinguishing between VaD and AD; further imaging studies on larger cohorts of subjects, characterized for brain amyloidosis, will allow to confirm and to integrate these findings and elucidate the mechanisms of mixed dementia. These steps will be essential to translate these advances to clinical practice, also in terms of future treatments.

Sporadic, Hereditary, and Inflammatory Cerebral Amyloid Angiopathies

One important link between VaD and AD, emerging in recent years, is cerebral amyloid angiopathy. CAA involves cerebrovascular amyloid deposition and, although mostly identified with Aβ deposition, it may be classified into several types according to the amyloid protein involved (e.g., cystatin C, prion protein, ABri/ADan, transthyretin, gelsolin, and immunoglobulin light chain amyloid) [62]. CAA due to Aβ deposition has a high frequency; it is found in clinic-based autopsy series in 83% of persons with pathologically-confirmed AD and in 64% to 68% of those with and without dementia [18]. Sporadic CAA affects arterioles and capillaries of the cerebral cortex and overlying leptomeninges, with a predilection for parieto-occipital regions, but it is almost never seen within subcortical white matter, deep grey matter, or brainstem. It may be seen infratentorial, affecting the leptomeningeal vessels overlying cerebellum. Neuropathologic features include fibrillar Aβ deposits among smooth muscle cells within the media of brain parenchymal arterioles, with eventual replacement (over months or years) of the smooth muscle cells by Aβ, which can easily be demonstrated by immunohistochemistry [58]. Aβ is cleaved from the β-amyloid precursor protein (APP) in peptides of different lengths; while Aβ42 easily aggregates and deposits in the brain parenchyma as senile plaques, Aβ40 does not aggregate as easily and is transported, through periarterial interstitial fluid drainage pathways, to blood vessels for clearance. In this process, Aβ40 aggregates on vascular basement membranes [62]. CAA-associated vasculopathies mainly lead to development of hemorrhagic lesions (spontaneous lobar intracerebral macrohemorrhage, cortical microhemorrhage, and cortical superficial siderosis) and less frequently, cortical microinfarcts. CAA can be accompanied by marked inflammation (CAA-related inflammation/angiitis), presenting with subacute leukoencephalopathy that is responsive to immunosuppressive therapies [63]. The clinical-radiological Boston criteria are commonly used for the diagnosis of CAA-related ICH (Table 5) [64]. MRI techniques, such as gradient-echo T2∗ imaging and susceptibility-weighted imaging, are useful for detecting microhemorrhages and cortical superficial siderosis (Fig. 5). In vivo markers for Aβ (e.g., amyloid PET and cerebrospinal fluid Aβ40, Aβ42, tau, and ptau) can support the diagnosis but need further validation. APOE epsilon 2 is also associated with sporadic CAA-related cerebral hemorrhage. Several familial forms of Aβ CAA, usually inherited as an autosomal dominant trait, are also recognized (e.g., mutations in APP, PSEN-1, and PSEN-2 genes).

Table 5 Modified Boston criteria for diagnosis of CAA-related hemorrhage [64]

Definite CAA Full postmortem examination demonstrating: • Lobar, cortical, or cortico-subcortical hemorrhage • Severe CAA with vasculopathy • Absence of other diagnostic lesions
Probable CAA with supporting pathology Clinical data and pathologic tissue (evacuated hematoma or cortical biopsy) demonstrating: • Lobar, cortical, or corticosubcortical hemorrhage • Some degree of CAA in the specimen • Absence of other diagnostic lesions
Probable CAA Clinical data and MRI or CT demonstrating: • Multiple hemorrhages restricted to lobar, cortical, or corticosubcortical regions (cerebellar hemorrhage allowed) or single lobar, cortical, or corticosubcortical hemorrhage, and focal or disseminated superficial siderosis • Age $\geq$ 55 years • Absence of other causes of hemorrhage or superficial siderosis
Possible CAA Clinical data and MRI or CT demonstrating: • Single lobar, cortical, or corticosubcortical hemorrhage or focal or disseminated superficial siderosis • Age $\geq$ 55 years • Absence of other causes of hemorrhage or superficial siderosis

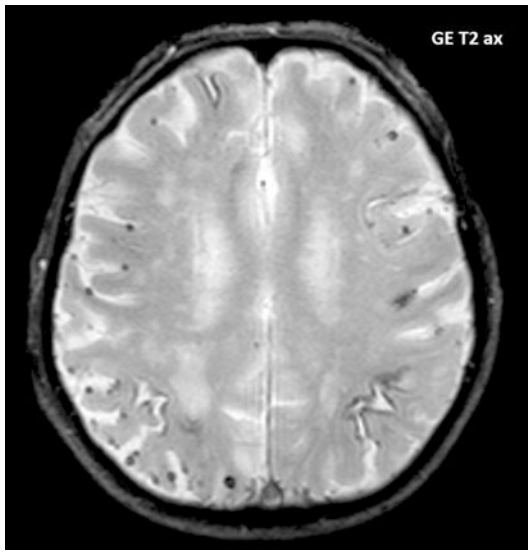

Fig. 5 Cerebral amyloid angiopathy. Cortico-subcortical microbleeds and cortical superficial siderosis, preferentially localized in the posterior areas, on gradient-echo T2∗ image

Conclusions

In conclusion, among the multifactorial nature of dementias (including the neurodegenerative types, such as sporadic AD), vascular changes play an important role in the disease process. It is therefore important to investigate vascular pathology before the disease becomes too severe to reverse. The mechanisms underlying these events, however, are far from clear and will be an important topic of future research. In recent years, the relationship between SVD and cognition has been actively investigated due to rapid advances in imaging technology. Amyloid and vascular pathologies have been found ever more to overlap, and it would now appear that they almost never occur in isolation. Although many clinical and radiological aspects are not yet fully standardized, this coexistence of pathologies appears to be interesting with respect to future trials focused on the treatment of cognitive impairment due to SVD. Targeting the vascular component may be indeed a strategy not only to reduce the risk of developing dementia, but also to decelerate the progression of degenerative processes. Vascular biomarkers will certainly facilitate preventive efforts and the development of more effective treatments for vascular as well as other dementias.

References

1. Fratiglioni L, Launer L, Andersen K, Breteler M, Copeland J, Dartigues J, et al. Incidence of dementia and major subtypes in Europe: a collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. Neurology. 2000;54(11 Suppl 5):S10–5.
2. Kalaria RN. The pathology and pathophysiology of vascular dementia. Neuropharmacology. 2018;134(Pt B):226–39.
3. Kalaria RN. Vascular basis for brain degeneration: faltering controls and risk factors for dementia. Nutr Rev. 2010;68(Suppl 2):S74–87.
4. Erkinjuntti T, Kurz A, Gauthier S, Bullock R, Lilienfeld S, Damaraju CD. Efficacy of galantamine in probable vascular dementia and Alzheimer's disease combined with cerebrovascular disease: a randomised trial. Lancet. 2002;359(9314):1283–90.
5. O'Brien JT, Thomas A. Vascular dementia. Lancet. 2015;386(10004):1698–706.

6. Pantoni L, Poggesi A, Inzitari D. Cognitive decline and dementia related to cerebrovascular diseases: some evidence and concepts. Cerebrovasc Dis. 2009;27 (Suppl 1):191–6.
7. Blessed G, Tomlinson BE, Roth M. The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. Br J Psychiatry. 1968;114(512):797–811.
8. Hachinski V, Iadecola C, Petersen RC, Breteler MM, Nyenhuis DL, Black SE, et al. National Institute of Neurological Disorders and Stroke-Canadian Stroke Network vascular cognitive impairment harmonization standards. Stroke. 2006;37(9):2220–41.
9. Román GC, Tatemichi TK, Erkinjuntti T, Cummings JL, Masdeu JC, Garcia JH, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN international workshop. Neurology. 1993;43(2):250–60.
10. Pohjasvaara T, Mäntylä R, Ylikoski R, Kaste M, Erkinjuntti T. Comparison of different clinical criteria (DSM-III, ADDTC, ICD-10, NINDS-AIREN, DSM-IV) for the diagnosis of vascular dementia. National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neuro. Stroke. 2000;31 (12):2952–7.
11. Hachinski V. Vascular dementia: a radical redefinition. Dementia. 1994;5(3–4):130–2.
12. Román GC, Sachdev P, Royall DR, Bullock RA, Orgogozo JM, López-Pousa S, et al. Vascular cognitive disorder: a new diagnostic category updating vascular cognitive impairment and vascular dementia. J Neurol Sci. 2004;226(1–2):81–7.
13. Breteler MM, Claus JJ, Grobbee DE, Hofman A. Cardiovascular disease and distribution of cognitive function in elderly people: the Rotterdam study. BMJ. 1994;308(6944):1604–8.
14. Wiesmann M, Kiliaan AJ, Claassen JA. Vascular aspects of cognitive impairment and dementia. J Cereb Blood Flow Metab. 2013;33(11):1696–706.
15. Snowdon DA, Greiner LH, Mortimer JA, Riley KP, Greiner PA, Markesbery WR. Brain infarction and the clinical expression of Alzheimer disease. The Nun Study. JAMA. 1997;277(10):813–7.
16. Pantoni L, Poggesi A, Basile AM, Pracucci G, Barkhof F, Chabriat H, et al. Leukoaraiosis predicts hidden global functioning impairment in nondisabled older people: the LADIS (Leukoaraiosis and disability in the elderly) study. J Am Geriatr Soc. 2006;54 (7):1095–101.
17. Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. Lancet Neurol. 2010;9(7):689–701.
18. Arvanitakis Z, Leurgans SE, Wang Z, Wilson RS, Bennett DA, Schneider JA. Cerebral amyloid angiopathy pathology and cognitive domains in older persons. Ann Neurol. 2011;69(2):320–7.
19. Hofman A, Ott A, Breteler MM, Bots ML, Slooter AJ, van Harskamp F, et al. Atherosclerosis, apolipoprotein E, and prevalence of dementia and Alzheimer's disease in the Rotterdam study. Lancet. 1997;349 (9046):151–4.
20. van Harten B, de Leeuw FE, Weinstein HC, Scheltens P, Biessels GJ. Brain imaging in patients with diabetes: a systematic review. Diabetes Care. 2006;29 (11):2539–48.
21. Ihara M, Yamamoto Y. Emerging evidence for pathogenesis of sporadic cerebral small vessel disease. Stroke. 2016;47(2):554–60.
22. Friedland RP. Mechanisms of molecular mimicry involving the microbiota in neurodegeneration. J Alzheimers Dis. 2015;45(2):349–62.
23. Nakano H, Hokamura K, Taniguchi N, Wada K, Kudo C, Nomura R, et al. The collagen-binding protein of Streptococcus mutans is involved in haemorrhagic stroke. Nat Commun. 2011;2:485.
24. Miyatani F, Kuriyama N, Watanabe I, Nomura R, Nakano K, Matsui D, et al. Relationship between Cnm-positive Streptococcus mutans and cerebral microbleeds in humans. Oral Dis. 2015;21(7):886–93.
25. Pussinen PJ, Alfthan G, Jousilahti P, Paju S, Tuomilehto J. Systemic exposure to Porphyromonas gingivalis predicts incident stroke. Atherosclerosis. 2007;193(1):222–8.
26. Wardlaw JM, Smith C, Dichgans M. Mechanisms of sporadic cerebral small vessel disease: insights from neuroimaging. Lancet Neurol. 2013;12(5):483–97.
27. Poggesi A, Pasi M, Pescini F, Pantoni L, Inzitari D. Circulating biologic markers of endothelial dysfunction in cerebral small vessel disease: a review. J Cereb Blood Flow Metab. 2016;36(1):72–94.
28. Kandel ER, Schwartz JH, Jessell TM. Principles of neural science. 4th ed. New York: McGraw-Hill; 2000.
29. Le Brocq M, Leslie SJ, Milliken P, Megson IL. Endothelial dysfunction: from molecular mechanisms to measurement, clinical implications, and therapeutic opportunities. Antioxid Redox Signal. 2008;10 (9):1631–74.
30. O'Sullivan M, Lythgoe DJ, Pereira AC, Summers PE, Jarosz JM, Williams SC, et al. Patterns of cerebral blood flow reduction in patients with ischemic leukoaraiosis. Neurology. 2002;59(3):321–6.
31. Deplanque D, Lavallee PC, Labreuche J, Gongora-Rivera F, Jaramillo A, Brenner D, et al. Cerebral and extracerebral vasoreactivity in symptomatic lacunar stroke patients: a case-control study. Int J Stroke. 2013;8(6):413–21.
32. Fernando MS, Simpson JE, Matthews F, Brayne C, Lewis CE, Barber R, et al. White matter lesions in an unselected cohort of the elderly: molecular pathology suggests origin from chronic hypoperfusion injury. Stroke. 2006;37(6):1391–8.
33. Skoog I, Wallin A, Fredman P, Hesse C, Aevarsson O, Karlsson I, et al. A population study on blood-brain barrier function in 85-year-olds: relation to Alzheimer's disease and vascular dementia. Neurology. 1998;50(4):966–71.

34. Wardlaw JM, Farrall A, Armitage PA, Carpenter T, Chappell F, Doubal F, et al. Changes in background blood-brain barrier integrity between lacunar and cortical ischemic stroke subtypes. Stroke. 2008;39 (4):1327–32.
35. Duncombe J, Kitamura A, Hase Y, Ihara M, Kalaria RN, Horsburgh K. Chronic cerebral hypoperfusion: a key mechanism leading to vascular cognitive impairment and dementia. Closing the translational gap between rodent models and human vascular cognitive impairment and dementia. Clin Sci (Lond). 2017;131 (19):2451–68.
36. Tomimoto H, Ihara M, Wakita H, Ohtani R, Lin JX, Akiguchi I, et al. Chronic cerebral hypoperfusion induces white matter lesions and loss of oligodendroglia with DNA fragmentation in the rat. Acta Neuropathol. 2003;106(6):527–34.
37. Shibata M, Ohtani R, Ihara M, Tomimoto H. White matter lesions and glial activation in a novel mouse model of chronic cerebral hypoperfusion. Stroke. 2004;35(11):2598–603.
38. Hattori Y, Enmi J, Iguchi S, Saito S, Yamamoto Y, Tsuji M, et al. Gradual carotid artery stenosis in mice closely replicates hypoperfusive vascular dementia in humans. J Am Heart Assoc. 2016;5(2):e002757.
39. Chao LL, Buckley ST, Kornak J, Schuff N, Madison C, Yaffe K, et al. ASL perfusion MRI predicts cognitive decline and conversion from MCI to dementia. Alzheimer Dis Assoc Disord. 2010;24(1):19–27.
40. Bucur B, Madden DJ, Spaniol J, Provenzale JM, Cabeza R, White LE, et al. Age-related slowing of memory retrieval: contributions of perceptual speed and cerebral white matter integrity. Neurobiol Aging. 2008;29(7):1070–9.
41. Bastin ME, Clayden JD, Pattie A, Gerrish IF, Wardlaw JM, Deary IJ. Diffusion tensor and magnetization transfer MRI measurements of periventricular white matter hyperintensities in old age. Neurobiol Aging. 2009;30(1):125–36.
42. Barker R, Wellington D, Esiri MM, Love S. Assessing white matter ischemic damage in dementia patients by measurement of myelin proteins. J Cereb Blood Flow Metab. 2013;33(7):1050–7.
43. Barker R, Ashby EL, Wellington D, Barrow VM, Palmer JC, Kehoe PG, et al. Pathophysiology of white matter perfusion in Alzheimer's disease and vascular dementia. Brain. 2014;137(Pt 5):1524–32.
44. Reimer MM, Reimer J, Searcy L, Scullion G, Zonta B, Desmazieres A, et al. Rapid disruption of axon-glial integrity in response to mild cerebral hypoperfusion. J Neurosci. 2011;31(49):18185–94.
45. McQueen J, Reimer MM, Holland PR, Manso Y, McLaughlin M, Fowler JH, et al. Restoration of oligodendrocyte pools in a mouse model of chronic cerebral hypoperfusion. PLoS One. 2014;9(2):e87227.
46. Knopman DS, DeKosky ST, Cummings JL, Chui H, Corey-Bloom J, Relkin N, et al. Practice parameter: diagnosis of dementia (an evidence-based review). Report of the quality standards Subcommittee of the American Academy of neurology. Neurology. 2001;56 (9):1143–53.
47. Hachinski V, Oveisgharan S, Romney AK, Shankle WR. Optimizing the Hachinski ischemic scale. Arch Neurol. 2012;69(2):169–75.
48. Salvadori E, Dieci F, Caffarra P. Qualitative evaluation of the immediate copy of the Rey-Osterrieth complex figure: comparison between vascular and degenerative MCI patients. Arch Clin Neuropsychol. 2019;34(1): 14–23.
49. Gupta M, Dasgupta A, Khwaja GA, Chowdhury D, Patidar Y, Batra A. Behavioural and psychological symptoms in poststroke vascular cognitive impairment. Behav Neurol. 2014;2014:430128.
50. Leys D, Hénon H, Mackowiak-Cordoliani MA, Pasquier F. Poststroke dementia. Lancet Neurol. 2005;4(11):752–9.
51. König IR, Ziegler A, Bluhmki E, Hacke W, Bath PM, Sacco RL, et al. Predicting long-term outcome after acute ischemic stroke: a simple index works in patients from controlled clinical trials. Stroke. 2008;39 (6):1821–6.
52. Munsch F, Sagnier S, Asselineau J, Bigourdan A, Guttmann CR, Debruxelles S, et al. Stroke location is an independent predictor of cognitive outcome. Stroke. 2016;47(1):66–73.
53. Zhao Y, Gong CX. From chronic cerebral hypoperfusion to Alzheimer-like brain pathology and neurodegeneration. Cell Mol Neurobiol. 2015;35(1):101–10.
54. Sarti C, Pantoni L, Bartolini L, Inzitari D. Cognitive impairment and chronic cerebral hypoperfusion: what can be learned from experimental models. J Neurol Sci. 2002;203–204:263–6.
55. Mendez MF, Cummings JL. Dementia: a clinical approach. 3rd ed. Philadelphia: Butterworth-Heinemann; 2003.
56. Xiong L, Reijmer YD, Charidimou A, Cordonnier C, Viswanathan A. Intracerebral hemorrhage and cognitive impairment. Biochim Biophys Acta. 2016;1862 (5):939–44.
57. Attems J, Lauda F, Jellinger KA. Unexpectedly low prevalence of intracerebral hemorrhages in sporadic cerebral amyloid angiopathy: an autopsy study. J Neurol. 2008;255(1):70–6.
58. Vinters HV, Zarow C, Borys E, Whitman JD, Tung S, Ellis WG, et al. Review: vascular dementia: clinicopathologic and genetic considerations. Neuropathol Appl Neurobiol. 2018;44(3):247–66.
59. Søndergaard CB, Nielsen JE, Hansen CK, Christensen H. Hereditary cerebral small vessel disease and stroke. Clin Neurol Neurosurg. 2017;155:45–57.
60. Dubois B, Feldman HH, Jacova C, Cummings JL, Dekosky ST, Barberger-Gateau P, et al. Revising the definition of Alzheimer's disease: a new lexicon. Lancet Neurol. 2010;9(11):1118–27.

61. Palesi F, De Rinaldis A, Vitali P, Castellazzi G, Casiraghi L, Germani G, et al. Specific patterns of white matter alterations help distinguishing Alzheimer's and vascular dementia. Front Neurosci. 2018;12:274.
62. Yamada M. Cerebral amyloid angiopathy: emerging concepts. J Stroke. 2015;17(1):17–30.
63. Auriel E, Charidimou A, Gurol ME, Ni J, Van Etten ES, Martinez-Ramirez S, et al. Validation of clinicoradiological criteria for the diagnosis of cerebral amyloid angiopathy-related inflammation. JAMA Neurol. 2016;73(2):197–202.
64. Linn J, Halpin A, Demaerel P, Ruhland J, Giese AD, Dichgans M, et al. Prevalence of superficial siderosis in patients with cerebral amyloid angiopathy. Neurology. 2010;74(17):1346–50.

Autonomic Dysfunction in Acute Stroke

27

Mechanisms and Possible Treatments

Giuseppe Micieli and Isabella Canavero

Contents

Abstract

Autonomic dysfunction is deeply associated with stroke, due to anatomy and pathophysiology of the cerebrovascular system and the related autonomic structures. Autonomic dysfunction plays an essential role in determining clinical course of acute stroke. In fact, diagnosis, prognosis, and treatment of acute cerebrovascular disorders frequently rely on the prompt recognition and the adequate management of the associated autonomic dysfunction. In acute stroke patients, the

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*,
https://doi.org/10.1007/978-3-030-28008-6_33

autonomic nervous system involvement determines the occurrence of specific signs and symptoms and of particular medical complications as well as impacts on clinical response to treatments and functional outcomes. Thus, it is essential to enhance awareness about the autonomic impairment in cerebrovascular diseases and consequently expertise for its management. Unfortunately, many "gray areas" still affect current knowledge about autonomic dysfunction management in acute ischemic stroke. Further studies are needed to evaluate pharmacological and non-pharmacological approaches to ensure better clinical outcomes.

Keywords

Acute stroke · Autonomic nervous system · Sympathetic activation · Parasympathetic dysfunction · Medical complications

Introduction

It is known that autonomic dysfunction occurs to various extents in association with cerebrovascular diseases, essentially due to anatomy and pathophysiology of the cerebrovascular system and the related autonomic, sympathetic, and parasympathetic structures. Autonomic dysfunction can affect cardiac, vascular, respiratory, sudomotor, or sexual systems [1] and can be detected both clinically and electrophysiologically [2].

The deep connection between stroke and autonomic nervous system is complex, multifaceted, and time-dependent and can be explored through different perspectives. As a matter of fact, diagnosis, prognosis, and treatment of acute cerebrovascular diseases rely on the prompt recognition and management of the associated autonomic dysfunction [3–8].

More precisely, in acute stroke patients, autonomic nervous system involvement [9–11]:

- Causes the onset of peculiar medical complications, such as blood pressure imbalance and arrhythmias
- Impacts on clinical response to treatments and functional outcomes
- In some cases is responsible for the occurrence of specific, pinpointing signs and symptoms

The underlying mechanisms are sometimes hardly identifiable, accounting for the high heterogeneity of stroke etiology and clinical course.

Besides the acute phase setting, autonomic dysfunction is also probably involved in producing "chronic" cardiocerebrovascular risk factors, such as hypertension and atrial fibrillation [9–11].

The aim of this chapter is to cover clinical features and pathophysiological mechanisms of the autonomic impairment in cerebrovascular diseases, especially in acute stroke, in order to provide awareness about its occurrence as well as practical tools to set adequate management.

Focused Overview of Anatomical Structures

As above mentioned, the link between autonomic dysfunction and cerebrovascular disorders is often a consequence of their tight anatomical or functional relationship.

In fact, several central nervous system (CNS) structures are involved in controlling the autonomic nervous system (ANS), and they can be summarized in different levels as follows [12]:

- The **spinal level** mediates segmental sympathetic or sacral parasympathetic reflexes.
- The **bulbopontine level** controls respiration and circulation.
- The **pontomesencephalic level** controls pain modulation and integration of behavioral responses to stress.
- The **forebrain level** includes the hypothalamus and the anterior limbic circuit and is involved in autonomic and endocrine responses for maintenance of general homeostasis and adaptation. The insular cortex, as part of the anterior limbic circuit, integrates visceral, pain, and temperature sensation and carries a visceromotor function controlling sympathetic and

parasympathetic outputs through a relay in the lateral hypothalamus. The anterior cingulate cortex has extensive connections with the insula, prefrontal cortex, hypothalamus, amygdala, and brainstem and controls sympathetic and parasympathetic function [12–17].

Furthermore, besides the sites located within the neuraxis, several other autonomic structures are characteristically positioned close to the vascular system, being potentially affected during cerebrovascular disorders.

The autonomic output of the CNS is divided into sympathetic and parasympathetic.

The **sympathetic** output, crucial for the maintenance of arterial pressure and regional blood flow as well as for thermoregulation, originates from the preganglionic neurons located in the spinal cord. These neurons are controlled by premotor neurons in the brainstem and hypothalamus to initiate appropriate responses to internal and external stressors. For the head and neck, the sympathetic pathway consists of a first-order neuron originating in the posterior hypothalamus, a second-order neuron in the intermediolateral cell column at spinal cord level C8–T2, and a third-order neuron in the superior cervical ganglion, next to the bifurcation of the common carotid artery. Third-order neurons carry two different types of sympathetic fibers: oculosympathetic and vaso−/sudomotor fibers. Oculosympathetic fibers ascend along the walls of the internal carotid artery, forming the internal carotid plexus, then distributing to deep structures (superior tarsal muscle and pupillary dilator muscles), and communicating with the trigeminal ganglion, the abducent nerve, the sphenopalatine ganglion, and the tympanic branch of the glossopharyngeal nerve. The vaso−/sudomotor fibers separate at the level of carotid bifurcation. Fibers innervating ipsilateral blood vessels and sweat glands of the medial forehead and nose travel along the internal carotid artery, whereas fibers for the remaining facial areas run along the external carotid artery.

The **parasympathetic** output includes the vagal and sacral outputs and is responsible for mediating organ-specific reflexes.

The vagus nerve is the main parasympathetic innervation of the thoracic and abdominopelvic viscera. Most vagal fibers are afferents with cell bodies originating from the superior and inferior vagal ganglion. The efferent vagal fibers (preganglionic visceromotor fibers) originate from the dorsal motor nucleus of the vagus (DMV) and the nucleus ambiguus in the medulla oblongata. Afferent projections of the vagus nerve are host by the nucleus of the tractus solitarius (NTS), the nucleus of the spinal tract of the trigeminal nerve, the medial reticular formation of the medulla, the area postrema, the DMV, and the nucleus ambiguus. The vagal parasympathetic output to the heart originates primarily from the ventrolateral portion of the nucleus ambiguus via the cardiac ganglia. Output of the nucleus ambiguus is activated by the NTS during the baroreflex and inhibited during inspiration. The nucleus ambiguus output inhibits sinoatrial node automatism [12, 13].

The sacral parasympathetic output originates from neurons located at the S2–S4 segments of the spinal cord and plays a critical role in the control of micturition, defecation, and sexual function [15].

As for cerebrovascular disorders, a peculiar parasympathetic pathway is that of the oculomotor nerve, whose Edinger-Westphal nucleus supplies parasympathetic fibers to the eye via the ciliary ganglion, thus controlling the sphincter pupillae muscle (affecting pupil constriction) and the ciliary muscle (affecting accommodation). On emerging from the brainstem, the oculomotor nerve passes between the superior cerebellar and posterior cerebral arteries, running in close proximity to the posterior communicating artery; it traverses the cavernous sinus, above the other orbital nerves receiving in its course fibers from the cavernous plexus of the sympathetic nervous system and a communicating branch from the ophthalmic division of the trigeminal nerve. Since the parasympathetic fibers run on the outside of the nerve, any potentially compressive damage would affect the parasympathetic fibers before any disruption of the motor fibers. Thus, the proximity of the nerve to the abovementioned

intracranial vessels could determine pupillary abnormalities in case of aneurysms [18].

How to Test Autonomic Dysfunction in Acute Stroke?

Many tests have been developed and validated for the clinical assessment of autonomic functions. Among them, the following have been widely applied in the setting of acute cerebrovascular conditions.

Heart Rate Variability (HRV)

HRV is defined by the variation in heartbeat intervals or correspondingly in the instantaneous heart rate, which is due to an autonomic neural regulation of the cardiocirculatory system. It reflects the balance between the sympathetic and parasympathetic nervous systems. Several methods used to analyze HRV are based on time-domain analysis, frequency-domain analysis, and nonlinear methods of analysis [12]. Indices of time-domain analysis derive from either direct RR interval measurements or the differences between successive RR intervals. They can be calculated over a full 24-h ECG recording or over shorter, e.g., 5-min, recordings in order to evaluate the influence of various factors on HRV [19]. HRV has been reported as altered after acute stroke in patients with middle cerebral artery infarction, possibly due to the involvement of insular control on autonomic function [20]. It has also been related to stroke prognosis and used to evaluate the interaction among the CNS, the regulation of the immune response, and cardiac autonomic control in ischemic stroke patients [12].

Baroreflex Sensitivity Variability

The baroreceptor reflex is the major neural mechanism for blood pressure control. Beat-to-beat variation in systemic blood pressure is the activator of baroreceptors located in the carotid arteries, cardiac chambers (right atrium), and the aortic arch. Afferents from these baroreceptors carry information to the nucleus tractus solitarius and the ventrolateral medulla, which is further processed in the insula, medial prefrontal cortex, cingulate cortex, amygdala, hypothalamus, thalamus, and cerebellum. Baroreflex sensitivity is measured in milliseconds of RR interval duration to each mmHg of arterial blood pressure, with a normal value of approximately 15 ms/mmHg [12]. It has been widely reported that baroreflex sensitivity is dysregulated during acute stroke, especially with insular cortex involvement [21]. Alteration of baroreflex sensitivity has also been associated with poor stroke outcome and alteration of cerebral perfusion [12].

Blood pressure variability can easily be assessed by means of a 24-h ambulatory blood pressure monitoring. Blood pressure is also continuously monitored, as well as heart rate and rhythm, during specific conditions to assess autonomic cardiovascular reflexes: Valsalva maneuver, deep breathing, isometric handgrip test, cold pressure test, mental arithmetic, active standing (or orthostatic test), and head-up tilt test [19]. However, since patients have to be able to comply with precision, acute stroke does not often represent a reliable setting for these diagnostic procedures.

What Kind of Poststroke Medical Complications Are Due to Autonomic Dysfunction? When and Why Do They Occur?

In this section, we will encompass the most relevant clinical events related to autonomic dysfunction, typically affecting the acute phase of stroke (Box 1).

Cardiovascular Dysregulation

Pathological activation of the sympathetic nervous system has been documented in ischemic infarction and hemorrhagic brain lesions since the 1980s [22]. This activation has been found to be associated with an increased incidence of severe cardiac arrhythmias [23], increased catecholamine concentration, takotsubo syndrome,

complications of myocardial damage, heart failure, pathological Q waves and QT prolongation, sudden death, paroxysmal arterial hypertension, neurogenic pulmonary edema, and other autonomic dysfunctions [22].

Several studies have demonstrated that cardiac dysfunction may occur after vascular brain injury without any evidence of primary heart disease [12]. A crucial role in autonomic cardiovascular disturbances in acute stroke is played by impaired baroreflex (or baroreceptor) sensitivity (BRS), which independently predicts mortality and incidence of adverse cardiovascular events. Complications such as hypertensive fits or high blood pressure variability occur in the acute phase of both ischemic and hemorrhagic stroke, in association with a constant depression of BRS [21, 24]. Baroreflex dysfunction in acute stroke is thought to be a consequence of a central autonomic network derangement. In fact, baroreceptors are connected to the nucleus tractus solitarius and the ventrolateral medulla and therefore linked to the insula, medial prefrontal cortex, cingulate cortex, amygdala, hypothalamus, thalamus, and cerebellum. Impaired BRS has been documented in stroke patients with left and/or right insular involvement [25], and concurrent involvement of both insulae has been found to participate in baroreflex regulation [26]. The insula is one of the most important cortical areas involved in autonomic control, and lesions (particularly of the right hemisphere) leading to disinhibition of the insular cortex are associated with increased sympathetic tone [27], increased catecholamine concentration with impaired BRS, and myocardial changes (myocytolysis). The functional lateralization of the insular cortex plays a key role in autonomic control. According to recent evidences from literature, the right and the left insula hosts the center for sympathetic and parasympathetic autonomic control, respectively. Oppenheimer et al. identified cortical sites involved exclusively in cardiac control. In the rat, stimulation of the left rostral posterior insula caused an increase in heart rate, while stimulation of left caudal posterior insula resulted in bradycardia; stimulation of the left insular cortex during the T wave of the cardiac cycle on electrocardiography resulted in arrhythmias, QT prolongation, ST-segment depression, and death in asystole. However, studying the functional lateralization of the insula is complicated by some facts, first and foremost since hemorrhagic and ischemic lesions are rarely limited to the insular region. Moreover, right-sided insular damage causes marked bradycardia and recurrent asystole as an effect of decreased sympathetic tone and consequent parasympathetic overactivity. Isolated lesions of the left insula have been shown to increase sympathetic tone and were found to be associated with a decrease in heart rate variability (HRV), while right insular lesions might be associated with hypertension and tachycardia. Inter-individual differences in insular lateralization mechanisms have been proposed to explain such findings: left-handed or ambidextrous stroke subjects with symptomatic carotid disease had a lower risk of sudden death than right-handed patients. Functional asymmetry is more frequently reported in men; however, a more diffuse pattern of physiological activation in both hemispheres is observed in women, which show more left-hemisphere than right-hemisphere intrahemispheric correlation, according with a left-hemispheric dominance. Furthermore, male rats are more susceptible than females to epinephrine-induced arrhythmias, but this female advantage is reduced after ovariectomy, and female left-hemisphere dominance is associated with a parasympathetic predominance (therefore with a greater frequency of paroxysmal supraventricular tachycardia). Although the main role is played by the insular cortex, other cerebral centers (e.g., cingulate gyrus, orbitofrontal area, and amygdala) are also involved in cardiovascular autonomic regulation. The link between cortical activation and neurogenic heart and BP alterations could be mediated by increases in neuropeptide Y in the basolateral nucleus of the amygdala and in Leucine enkephalin, dynorphin, neurotensin, and tyrosine hydroxylase in the central nucleus (important for catecholamine synthesis) [28].

Abnormal Heart Rhythm

Hemispheric stroke has been reported to be associated with increased risk of cardiac arrhythmia and sudden death. The incidence of poststroke arrhythmias is higher in studies using 24-h Holter

monitoring compared with electrocardiogram (ECG) recordings.

Atrial Fibrillation

Previous studies suggested that exercise-induced atrial fibrillation (AF) is usually driven by sympathetic stimuli, although AF in young patients is probably mediated by the parasympathetic system. Activated β-adrenergic signal pathways increase Ca2+ entry and the spontaneous release of Ca2+ from the sarcoplasmic reticulum. However, experimental vagal stimulation or perfusion of ACh contributes to the development of AF through a heterogeneous shortening of action potential duration and of the refractory period. Briefly, the pathophysiology of AF revolves around four general types of disturbance that promote ectopic firing and reentrant mechanisms, namely: (1) ion channel dysfunction, (2) Ca(2+)-handling abnormalities, (3) structural remodeling, and (4) autonomic neural dysregulation. Aging, hypertension, valve disease, heart failure, myocardial infarction, obesity, smoking, diabetes mellitus, thyroid dysfunction, and endurance exercise training cause structural remodeling. Heart failure and prior atrial infarction also cause Ca(2+)-handling abnormalities that lead to focal ectopic firing via delayed afterdepolarizations/triggered activity. Neural dysregulation is central to atrial arrhythmogenesis associated with endurance exercise training and occlusive coronary artery disease. Monogenic causes of AF seem to promote arrhythmia via ion channel dysfunction, while the mechanisms of the more common polygenic risk factors are still poorly understood and under intense investigation [29].

Hypertension

An acute hypertensive response is frequently observed in the acute phase of stroke and thought to be a consequence of increased sympathoadrenal tone with subsequent release of renin and vasoconstriction of arterioles. It may result from direct injury to inhibitory or modulatory brain regions or be an indirect effect of reduced parasympathetic activity, which leads to impaired cardiac BRS in patients with stroke. An indirect effect of muscle paralysis or the release of neurotransmitters such as nitric oxide during ischemia may be other factors contributing to altered activity of these nuclei. An increase in systemic blood pressure has been reported to be associated with an increase in intracranial pressure and with brainstem compression. Furthermore, in acute stroke, hypertensive responses to stress and pain are exaggerated and additive, probably because of impaired parasympathetic activity and BRS. The abnormal autonomic responses underlying the abrupt increase in blood pressure accompanying the onset of stroke normalize over a few hours, presumably as a result of spontaneous or therapeutic recanalization and resolution of the ischemia and other neural compensatory mechanisms [30]. Accordingly, the primary cause of the acute hypertensive response is damage or compression of specific regions in the brain that mediate autonomic control. Another possible mechanism of acute BP raise is an attempt to compensate for the reduced blood flow in the ischemic area. In fact, higher systolic BP at admission has been reported as a protective factor for poststroke outcome. Furthermore, the etiological stroke subtype is thought to influence BP response during the acute phase: specifically, the cardioembolic subtype has been found to be related to a lower BP during the acute phase when compared to atherothrombotic and lacunar stroke [31].

Neurogenic Pulmonary Edema

Sympathetic outflow has been claimed to lie at the origin of neurogenic pulmonary edema (NPE), and some centers in the brain, including the hypothalamus, medulla, areas A1 and A5, NTS, and area postrema, have been identified as "NPE trigger zones." These areas are also related to respiratory regulation and receive input from the carotid sinus; in animal models bilateral stimulation of the NTS causes severe hypertension and NPE, while unilateral stimulation of the area postrema induces severe hemodynamic changes such as increased cardiac output, peripheral vascular resistance, and hypertension. NPE may also develop after lesions of the hypothalamus: in a case series of 22 patients with NPE, 11 had significant abnormalities in the hypothalamus. The presence of lesions of the hypothalamus is associated with a worse prognosis

[32]. Finally, both cardiac and hemodynamic factors have been considered causes of NPE: alterations in hydrostatic and Starling forces are crucial for the formation of pulmonary edema following central nervous system (CNS) injury. Moreover, since the presence of red blood cells and protein in the alveolar fluid of many NPE subjects cannot be explained by hydrostatic pressures alone, the "blasty theory" has been proposed, according to which NPE results from the concomitance of high hydrostatic pressure effects and pulmonary endothelial injury [33].

Disordered Immunomodulation

Insular lesions in acute stroke have also been suggested to play a role in the pathogenesis of stroke-induced immunodepression, a systemic anti-inflammatory response (occurring in about one-third of stroke patients) that increases susceptibility to infections. These mostly involve the respiratory and urinary systems and have a major impact on 30-day mortality.

Stroke interferes with the balanced interplay between sympathetic and parasympathetic neural connections with the immune system, including lymphoid organs and humoral components such as the hypothalamic-pituitary-adrenal (HPA) axis [34]. Poststroke decreased BRS has also recently been found to be independently associated with infections after intracranial hemorrhage. The early development of infections after acute ischemic stroke is associated with enhanced activation of the sympathetic adrenomedullary pathway, as indicated by the finding of significantly increased plasma catecholamine levels on day 1 after stroke in patients who subsequently (days 2–7) develop infections [35]. Similarly, in the PANTHERIS trial, the placebo group patients with infections had significantly higher urine norepinephrine levels on days 1 and 2 after stroke compared with those without infections. It has been hypothesized that a "CNS injury-induced immunosuppression" starts with activation of the sympathetic nervous system and the HPA axis, causing a downregulation of immune response by catecholamine and glucocorticoids [36]. Neuroendocrine and autonomic centers are synchronized through the paraventricular nucleus of the hypothalamus. These systems contribute together to induce immune system alteration after stroke [35]. The activation of the autonomic parasympathetic centers by means of increased cholinergic activity may suppress peripheral cytokine release through macrophage nicotine receptors. This effect has been demonstrated in adult male Lewis rats by electrical stimulation of the vagal nerve.

No specific brain region has been clearly associated with higher infection frequency after stroke; however, since the activation of the sympathetic nervous system and the HPA axis is triggered by cytokine released from the ischemic tissue, it can be hypothesized that lesion size may be more important in the development of an immunosuppressive status after stroke than the location of the lesion. However, recent data support the concept that neither stroke severity nor stroke volume are independently associated with poststroke infections and that sympathetic activation and an ischemic lesion in the anterior MCA cortex might be major determinants of stroke-associated infection [34–36].

Bladder Dysfunction

Almost one third of subjects hospitalized for acute stroke show urinary incontinence, and a quarter of these subjects are still incontinent at 1 year from the acute episode. Stroke is associated with different kinds of urinary disturbances: detrusor hyperreflexia (urge incontinence), detrusor hyporeflexia (overflow incontinence), impaired awareness of urinary incontinence (dribbling or leakage of urine), functional incontinence, stress incontinence, and incontinence related to exogenous factors (drugs, infections, delirium).

Poststroke incontinence is probably caused by different factors. Micturition is controlled through a complex neural mechanism located in the brain, spinal cord, and peripheral ganglia that, acting on the smooth and striatal muscle activity of the bladder, bladder neck, urethra, and urethral sphincter, allows bladder filling and voiding to occur through a coordinated series of events

[37]. During bladder filling, low-intensity afferent signals travel along the pelvic nerves to the spinal cord inhibiting the parasympathetic innervation of the detrusor muscle. This process stimulates sympathetic outflow in the hypogastric nerve, resulting in contraction of the bladder outlet, and pudendal outflow in Onuf's nucleus, resulting in contraction of the external urethral sphincter (guarding reflex). When bladder distension reaches a critical level, afferent signals in the spinobulbospinal pathway are maximally intensified. Afferent impulses from the spinal cord are relayed via the periaqueductal gray (PAG) to the pontine micturition center (PMC). Activation of the PMC inhibits the sympathetic and pudendal outflow, leading to urethral relaxation, and stimulates parasympathetic outflow to the bladder, resulting in detrusor contraction. Higher centers (prefrontal cortex, insula, anterior cingulate cortex) control the voiding pattern (voluntary). Alteration of the pathways controlling bladder contraction will lead to detrusor overactivity and therefore the appearance of urge incontinence (the main form of poststroke urinary incontinence) [38].

Gastrointestinal Disorders

The CNS is involved in the control of visceral functions, and CNS damage can lead to gastrointestinal impairment. Lesions affecting the pontine defecatory center may disrupt the sequence of sympathetic and parasympathetic components of defecation and impair the coordination of the peristaltic wave and the relaxation of the pelvic floor and external sphincter [39]. The most frequent gastrointestinal manifestations of stroke are constipation (reported in about a quarter of acute stroke patients), masticatory difficulty and dysphagia, incomplete bowel evacuation, fecal incontinence, and sialorrhea [12, 40].

Thermoregulation Disorders

Several studies reported sweating dysfunction after acute hemispheric stroke, more specifically contralateral hyperhidrosis and asymmetric skin temperature sensation, whose severity correlates with the severity of motor deficits. Conflicting results of reduced and increased skin sensation in paretic limbs have been reported. Paretic limbs have also been found as colder than the contralaterals, possibly due to decreased cortical and subcortical inhibitory effect on vasomotor neurons, which increases the vasoconstricting tone and reduces the cutaneous blood flow and skin temperature [12].

Sympathetic Skin Response Abnormalities

Sympathetic skin response (SSR), which represents a potential generated in skin sweat glands, originates by activation of the reflex arc with different types of stimuli. A significant decrease in latencies and amplitude of SSR in hemispheric infarction compared with the control subjects was observed [41, 42]. The observed abnormalities of SSR after hemispheric stroke may be related to damage in the ascending and descending corticoreticular pathways or the cerebral cortex [12].

How Signs and Symptoms of Autonomic Dysfunction Can Suggest the Occurrence of Specific Cerebrovascular Disorders?

The close anatomical relationship between cerebrovascular and autonomic nervous structures is responsible for the occurrence of peculiar clinical syndromes, whose prompt recognition is crucial for making the correct diagnosis and consequently setting the appropriate medical management. In fact, in some cases, signs of autonomic dysfunction can be the only clinical expression of potentially life-threatening cerebrovascular diseases, such as arterial dissections that can disrupt sympathetic fibers located within the vessel walls.

Horner's syndrome is a combination of dysautonomic signs that arises when the oculosympathetic trunk of the same side is damaged. In its complete form, it is characterized by miosis (due to the inactivation of the pupillary dilator muscle), partial eyelid ptosis and apparent

enophthalmos (due to inactivation of the superior tarsal muscle), anhidrosis (due to inactivation of sudomotor fibers). Sometimes there is flushing on the affected side of the face due to vasodilation of skin vessels. Cavernous sinus thrombosis and carotid artery dissection can produce postganglionic interruption of the sympathetic outflow, thus causing Horner's syndrome without anhidrosis. The clinical features (way of onset, associated symptoms such as headache, cervical pain, cranial nerve palsy) can help the diagnostic work-up [43].

Harlequin sign is featured by an asymmetrical facial flushing and sweating. It is determined by both pre- and postganglionic injury of vaso-/sudomotor fibers, resulting in ipsilateral paleness and anhidrosis of half of the face, and it has been reported in association with internal carotid dissections, although more rarely than Horner's syndrome [44].

The occurrence of **mydriasis**, especially if painful and/or associated with ipsilateral signs of oculomotor nerve palsy, should raise awareness about the possibility of intracranial vascular pathologies affecting the vessels that are located next to the nerve (see above). Berry aneurysms at the junction between the posterior communicating artery and the internal carotid artery are known to produce many cases of oculomotor nerve palsy [18].

Does Acute Stroke Care Setting Allow Monitoring of Autonomic Functions?

Irrespective of age, gender, stroke subtype, or stroke severity, admission to a stroke unit significantly reduces death, poststroke disability, as well as the need for institutional care after stroke. Its technical equipment allows assessment of neurological status and continuous monitoring of vital parameters and ensures early mobilization and rehabilitation after stroke. In this setting of care, the continuous monitoring of physiological parameters (EKG, blood pressure, respiratory rate, oxygen saturation) for the first few days after symptoms onset improves outcomes and prevents complications [45; Table 1]. Attention to the changes in physiological variables is a key feature of a stroke unit, and continuous monitoring can aid in the detection of critical changes without complications related to immobility and help trigger treatments through the relief of abnormal physiological variables [46].

Stroke unit-monitored parameters are focused on the detection of acute care early warning systems and include blood pressure, heart rate, respiratory rate, oxygen saturation, temperature, glycemia, level of consciousness, and neurological deficit assessment. In acute ischemic stroke, thresholds for the triggering of a clinical response may change depending on interval from symptoms onset and on time taken to reach the threshold. In addition, thresholds and the subsequent clinical response are still not well defined for all the parameters, and little is known about how to identify preclinical change markers of a risk of higher occurrence of medical complications. The duration and settings of monitoring in ischemic stroke and its etiopathogenetic subtypes are still not well defined. Almost all available guidelines suggest the monitoring of stroke patients for at least 24 h from admission. The monitoring procedures can be prolonged if required, depending on the patients' comorbidities and medical or neurological complications. The relevance of a well-trained treating team in diagnosis and treatment of cardiac arrhythmias is crucial [47]. Since stroke unit monitoring is not yet geared for the detection of autonomic derangement as a marker of a higher risk of neurological deterioration and medical complications, stroke physicians are rarely aware of the importance of autonomic involvement in the outcome of ischemic stroke patients. The impossibility of carrying out validated tests and the diagnostic limits of neuroendocrine and neurophysiologic assessment prevent an adequate monitoring of autonomic function in an acute setting. The analysis of HRV and BRS could be easily performed in an acute stroke setting, but the lack of a validated method, cutoff values, and knowledge about the influence of possible confounders (medications, hospital stress, previous medical conditions, lifestyle factors) hinders the evaluation of autonomic function in acute ischemic stroke difficult and its transferability to clinical care [48]. Sykora et al. suggested that baroreflex impairment in acute stroke is independent of carotid atherosclerosis, antihypertensive

Table 1 Methods to evaluate autonomic dysfunction in stroke patients

Methods	Strengths and limitations
24 h urinary norepinephrine and metabolites	Index of norepinephrine turnover Easy to perform Static assessment of the sympathetic activity Inadequate for acute effects of adrenergic stimuli
Plasma norepinephrine	Crude estimation of overall sympathetic activity Easy to perform Low sensitivity and reproducibility
Microneurography and organ-specific norepinephrine spillover	Appropriate measure of sympathetic activity Invasive Technical difficulty Not useful in clinical practice
Heart rate variability (HRV) and baroreflex sensitivity (BRS)	Assessment of the sympathovagal balance Noninvasive Easy to perform Relatively good reproducibility Not usually available Not validated methods Lack of cutoffs Influenced by confounders
Shock index	Risk stratification of very early death and/or inhospital complications Easily obtainable Not validated
NIHSS score monitoring	Predictor of autonomic dysregulation risk Readily available Lack of cutoff
Bladder post-void residual monitoring	Predictor of poststroke incontinence Readily available
Dysphagia screening	Predictor of pneumonia, dehydration, malnutrition, and death Readily available Lack of consensus on the best screening instrument

therapy, and age and that confounders like age and concomitant medication are inevitable and have to be included in the analysis [23]. Chen et al. proposed to quantify short-term HRV spectral analysis to assess autonomic nervous system function in each patient admitted to a stroke unit in order to identify stroke patients who need more intensive blood pressure monitoring soon after the acute stage [49]. Tang et al. suggested to evaluate the complexity of HRV by applying the multiscale entropy analysis to a 1 h ECG data in order to identify patients with atrial fibrillation and to predict outcomes in patients without atrial fibrillation [50]. All these suggestions require confirmatory studies, and their transferability to clinical practice seems far away. The shock index, a very simple index, easy to assess in clinical setting, is a promising tool for the stratification of patients' risk of very early mortality and of inhospital complications, but further studies should be done for its definite validation [51]. Regular monitoring of the neurological state with the NIHSS together with careful evaluation of vital parameter modifications can help to quantify the risk of autonomic dysfunctions, to stratify the allocation of monitoring capabilities, and to promptly and adequately treat neurological, cardiovascular, and general complications [52]. Regular monitoring of bladder dysfunction with serial evaluation of post-void residual can reduce the incidence of poststroke incontinence, and a regular assessment of the presence of dysphagia can prevent malnutrition, aspiration, and pneumonia [53, 54].

How Is Stroke Therapeutic Approach Influenced by Autonomic Dysfunction?

The main aim of the admission to stroke unit care is to provide non-pharmacological neuroprotection by controlling the physiological functions usually involved in cerebral metabolism (blood pressure, temperature, glycemia, and arterial oxygen saturation) that play a key role in the modulation of the ischemic process and are mainly regulated by the autonomic nervous system. The attempts to use drugs able to control and modulate baroreflex sensitivity in order to ameliorate the outcome of acute ischemic stroke patients have led to controversial and conflicting results (Table 2). Theoretically, beta-blockers can positively influence baroreflex sensitivity and stroke-induced immunodepression and are the most studied drugs. The BEST trial reported a trend toward increased death rates and disability in the beta-blockers treatment group [55]. Dziedzic et al. in their retrospective study reported a neuroprotective effect of beta-blockers in acute ischemic stroke patients documenting a decreased risk of early death [56]. The Cochrane systematic revision failed to demonstrate that beta-blocker treatment is able to reduce stroke recurrence in patients with previous stroke or TIA [57]. Maier et al. failed to detect any effect of beta-blocker therapy on infectious complications after stroke [58]. These results could be at least partially explained by the different pharmacological properties of beta-blockers. For example, the increase of systolic BP variability, a parameter associated with worse outcomes in acute ischemic stroke, is more marked with nonselective β-blockers than with β-1-selective agents; thus the use of β1-selective may be advisable when β-blockers are indicated for patients at risk of stroke [59]. Several other drugs have been proposed although only preclinical data or results based on small clinical series are available [27; Table 2].

Currently, the awareness of the presence of an autonomic dysregulation in the acute phase of stroke may change the therapeutic strategies.

Mild-to-moderate variation in blood pressure may result in a critical fall in cerebral blood flow and transform areas of oligemia in penumbra and areas of penumbra into infarction. Despite the clinical relevance of blood pressure control, few evidences about management of hypertension in acute ischemic stroke patients are currently available. Several trials have investigated the safety and efficacy of different drugs and strategies that lower BP, but their results on functional outcome

Table 2 Possible therapeutic interventions

Therapeutic options	Target	Effects
Beta-blockers	Reduction of sympathetic overactivity	No effects on stroke outcomes Pre-stroke use reduces risk of stress-induced hyperglycemia No data on the hypothesis that beta-blockers may lower the glucose level in acute stroke patients Pre-stroke use reduces risk of urinary tract infection and of pneumonia
Alpha2-adrenergic	Inhibition of the release of norepinephrine	No neuroprotective function
Nitric oxide donors	Inhibitor of central sympathetic outflow	Transdermal glyceryl trinitrate: acceptable safety, no effects on functional outcome
Cholinesterase inhibitors	Activation of the vagal pathways	No data in acute stroke patients
Ghrelin (growth hormone-releasing peptide)	Modulation of sympathovagal balance	Can improve neuronal cell survival in animal models No data after stroke in the clinic
Lipophilic statins	Reduction in oxidative stress in central brain regions involved in sympathetic and parasympathetic pathways	Improve stroke outcomes

are inconsistent. The ENOS trial documented that transdermal glyceryl trinitrate is effective in lowering BP in acute and hemorrhagic stroke patients with acceptable safety levels but without effects on functional outcome [60]. A recent systematic review showed no effect of early blood pressure lowering versus control on functional outcome with a slight increase on mortality [61]. Current guidelines state that in the absence of other clinical conditions that require urgent BP treatment, the BP goal is lower than/equal to 220/120 mm hg during the first 24 h of symptoms onset, starting the drug treatment after 24 h and gradually reducing BP values. Any previous antihypertensive treatment should be restarted after the first 24 h if the patient is neurologically stable. An exception is the presence of ongoing cardiovascular conditions such as aortic dissection or acute heart failure. In such cases BP reduction should be as gradual and as modest as the condition allows. In patients treated with EV-tPA BP, values must be less than or equal to 180/105 mmHg for the next 24 h. No data are available to guide drug selection for the lowering of blood pressure in the setting of acute ischemic stroke. Saline 0.9% or volume expanders can be used to raise blood pressure when arterial hypotension is associated with neurological deterioration. Inotropic agents are indicated in patients with hypotension due to low cardiac output [47].

Cardiac arrhythmias may be encouraged by the presence of electrolyte disorders that must be promptly corrected. Specific drug treatment should be introduced only when cardiac arrhythmias are able to reduce cardiac output; however no clear guidelines are available.

Hypoxemia is poorly tolerated in areas of focal cerebral ischemia. Patient positioning can influence oxygen saturation, cerebral perfusion pressure, mean cerebral artery, mean flow velocity, and intracranial pressure. However, it is hard to define the ideal position for stroke patients. Patients at risk for airway obstruction/aspiration or with suspected intracranial hypertension should be positioned with a head-over-bed tilt of 15°–30° that may help in reducing the central venous pressure by avoiding the obstruction of the jugular veins. Careful monitoring of SpO2 and supplemental oxygen should be provided to maintain oxygen saturation by >94% [47].

Persistent inhospital hyperglycemia during the first 24 h after stroke is associated with worse outcomes, and it is reasonable to treat hyperglycemia to achieve blood glucose levels in a range of 140 to 180 mg/dL and to closely monitor glycemia to prevent hypoglycemia [47].

The possible presence of stroke-induced immunodepression requires careful monitoring of body temperature and a prompt recognition and treatment of the causes of hyperthermia. Body temperature above 37 °C–37.5 °C must be treated. If pneumonia or urinary tract infections are suspected, antibiotic therapy should be started [47]. The high incidence of poststroke infection and the presence of a brain-induced immunodepression have prompted researchers to investigate preventive antibiotic use in experimental and clinical settings. In a recent meta-analysis, preventive antibiotic therapy appeared to reduce the risk of infection, but did not reduce dependence or mortality. However, the studies included were small and heterogeneous, and the author suggests the need for large randomized trials [62].

Early mobilization of less severely affected patients is safe and feasible and lowers the likelihood of complications such as pneumonia, DVT, PE, and pressure sores [63]. Sustaining nutrition is important because dehydration or malnutrition may slow recovery and dehydration is also a risk factor for DVT. The Feed Or Ordinary Diet (FOOD) trial showed that early NG tube feeding may substantially decrease the risk of death and that early feeding via an NG tube resulted in better functional outcomes than feeding by PEG [64].

Conclusions

Autonomic dysfunction plays an essential role in determining clinical course of acute stroke. Being aware of the various autonomic-related medical complications could enhance their prompt and adequate management, thus affecting prognosis. However, today, there are still many "gray areas" about autonomic dysfunction management in acute ischemic stroke. Further studies

are needed to evaluate pharmacological and non-pharmacological approaches to ensure better outcomes for acute stroke patients.

Box 1 Multisystemic Autonomic Involvement During Stroke

Cardiovascular complications

- Reduced heart rate variability (HRV)
- Arrhythmias
  - Atrial fibrillation
  - Sinus bradycardia
  - Sinus tachycardia
  - Pathological Q waves
  - QT prolongation
  - Prominent U waves
  - ST-segment elevation
  - ST-segment depression
  - Ventricular ectopic beats
  - Polymorphic VTs
  - Cardiac Arrest
- Myocardial damage
  - Myocardial infarction
  - Serum troponin I and natriuretic factor elevation
  - Impairment in regional myocardial perfusion
  - Heart failure
  - Takotsubo syndrome
- Neurogenic pulmonary edema
- Hypertension

Infections

- Pneumonia
- Urinary tract infections

Urinary and gastrointestinal disorders

- Detrusor hyperreflexia (urge incontinence)
- Detrusor hyporeflexia (overflow incontinence)
- Impaired awareness of urinary incontinence (dribbling or leakage of urine)
- Functional incontinence
- Stress incontinence
- Incontinence related to exogenous factors (drugs, infections, delirium)
- Constipation
- Masticatory difficulty and dysphagia
- Incomplete bowel evacuation
- Fecal incontinence
- Sialorrhea

Thermoregulation disorders

Sympathetic skin response abnormalities

References

1. Benarroch EE. The central autonomic network: functional organization, dysfunction, and perspective. Mayo Clin Proc. 1993;68:988–1001.
2. Colivicchi F, Bassi A, Santini M, Caltagirone C. Cardiac autonomic derangement and arrhythmias in right-sided stroke with insular involvement. Stroke. 2004;35:2094–8.
3. Orlandi G, Fanucchi S, Strata G, Pataleo L, Landucci Pellegrini L, Prontera C, Martini A, Murri L. Transient autonomic nervous system dysfunction during hyperacute stroke. Acta Neurol Scand. 2000;102:317–21.
4. Xiong L, Leung H, Chen XY, Han JH, Leung T, Soo Y, Wong E, Chan A, Lau A, Wong KS. Preliminary findings of the effects of autonomic dysfunction on functional outcome after acute ischemic stroke. Clin Neurol Neurosurg. 2012;114:316–20.
5. Ko SH, Song KH, Park SA, Kim SR, Cha BY, Son HY, Moon KW, Yoo KD, Park YM, Cho JH, Yoon KH, Ahn YB. Cardiovascular autonomic dysfunction predicts acute ischaemic stroke in patients with type 2 diabetes mellitus: a 7-year follow-up study. Diabet Med. 2008;25:1171–7.
6. Micieli G, Cavallini A. The autonomic nervous system and ischemic stroke: a reciprocal interdependence. Clin Auton Res. 2008;18:308–17.
7. Bassi A, Colivicchi F, Santini M, Caltagirone C. Cardiac autonomic dysfunction and functional outcome after ischaemic stroke. Eur J Neurol. 2007;14:917–22.
8. Colivicchi F, Bassi A, Santini M, Caltagirone C. Prognostic implications of right-sided insular damage, cardiac autonomic derangement, and arrhythmias after acute ischemic stroke. Stroke. 2005;36:1710–5.
9. Meyer S, Strittmatter M, Fischer C, Georg T, Schmitz B. Lateralization in autonomic dysfunction in ischemic stroke involving the insular cortex. Neuroreport. 2004;15:357–61.
10. Muslumanoglu L, Akyuz G, Aki S, Karsidaq S, Us O. Evaluation of autonomic nervous system functions in post-stroke patients. Am J Phys Med Rehabil. 2002;81:721–5.
11. Korpelainen JT, Sotaniemi KA, Myllylä VV. Autonomic nervous system disorders in stroke. Clin Auton Res. 1999;9:325–33.

12. Al-Qudah ZA, Yacoub HA, Souayah N. Disorders of the autonomic nervous system after hemispheric cerebrovascular disorders: an update. J Vasc Interv Neurol. 2015;8(4):43–52.
13. Benarroch E, Biaggioni I. Central autonomic control Primer on the autonomic nervous system. San Diego: Academic Press; 2012. p. 9–12.
14. Saper CB. The central autonomic nervous system: conscious visceral perception and autonomic pattern generation. Annu Rev Neuro-Sci. 2002;25:433–69.
15. Cechetto DF. Central representation of visceral function. Fed Proc. 1987;46:17–23.
16. Verberne AJ, Owens NC. Cortical modulation of the cardiovascular system. Prog Neurobiol. 1998;54: 149–68.
17. Cheyuo C, Jacob A, Wu R, Zhou M, Coppa GF, Wang P. The parasympathetic nervous system in the quest for stroke therapeutics. J Cereb Blood Flow Metab. 2011;31:1187–95.
18. Jefferson G. Isolated oculomotor palsy caused by intracranial aneurysm. Proc R Soc Med. 1947;40(8): 419–32.
19. Zygmunt A, Stanczyk J. Methods of evaluation of autonomic nervous system function. Arch Med Sci. 2010;6 (1):11–8. https://doi.org/10.5114/aoms.2010.13500.
20. Korpelainen JT, Sotaniemi KA, Huikuri HV, Myllyä VV. Abnormal heart rate variability as a manifestation of autonomic dysfunction in hemispheric brain infarction. Stroke. 1996;27:2059–63.
21. Sykora M, Diedler J, Rupp A, Turcani P, Steiner T. Impaired baroreceptor reflex sensitivity in acute stroke is associated with insular involvement, but not with carotid atherosclerosis. Stroke. 2009;40:737–42.
22. Kolin A, Norris JW. Myocardial damage from acute cerebral lesions. Stroke. 1984;15:990–3.
23. Togha M, Sjarifpour A, Asharf H, Moghadam M, Sahraian MA. Electrocardiographic abnormalities in acute cerebrovascular events in patients with/without cardiovascular disease. Ann Indian Acad Neurol. 2013;16:66–71.
24. Sykora M, Steiner T, Rocco A, Turcani P, Hacke W, Diedler J. Baroreflex sensitivity to predict malignant middle cerebral artery infarction. Stroke. 2012;43: 714–9.
25. Sykora M, Diedler J, Turcani P, Hacke W, Steiner T. Baroreflex: a new therapeutic target in human stroke? Stroke. 2009;40:e678–82.
26. Saleh TM, Connell BJ. Role of the insular cortex in the modulation of baroreflex sensitivity. Am J Phys. 1998;274:R1417–24.
27. Abboud H, Berroir S, Labreuche J, et al. On behalf of the GENIC investigators. Insular involvement in brain infarction increases risk for cardiac arrhythmias and death. Ann Neurol. 2006;59:691–9.
28. Cechetto DF, Hachinski V. Cardiovascular consequences of experimental stroke. In: Cechetto DF, Hachinski V, editors. Bailliere's clinical neurology. Neurocardiology. London: WB Saunders; 1997. p. 297–308.
29. Xi Y, Cheng J. Dysfunction of the autonomic nervous system in atrial fibrillation. J Thorac Dis. 2015;7: 193–8.
30. Qureshi AI, Luft AR, Sharma M, Janardhan V, Lopes DK, Khan J, Guterman LR, Hopkins LN. Frequency and determinants of postprocedural hemodynamic instability after carotid angioplasty and stenting. Stroke. 1999;30:2086–93.
31. Marcheselli S, Cavallini A, Tosi P, Quaglini S, Micieli G. Impaired blood pressure increase in acute cardioembolic stroke. J Hypertens. 2006;24(9): 1849–56.
32. Imai K. Radiographical investigations of organic lesions of the hypothalamus in patients suffering from neurogenic pulmonary edema due to serious intracranial diseases: relationship between radiographical findings and outcome of patients suffering from neurogenic pulmonary edema. No Shinkei Geka. 2003;31:757–65.
33. Davison DL, Terek M, Chawla LS. Neurogenic pulmonary edema. Crit Care. 2012;16(2):212.
34. Chamorro A, Meisel A, Planas AM, Urra X, van de Beek D, Veltkamp R. The immunology of acute stroke. Nat Rev Neurol. 2012;8:401–10.
35. Chamorro A, Urra X, Planas AM. Infection after acute ischemic stroke: a manifestation of brain-induced immunodepression. Stroke. 2007;38:1097–103.
36. Dirnagl U, Kiemet J, Braun JS, Harms H, Meisel C, Ziemssen T, Prass K, Meisel A. Stroke-induced immunodepression: experimental evidence and clinical relevance. Stroke. 2007;38:770–3.
37. Fowler CJ, Griffiths D, de Groat WC. The neural control of micturition. Nat Rev Neurosci. 2008;9: 453–66.
38. Gelber DA, Good DC, Laven LJ, Verhulst SJ. Causes of urinary incontinence after acute hemispheric strokes. Stroke. 1993;24:378–82.
39. Ullman T, Reding M. Gastrointestinal dysfunction in stroke. Semin Neurol. 1996;16:269–75.
40. Otegbayo JA, Talabi OA, Akere A, Owolabi MO, Owolabi LF, Oguntoye OO. Gastrointestinal complications in stroke survivors. Trop Gastroenterol. 2006;27:127–30.
41. Zimmermann KP, Monga TN, Darouiche RO, Lawrence SA. Post- stroke autonomic nervous system function: palmar sympathetic skin responses thirty or more days after cerebrovascular accident. Arch Phys Med Rehabil. 1995;76:250–6.
42. Korpelainen JT, Tolonen U, Sotaniemi KA, Myllylä VV. Suppressed sympathetic skin response in brain infarction. Stroke. 1993;24:1389–92.
43. Martin TJ. Horner syndrome: a clinical review. ACS Chem Neurosci. 2018;9(2):177–86. https://doi.org/10.1021/acschemneuro.7b00405.
44. Drexler I, Traenka C, von Hessling A, Gensicke H. Internal carotid artery dissection and asymmetrical facial flushing: the Harlequin sign. Stroke. 2014 May;45(5):e78–80. https://doi.org/10.1161/STROKEAHA.114.004830.

45. Cavallini A, Micieli G, Marcheselli S, Quaglini S. Role of monitoring in management of acute ischemic stroke patients. Stroke. 2003;34(11):2599–603.
46. Ciccone A, Celani MG, Chiaramonte R, Rossi C, Righetti E. Continuous versus intermittent physiological monitoring for acute stroke. Cochrane Database Syst Rev. 2013;5:CD008444.
47. Jauch EC, Saver JL, Adams HP Jr, Bruno A, Connors JJ, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013;44(3):870–947.
48. De Raedt S, De Vos A, De Keyser J. Autonomic dysfunction in acute ischemic stroke: an underexplored therapeutic area? J Neurol Sci. 2015;348(1–2):24–34.
49. Chen CF, Lai CL, Lin HF, Liou LM, Lin RT. Reappraisal of heart rate variability in acute ischemic stroke. Kaohsiung J Med Sci. 2011;27(6):215–21.
50. Tang SC, Jen HI, Lin YH, Hung CS, Jou WJ, et al. Complexity of heart rate variability predicts outcome in intensive care unit admitted patients with acute stroke. J Neurol Neurosurg Psychiatry. 2015;86 (1):95–100.
51. McCall SJ, Musgrave SD, Potter JF, Hale R, Clark AB, et al. The shock index predicts acute mortality outcomes in stroke. Int J Cardiol. 2015;182C:523–7.
52. Hilz MJ, Moeller S, Akhundova A, Marthol H, Pauli E, et al. High NIHSS values predict impairment of cardiovascular autonomic control. Stroke. 2011;42 (6):1528–33.
53. Pizzi A, Falsini C, Martini M, Rossetti MA, Verdesca S, et al. Urinary incontinence after ischemic stroke: clinical and urodynamic studies. Neurourol Urodyn. 2014;33(4):420–5.
54. Martino R, Foley N, Bhogal S, Diamant N, Speechley M, et al. Dysphagia after stroke: incidence, diagnosis, and pulmonary complications. Stroke. 2005;36(12):2756–63.
55. Barer DH, Cruickshank JM, Ebrahim SB, Mitchell JR. Low dose beta blockade in acute stroke ("BEST" trial): an evaluation. Br Med J (Clin Res Ed). 1988;296 (6624):737–41.
56. Dziedzic T, Slowik A, Pera J, Szczudlik A. Beta-blockers reduce the risk of early death in ischemic stroke. J Neurol Sci. 2007;252(1):53–6.
57. De Lima LG, Saconato H, Atallah AN, da Silva EM. Beta-blockers for preventing stroke recurrence. Cochrane Database Syst Rev. 2014;10:CD007890.
58. Maier IL, Karch A, Mikolajczyk R, Bähr M, Liman J. Effect of Beta-blocker therapy on the risk of infections and death after acute stroke - a historical cohort study. PLoS One. 2015;10(2):e0116836.
59. Webb AJ, Fischer U, Rothwell PM. Effects of β-blocker selectivity on blood pressure variability and stroke: a systematic review. Neurology. 2011;77 (8):731–7.
60. Bath PM, Woodhouse L, Scutt P, Krishnan K, Wardlaw JM, et al. Efficacy of nitric oxide, with or without continuing antihypertensive treatment, for management of high blood pressure in acute stroke (ENOS): a partial-factorial randomised controlled trial. Lancet. 2015;385(9968):617–28.
61. Wang H, Tang Y, Rong X, Li H, Pan R, et al. Effects of early blood pressure lowering on early and long-term outcomes after acute stroke: an updated meta-analysis. PLoS One. 2014;9(5):e97917.
62. Westendorp WF, Vermeij JD, Vermeij F, Den Hertog HM, Dippel DW, et al. Antibiotic therapy for preventing infections in patients with acute stroke. Cochrane Database Syst Rev. 2012;1:CD008530.
63. Bernhardt J, Dewey H, Thrift A, Collier J, Donnan G. A very early rehabilitation trial for stroke (AVERT): phase II safety and feasibility. Stroke. 2008;39:390–6.
64. Dennis MS, Lewis SC, Warlow C. Effect of timing and method of enteral tube feeding for dysphagic stroke patients (FOOD): a multicentre randomised controlled trial. Lancet. 2005;365(9461):764–72.

Heart and Embolic Stroke of Undetermined Source

28

Anna Cavallini, Serena Magno, Alessandra Persico, and Andrea Morotti

Contents

Abstract

In 1947, Byer et al. first reported that cerebral vascular disease can cause myocardial damage and arrhythmia suggesting an interaction between heart and brain dynamics. Clinical and experimental evidence has accumulated since then, supporting the hypothesis that the brain can influence heart function and the heart can be responsible for secondary brain damage. It is crucial to determine whether heart dysfunction is triggered by stroke or vice-versa as this may influence the therapeutic strategy for secondary prevention. This is particularly true when dealing with those cryptogenic strokes whose clinical and neuroimaging characteristics suggest that their etiology is likely embolic, the so-called embolic stroke of undetermined source (ESUS). This chapter will explore the strengths and limitations of the ESUS definitions, its clinical and epidemiological aspects providing a description of patients who may fit this definition. The role of the possible sources of embolism in ESUS including arterial, minor-risk cardioembolic source such as structural abnormalities, subclinical atrial fibrillation, atrial high-rate episodes, and the influence of systemic inflammation are discussed as well. A brief review of the recent and ongoing clinical trial on this topic is also provided, highlighting the importance to validate standardized markers of atrial cardiopathy. These markers could improve the stratification of stroke recurrence risk and detect those patients with a cryptogenic stroke that are more likely to benefit from anticoagulant therapy.

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*, https://doi.org/10.1007/978-3-030-28008-6_35

Keywords

Embolic stroke of undetermined source · Atrial fibrillation · Neurogenic · Atrial high-rate episodes · Thromboembolism · Atrial abnormality · Atrial cardiopathy

Introduction

The brain-heart connection may be conceptualized into three major categories: the heart's effects on the brain (e.g., cardiac source of stroke), the brain's effects on the heart (e.g., post-stroke autonomic nervous system imbalance and arrhythmias onset), and neurocardiac syndrome (e.g., Friedrich disease) [1]. The brain can influence heart dynamics and the heart can be responsible for secondary brain damage. Stroke may simultaneously be both the cause and consequence of a cardiac embolic source. This aspect can make the pathogenetic characterization of ischemic stroke particularly complex and the choice of the antithrombotic therapy for ischemic stroke prevention very hard.

Ischemic stroke can result from a variety of causes and it is usually classified into: large-artery, small-vessel, cardioembolic, cryptogenic, and unusual causes (dissection, genetic, infectious, paraneoplastic, etc.). Cardioembolic strokes are more severe than other ischemic stroke subtypes and its frequency has tripled during the past few decades. Oral anticoagulant therapy can prevent about 70% of stroke in patients with atrial fibrillation (AF), the most common cardiac source of embolism [2].

However, about 25% of ischemic strokes remain cryptogenic although their clinical and neuroimaging characteristics often suggest that their etiology is likely embolic. In the last few years, stroke research has made many efforts to reduce the burden of cryptogenic stroke and to identify that subgroup of patients with an embolic cryptogenic stroke who could benefit from a secondary prevention therapy with oral anticoagulants [3]. This led to the definition of a new entity called embolic stroke of undetermined source (ESUS), to prolong the monitoring of heart rate and rhythm during follow-up to increase the chance of detecting covert AF, and to hypothesize the existence of a thrombogenic atrial substrate as a possible source of embolism even when AF is not yet apparent.

In this chapter, we will discuss the strengths and limitations of the definition of ESUS, its clinical and epidemiological aspects, and its adequacy as the rationale for randomized clinical trials on secondary prevention. In this regard, we will discuss the pathogenetic role of covert AF and the hypothesis that atrial thrombosis can occur also without AF.

Embolic Stroke of Undetermined Source (ESUS)

Cryptogenic stroke is a heterogeneous disease with several possible pathophysiological mechanisms. The TOAST classification [4], the most widely used system to define stroke etiology, includes in the category of cryptogenic stroke or stroke of unknown cause: stroke with incomplete diagnostic assessment, stroke with no cause despite extensive assessment, and stroke with more than one possible cause. This heterogeneous definition has led to different diagnostic evaluation in clinical practice and to a major knowledge gap regarding the best therapeutic approach (e.g., no clinical trial to identify the best secondary prevention is available).

In 2014, Hart RG et al. [3] hypothesized that the predominant underlying mechanism of cryptogenic stroke is embolism and introduced the clinical construct of "embolic stroke of undetermined source" to classify patients with nonlacunar stroke, absence of intracranial or extracranial atherosclerosis causing $\geq$50% luminal stenosis in arteries supplying the ischemic area, lack of known cardioembolic source of embolism (AF, sustained atrial flutter, intracardiac thrombus, prosthetic cardiac valve, atrial myxoma or other cardiac tumor, mitral stenosis, recent (<4 weeks) myocardial infarction, left ventricular ejection fraction$\leq$30%, valvular vegetations, or infective endocarditis).

The diagnostic assessment necessary for a designation of ESUS is a stroke unit routine

assessment including: brain CT or MRI, 12-lead ECG, echocardiography, cardiac monitoring for ≥24 h with automated rhythm detection, and imaging for both the extracranial and intracranial arteries supplying the area of brain ischemia. The possible sources of embolism in ESUS includes minor-risk cardioembolic source, arterial source (aortic arch atherosclerotic plaques, cerebral artery nonstenotic plaques with ulceration), cancer-associated (covert nonbacterial thrombotic endocarditis, tumor emboli from occult cancer) and paradoxical embolism (patent foramen ovale, atrial septal defect, pulmonary arteriovenous fistula). The minor-risk cardioembolic sources are the following: myxomatous mitral valve disease with prolapse, mitral annular calcification, aortic valve stenosis, calcific aortic valve, moderate left ventricular systolic or diastolic dysfunction, left ventricular noncompaction, left ventricular myocardial fibrosis, atrial structural abnormalities (atrial septal aneurysms, Chiari network), atrial dysrhythmias and stasis (atrial asystole and sick sinus syndrome, atrial heart rate episodes, atrial appendage stasis with reduced flow velocities or spontaneous echodensities), and covert paroxysmal atrial fibrillation. The aim of the authors was to clearly define a subset of patients with cryptogenic stroke and a probable embolic mechanism as the basis for randomized trials for secondary prevention.

The average frequency of ESUS, reported in a systematic review of nine studies, was of 17% (9–25%) with no geographical differences. The mean age of ESUS patients was 65 years with a prevalence of male sex. They were younger than non-ESUS patients with ischemic stroke, and they had a lower prevalence of conventional vascular risk factors. The average severity of ESUS, assessed with the NIH Stroke Scale score, was 5 [5]. The 30-days mortality rate, in the Global ESUS Registry involving 19 stroke research centers in 19 different countries, was 2% in ESUS patients, 10% in stroke patients with AF, and 5% in non-ESUS non-AF stroke patients. The risk of death was similar between ESUS and non-ESUS non-AF strokes, and it was significantly lower when compared to cardioembolic strokes [6]. The Athene Stroke Registry, with a mean follow-up >30 months, confirmed a lower risk of mortality in ESUS than in cardioembolic patients. In fact, in this Registry, the cumulative probability of survival at 30 months from the index event was 65.5% in ESUS and 38.8% in cardioembolic strokes. However, this study documented a cumulative probability of stroke recurrence in ESUS (29%) similar to cardioembolic strokes (26.8%) but significantly higher compared to all types of non-cardioembolic stroke [7]. Age but not sex seems to be a strong predictor of stroke recurrence. In a pooled dataset of 11 stroke registries, the risk of recurrent stroke/TIA and death were higher in the group 60- to 80-years-old (HR 1.90, 95% CI 1.21–2.98; HR 4.43, 95%CI 2.32–8.44) and in the group >80-years-old (HR 2.71, 95%CI 1.57–4.70; HR 8.01, 95%CI 3.98–16.10) when compared with the group <60-years-old [8].

The risk of embolic stroke in ESUS patients can be reliably stratified by the CHADS2 and CHA2DS2-VASc scores, two well-validated scores to quantify the risk of stroke in patients with AF. In the study of Ntaios G et al., conducted on 1095 ESUS patients, these two scores were independently associated with the risk of ischemic stroke/TIA recurrence and death in ESUS. With a CHA2DS2-VASc scores ≥2, the risk of stroke recurrence is increased by approximately three-fold and the risk of death of 15-fold when compared with a CHA2DS2-VASc scores of 0 [9].

About three quarters of ESUS patients had at least one minor-risk embolic source defined as mitral annular calcification or myxomatous changes, aortic valve stenosis or calcification, hypokinetic/akinetic left ventricle, aortic arch atherosclerotic plaque, and patent foramen ovale (PFO) [6].

Complex aortic arch atheroma (AAA) >4 mm has been associated with an increased risk of stroke in the elderly [10]. Ryoo et al. found that vulnerable AAA could be causative in 12.5% of ESUS patients. This subgroup of ESUS was older, more frequently with hypertension and multiple, small cortical or border zone infarct [11]. Furthermore, no stenotic carotid plaques (<50%) have been reported in 79% of ESUS patients [6]. In these patients, the presence of

ultrasound-detected stenotic carotid plaques was inversely correlated with PFO and markers of atrial cardiopathy in ESUS patients [12, 13]. In the last years, the evolution of imaging technology has made possible to identify high-risk plaque features including intraplaque hemorrhage, plaque ulceration, neovascularization, fibrous cap thickness, presence of lipid-rich necrotic core, and to evaluate the plaque inflammation activity [14–16]. These has led to a revisitation of the role of nonstenotic carotid plaque in ESUS [17]. In the study of Freilinger et al., 37.5% of cryptogenic stroke patients presented an American Heart Association lesion type VI plaque in the carotid artery ipsilateral to ischemic stroke and 0% in the contralateral one. The most common feature was intraplaque hemorrhage (75%). This finding was present in cryptogenic stroke but not in strokes due to cardioembolism or small vessel occlusion [18]. In patients with at least one complicated plaque on MRI, the 18F-FDG uptake during PET was higher in both arterial carotids suggesting a diffuse inflammatory process associated with carotid vulnerable plaques [19]. Conversely, the population-based Oxfordshire Vascular Study [20] and the Plaque At RISK multicenter study in Europe [21] did not confirm the association between nonstenosing vulnerable carotid plaque and stroke. The evidence on the causative role of vulnerable carotid plaque in ESUS is controversial and well-designed prospective controlled study to evaluate the role of different embolic source in this stroke subtype is needed.

A covert AF has been reported in 10–20% of patients with cryptogenic ischemic stroke, and so it is considered the most frequent source of embolism in ESUS. The CRYSTAL AF study [22] prospectively evaluated the incidence of AF in patients with a cryptogenic stroke within the previous 90 days. AF was defined as an irregular heart rhythm, without detectable P waves, lasting more than 30 s. Patients were randomly assigned to ICM (Reveal XT) or standard monitoring. The rate of AF detection was 8.9%, 12.4%, and 30.0% in the ICM group and 1.4%, 2.0%, and 3.0% in the standard monitoring group at 6, 12, and 36 months. The 79% of AF episodes in ICM group at 12 months follow-up was asymptomatic. Sposato LA et al. [23] reported that the proportion of patients diagnosed with covert AF was 7.7% in the emergency room, 5.1% during hospitalization, 10.7% after ambulatory Holter, and 16.9% after mobile cardiac outpatient telemetry, external loop recording, and implantable loop recording. The overall AF detection yield was 23.7%. These data suggest that in about one-fourth of patients with cryptogenic stroke the underlying stroke mechanism was a covert AF. Anyhow, the fact that AF is absent in 70% of ESUS raises questions about the role of AF as the main cause of embolism in this type of stroke.

Recently, the clinical characteristics of ESUS patients, provided by published small cohorts and pooled data derived from registries, have been confirmed by the analysis of the patients enrolled in the first published randomized trial on ESUS the "NAVIGATE ESUS" supporting the validity and generalizability of the ESUS concept. In this trial, covert AF was not systematically screened during follow-up, but it was detected in 3% of patients at a median of 5 months after randomization [24].

Another line of research followed to better support the ESUS concept is the analysis of thrombus composition [25]. The introduction of endovascular treatment of acute ischemic stroke has made available a much higher number of thrombus samples, and some studies have evaluated the differences in basic thrombus morphology between different stroke subtypes. The main components of thrombus are fibrin/platelet (F/P) conglomerates and red and white blood cells (RBCs and WBCs, respectively). In the largest study published so far, conducted on 145 consecutive stroke patients, cardioembolic thrombi were characterized by higher proportions of F/P conglomerates, less RBCs, and more WBCs than noncardioembolic stroke. Thrombus composition, procedural and clinical parameters were similar between ESUS and cardioembolic strokes but significantly different when compared with noncardioembolic strokes [26]. These data are in line with some previous results but in contrast with a smaller study by Kim et al. [27], conducted on only 37 patients, which supported the traditional

concept that clots from cardioembolism had a significantly higher proportion of RBCs and a lower proportion of fibrin compared with those from large-artery atherosclerosis. Again, the results of neuroimaging studies aiming to differentiate thrombus components in ischemic stroke subtypes are conflictual. The retrospective MRI-imaging study by Cho et al. [28] found a relationship between the "T2*-weighted gradient echo imaging susceptibility vessel sign" (GRE SVS) and cardioembolic stroke. This hypodense signal on GRE in the symptomatic occlusive vessels is related to the deoxygenated hemoglobin in red thrombi, suggesting a high content of RBCs. On the other hand, Niesten et al. [29] in their CT study found that cardioembolic thrombi had the least hyperdense vessels signs and the lowest attenuation when compared with those due to large artery atherosclerosis or arterial dissections. The hyperdense sign reflects the degree of RBCs content supporting the hypothesis that cardioembolic thrombi are rich of fibrin and contain a small amount of RBCs.

In summary, the ESUS construct includes patients with nonlacunar, cardioembolic, or large artery atherothrombotic ischemic stroke. It is characterized by younger age, mild severity of stroke, and high frequency of minor-risk embolic sources or covert AF. When compared with cardioembolic stroke patients, ESUS patients have a lower risk of death, the same risk of stroke recurrence, and probably similar characteristic in thrombus morphology. Based on ESUS construct, their source of embolism could be cardiac, arterial (vulnerable arterial plaques), or venous due to paradoxical embolism such as PFO.

From a therapeutic point of view, previous studies have suggested that embolic strokes could respond better to anticoagulant therapy than to aspirin. However, the beneficial effect of anticoagulation in reducing ischemic events may be outweighed by an excess of major bleeding complications. In the subgroup analysis of the Warfarin-Aspirin Recurrent Stroke Study (WARSS), conducted on 338 patients with cryptogenic stroke and a CT scan suggesting an embolic pattern, the rate of ischemic stroke recurrence or death at 2 years was 12% with warfarin and 18% with aspirin (HR: 0.66, 95%CI 0.4–1.2). In this study, the target international normalized ratio (INR) was 1.4–2.8, the median achieved INR was 1.9 and therefore lower than the target suggested for stroke prevention in AF patients (target INR 2.0–3.0) [30]. In the Patent Foramen Ovale in Cryptogenic Stroke Study [31], a substudy of WARSS, the rate of stroke recurrence and death was lower in warfarin group than in aspirin one (9% vs. 17%, respectively). The CLOSE study [32], one of the two recent studies that demonstrated the superiority of PFO closure combined with antiplatelet on other antithrombotic treatment in patients with cryptogenic stroke and PFO, showed that in the noninterventional arm, the 5-year cumulative probability of stroke was 1.5% in the anticoagulation group and 3.8% in the antiplatelet-only group. Unfortunately, the study was underpowered to detect a significant difference between these two groups.

The evidence in favor of anticoagulation after cerebral ischemia of arterial origin is weaker. The Stroke Prevention in Reversible Ischemia Trial (SPIRIT) [33], in which high intensity anticoagulation with warfarin (target INR: 3.0–4.5) was compared to aspirin in patients with TIA or minor stroke of arterial origin, was stopped prematurely because of an excess in major bleeding complications in the anticoagulant group. The European/Australasian Stroke Prevention in Reversible Ischaemic Trial (ESPRIT) [34] replicated the SPIRIT paradigm using a medium intensity anticoagulation (target INR: 2.0–3.0). Once again, oral anticoagulants were not superior to aspirin in preventing serious vascular events, both ischemic or hemorrhagic. The possible beneficial effects in the prevention of ischemic events were completely offset by an excess of major bleedings.

An unanswered question is whether aortic arch atheromas may benefit from anticoagulation. Some nonrandomized controlled observational case series showed a superiority of anticoagulants on aspirin in treating mobile aortic arch atheroma. In a matched-paired analysis on 519 patients with severe thoracic aortic plaque, warfarin or antiplatelet showed no significant benefit on the

incidence of stroke and other embolic events. There was a protective effect only with statin therapy [35].

The direct oral anticoagulants (Dabigatran, a direct thrombin inhibitor; Apixaban, Edoxaban, and Rivaroxaban, direct factor Xa inhibitors) have demonstrated in AF patients at least the same effectiveness of warfarin in preventing thromboembolic events with a significant reduced risk of major bleeding [36]. This has led to hypothesize that direct oral anticoagulants could be more effective than antiplatelet for the prevention of recurrent stroke in patients with ESUS.

Two trials have been implemented based on the ESUS construct: the NAVIGATE ESUS trial, which compared the efficacy and safety of rivaroxaban 15 mg o.d. with aspirin 100 mg o.d., and the RE-SPECT ESUS trial, which compared dabigatran 150 mg b.i.d. or 110 mg b.i.d. with aspirin 100 mg o.d. These trials did not selectively enroll patients based on markers of potential cardioembolic stroke but also patients with paradoxical or artery to artery embolism.

To date, the results of the NAVIGATE ESUS trial are available. Rivaroxaban was not superior to aspirin for the prevention of recurrent stroke (HR: 1.7, 95%CI 0.87–1.33) and was associated with a significantly higher risk of major bleeding (HR: 2.72, 95%CI 1.68–4.39) [37].

The failure of the NAVIGATE ESUS trial underlines the gray areas behind ESUS construct that include the heterogeneous sources of embolism (arterial, cardiac, or paradoxical) with a various composition of thrombi that may not benefit from anticoagulation. The possibility of artery-to-artery cerebral embolism could be relevant as well. Arterial emboli could resemble those found in atherothrombotic strokes and could be less responsive to anticoagulants. Probably, the degree of stenosis does not correctly identify those patients with atherosclerotic plaque at high risk of recurrent cerebral embolism, who may therefore benefit from aggressive medical therapy (e.g., dual antiaggregant therapy plus high dose of statin).

In the future, it will be necessary to refine the diagnostic work-up of ESUS cases in order to identify with greater certainty the subset of patients with higher chance of having a cardiac source of embolism and a higher risk of cardioembolic stroke recurrence that justifies and derives benefit from long-term anticoagulation.

Asymptomatic Paroxysmal Atrial Fibrillation

AF is the cause embolism in half of the patients who suffered a cardioembolic stroke. Clinically, apparent AF has been associated with a three- to fivefold higher risk of ischemic stroke. The risk of stroke is driven by the presence of other vascular risk factors and in patients with AF lacking other risk factors is barely distinguishable from that of patients without AF, and patients with paroxysmal AF are at risk even when the atrial rhythm is sinus or paced [38]. In about 5% of patients, stroke precedes AF, and AF is detected in stroke unit especially when continuous electrocardiographic monitoring is initiated soon after symptoms onset [23]. Longer periods of monitoring can substantially increase detection of AF after a stroke or TIA. AF detected after stroke (AFDAS) can be evaluated by in hospital monitoring, serial ECG, 24–48 h Holter cardiac monitoring, cardiac event recorders, wearable external loop recorders, cardiac implantable electronic device (CIED), and insertable cardiac monitors (ICMs, including implantable loop recorder). The gold standard for cardiac monitoring after ischemic stroke remains unclear. Early initiation and longer duration of monitoring are the two main determinants of AFDAS diagnosis. In a retrospective study by Sposato et al. [39], the diagnostic rate of AFDAS in patients who underwent continuous cardiac monitoring immediately after hospital admission and those who did not were 18.2% and 2.2%, respectively. Over 70% of cases were diagnosed within the first 3 days. Episodes of poststroke AF are usually asymptomatic and half of them last less than 30 s.

It is important to consider that subclinical atrial fibrillation (SCAF), detected by device-related monitoring, is different from permanent, persistent, and paroxysmal AF (clinical AF), which are

diagnosed by conventional ECG. Both SCAF and poststroke AF detected with conventional ECG would be different in terms of risk of thromboembolic events from a known AF (KAF) [40]. For example, in a recent retrospective study of the Paradise Study group, the 1-year ischemic stroke recurrence was similar between patients with AFDAS or sinus rhythm and the prevalence of heart disease was lower in AFDAS compared to KAF [41].

SCAF is defined as atrial high-rate episodes (AHRE), lasting >6 min and <24 h, without correlated symptoms in patients with CIED, with continuous intracardiac monitoring and without prior diagnosis of AF. It has been suggested to be the main underlying cause in ESUS. Only 13–16% of patients with AHRE will develop a clinical diagnosed AF after 2.5 years. Data from large prospective trials have demonstrated that AHRE increases the risk of stroke. The stroke rate reported in patients with AHRE ranged from 0.32% to 2.2% per year, significantly lower than the stroke rate detected in patients with clinically diagnosed AF [42].

The MOST trial (the Atrial Diagnostics Ancillary Study of the MOde Selection Trial) [43] reported that a pacemaker-detected AHRE (>200 bpm) lasting longer than 5 min. was associated with sixfold increased risk of AF. Patients who developed AF had 2.8-fold increase of death or stroke. The TREND study [44] evaluated the association between AT (atrial tachycardia)/AF burden and the risk of systemic thromboembolism. A daily AT/AF burden >5.5 h had a hazard ratio of risk of systemic thromboembolism of 2.2 compared to patients with zero AT/AF burden. In the ASSERT trial, only patients with AHRE>24 h had a significantly higher risk of ischemic stroke or systemic embolism as compared to patients with no AHRE (HR 3.4, 95%CI 1.51–6.95). In patients with AHRE of shorter duration (<24 h), the risk did not differ from that reported in patients without AHRE [45].

These studies highlight the challenge to identify a threshold for a significant increase of thromboembolic events and so, the ESUS patients with poststroke SCAF at highest risk of stroke recurrence.

Another issue in understanding the correct role of SCAF in ESUS pathogenesis is represented by the difficulty to detect a temporal and causal relationship between AHRE and ESUS. In a subanalysis of the TRENDS study, only 20 (50%) patients experienced an atrial tachyarrhythmias prior to the thromboembolic event. Moreover, 29 (73%) patients with thromboembolic events did not have any AT/AF within 30 days before the thromboembolic episodes [46]. A subanalysis of the ASSERT study confirmed these findings. In this study, only 4 (8%) patients had SCAF detected within 30 days before the thromboembolism [47]. These studies suggest that SCAF may be simply a risk marker or, even if it is causal, it may be indirectly related to thromboembolism. More recently, the study of Turakhia et al. showed that patients with AHRE >5.5 h had an increased risk of TE events in the first 5 days after the episode, with the risk progressively returning to baseline after 3–4 weeks [48]. These data suggest a time dependency of TE risk and again questions the causative role of arrhythmic events recorded at a long-time distance from stroke.

Taken together, findings from implantable device suggest that the presence of AF may not be a necessary component in the pathophysiology of thrombogenesis and embolization.

Furthermore, an AF detected in the first period after stroke could be both neurogenic or cardiogenic. The neurogenic AF, triggered by the derangement of the autonomic nervous system (ANS) in the acute phase of stroke, could simply represent an innocent bystander. The concept of neurogenic AF has stimulated an increasing debate.

In the acute phase of ischemic stroke, both the involvement of cerebral cortex areas, especially insula but also other cortical areas (i.e., cingulate and prefrontal) responsible of the brain control over heart rhythm, and the systemic inflammation response induced by stroke can trigger the onset of a paroxysmal AF which is the consequence and not the cause of the ESUS.

The right and the left insular cortices are connected with the hypothalamus, the limbic system, and the brainstem nuclei. These structures form the “extrinsic” or “cerebral”

ANS. The "intrinsic" ANS is constituted by ganglionated plexi distributed along the ending of pulmonary veins in the left atrium and within pericardium and it is regulated by the "extrinsic" ANS. In patients with insular or other cortical acute ischemic stroke, autonomic imbalance or abrupt loss of central modulation can induce the intrinsic system to generate arrhythmogenic stimuli triggering focal ectopic firing at pulmonary and nonpulmonary vein sites which can induce paroxysmal AF.

Systemic inflammation can also play a role in AFDAS. Immediately after the stroke onset, there is a short-lasting inflammation response with the release of cytokines, adhesion molecules, and chemokines into the blood stream. Inflammatory processes could induce focal firing (autonomic cascade) and reentry circuits (atrial myocarditis). This inflammatory response is stronger in acute cardioembolic strokes than in other acute stroke subtypes. Both autonomic and inflammatory responses tend to extinguish within the first days after ischemic stroke and so neurogenic post-stroke AF could have a lower probability of long-term recurrence [49–51].

ESUS patients undergoing prolonged ECG monitoring can be subdivided based on their heart rhythm into three categories: normal sinus rhythm, preexisting newly diagnosed AF, and newly diagnosed atrial fibrillation. The pre-existing newly diagnosed AF is most likely due to pre-stroke cardiac structural changes and could be considered "cardiogenic." The newly diagnosed AF could be the consequence of the stroke itself and therefore could be considered as "neurogenic." Actually, it is difficult to differentiate between preexisting newly diagnosed AF and newly diagnosed AF. An attempt to solve this dilemma is to compare the clinical presentation, the prevalence of cardiovascular risk factors, and the long-term risk of stroke recurrence and peripheral embolism in AF diagnosed after stroke (AFDAS) and in AF known before stroke (KAF). Newly diagnosed cardiogenic AF patients should be similar to KAF patients; however, available data on this topic are conflictual. In a recent retrospective cohort study based on data collected in the Ontario Stroke Registry, the rate of stroke recurrence at 1 year was 6.6% in AFDAS, 9.6% in KAF, and 8.0% in sinus rhythm (SR), with a higher risk of recurrence in KAF and a similar risk between AFDAS and SR. The prevalence of coronary artery disease, myocardial infarction, and heart failure were lower in AFDS than in KAF [41]. In another study of the same research group, AFDAS patients had a lower proportion of left atrial enlargement, a smaller left atrial area, and a higher frequency of insular involvement than patients with KAF [52]. On contrast, the study of Hsieh et al., based-on data derived from a national claims database in Taiwan, showed the same risk of a composite outcome of ischemic stroke, intracranial hemorrhage, or death within 1 year between KAF and AFDAS. They confirmed the higher prevalence of underlying heart disease in KAF [53]. Similarly, a French longitudinal cohort study found a higher prevalence of preexisting cardiovascular comorbidities in AFDAS patients than in no-AF and KAF patients. The main independent predictors of incident AF were older age, hypertension, heart failure, systemic embolism, coronary artery disease, abnormal renal function, anemia, lung disease, pacemaker/implantable cardioverter defibrillator implantation and valvular disease. The mean CHA2DS2-VASc score was similar among AFDAS and KAF patients [54]. The Athene Stroke Registry compared clinical severity and risk of stroke recurrence and peripheral embolism in ESUS patients with or without AF detection during follow-up. Stroke severity was similar between the two groups, but the risk of recurrent stroke and peripheral embolism was higher in the AF ESUS group [55].

The neuroimaging features of AFDAS and KAF have also been compared to explore whether the prevalence of an embolic lesion pattern was similar between the two groups and if an involvement of insular cortex was more prevalent in AFDAS than in other stroke subtypes.

Kim Y and Lee SH defined an embolic lesion pattern as: (1) cortico-subcortical territorial lesion without relevant large artery disease and (2) multiple noncontiguous lesions in bilateral hemispheres or both anterior and posterior circulation. An embolic lesion pattern was present in approximately 90% of KAF versus 58% of

AFDAS patients, suggesting that at least some of them might have had a neurogenic AF, therefore not causally related to stroke [56]. The idea of a neurogenic AF behind AFDAS was also supported by the neuroimaging study of Scheitz et al. [57]. They reported a significant association between insular cortex involvement and AFDAS. However, this study did not consider stroke size and severity, and the frequency of insular involvement was the only parameter recorded. Furthermore, Rizos et al. explored the influence of infarct volume on insular involvement in an MRI-based study. The authors confirmed that patients with AFDAS were more likely to have lesions involving the right insula compared with patients without AF, but when these findings were controlled for infarct volume, the difference was no longer significant, raising therefore doubts on the hypothesis of neurogenic AF [58].

Data on the role of AFDAS in stroke pathogenesis are conflictual. AFDAS is probably a heterogeneous group constituted by a variety of possible phenotypes with an extreme including patients with preexisting AF not diagnosed because of insufficient monitoring (cardiogenic AFDAS) and the other extreme including patients who had never had AF before stroke, with normal heart function and with a stroke involving brain structures implicated in the central autonomic regulation of heart rhythm (neurogenic AF). The whole spectrum of patients in between these two phenotypes might be considered to have mixed AFDAS.

There is a considerable debate regarding both clinical significance and therapeutic implications of AFDAS. Further insights on this topic will be provided by the Pathophysiology and Risk of Atrial Fibrillation Detected after Ischemic Stroke (PARADISE) study. This study comprises experimental, clinical, and epidemiological research aimed to define clinical features, pathophysiology, and outcomes of neurogenic AFDAS. The results will be available in 2020 [59].

In the meanwhile, a recent consensus document of the European Heart Association regarding subclinical atrial tachyarrhythmias recommends oral anticoagulation for patients with at least two additional CHA2DS2-VASc risk factors (score: $\geq$2 in males or $\geq$3 in female) and with a burden of AF >5.5 h/day [60]. Two large-scale randomized trials of anticoagulation for patients with AHRE are ongoing: ARTESIA trial (Apixaban for the Reduction of Thrombo-Embolism in Patients with Device-Detected Sub-Clinical Atrial Fibrillation) and the NOAH trial (Non-vitamin K Antagonist Oral Anticoagulants in Patients with Atrial High Rate Episodes) [61, 62].

The above data on SCAF have also induced to revisit the classic direct mechanistic explanation of left atrial thromboembolism in AF patients which implies intracavitary stasis during the irregular atrial wall contraction. This mechanism is consistent with the findings from numerous clinical trials that anticoagulation reduces the risk of ischemic stroke in AF, but not enough to explain the cause of stroke in patients with AF detected for the first time after stroke and the lack of temporal relationship between AF and stroke documented by device-related monitoring. These inconsistencies could be explained by the presence of thrombogenic atrial substrate even in the absence of AF.

Atrial Cardiopathy

It is well defined that AF is characterized by a high risk of thromboembolism, but in AF patients without other risk factors, their risk of stroke is hardly distinguishable from that of patients without AF. These risk factors, included in the CHA2DS2-VASc score, a validated score to predict the risk of stroke and systemic embolism in AF patients, are: chronic heart failure, hypertension, vascular disease, diabetes mellitus, prior stroke or TIA, gender, and age ($\geq$ 64, 65–74, and $\geq$75 years). AF male patients aged $\leq$64 years has a CHA2DS2-VASc score of 0 and have an adjusted stroke rate of 0% per year, and AF female patients with the same age have a score of 1 and an adjusted stroke rate of 1.3% per year. These data suggest that other factors beyond AF could promote atrial thrombogenesis [63].

AF is associated with tissue as well as other atrial chamber structural remodelling which represents the substrate for its maintenance.

Thrombogenic atrial abnormalities often detected in AF such as endothelial dysfunction, fibrosis, impaired myocyte function, chamber dilatation, and mechanical dysfunction in the left atrial appendage may be present independently of AF and may facilitate its onset and correlate with stroke risk [64, 65].

Atrial fibrosis is the chief structural alteration in AF. An increase in atrial fibrosis could lead to stasis and endocardium changes that promote thromboembolism. It has been linked to cardiac factors (genetic, valvular, ischemic, infiltrative, inflammatory) and extracardiac factors (hypertension, obesity, sleep apnea, autonomic). Furthermore, atrial fibrosis detected with late gadolinium enhancement MRI (LGE-MRI) has been associated to stroke, atrial mechanical dysfunction, and presence of thrombus in the left atrial appendage. Stroke patients with AF show a higher degree of fibrosis when compared to AF patients without a history of stroke [38]. ESUS patients, in a cardiac magnetic resonance imaging study, were characterized by a higher percentage of left atrial fibrosis compared with patients with other stroke causes, and in ESUS, the left atrial ejection fraction was lower although not significantly different. ESUS and cardioembolic stroke had similar values of atrial fibrosis [66]. Left atrial (LA) diameter was shown to predict the occurrence of atrial fibrillation, and it has been associated with both first and recurrent episodes of stroke even in the absence of AF [67]. Left atrial size has been associated with risk of stroke and death in the Framingham Heart Study [68]. In the Manhattan Stroke Study, a moderate to severe left atrial enlargement was an independent marker of recurrent cardioembolic or cryptogenic stroke [69]. Spontaneous atrial echocardiographic contrast and left atrial appendage (LAA) thrombus have been associated with highest level of atrial fibrosis, and LAA involvement with fibrosis was associated with reduced blood flow velocities exit from the appendage. The decrease of LAA velocity has been associated with a higher risk of stroke and thromboembolic events. An atrial fibrosis >20% improved the prediction model for the presence of appendage thrombus on transoesophageal echocardiography by 16%. The possible causative mechanism would be the flow stasis determined by an impaired LA function with a consequent increase in the risk of embolism [70]. This hypothesis has been supported by the echocardiographic study of Kim et al. [71] which demonstrated that, in acute ischemic stroke patients, LA enlargement and impaired mechanical function assessed by 2D transthoracic echocardiography with speckle tracking imaging were markers of high-risk findings for cardioembolism assessed by transoesophageal echocardiography. In this population, global LA longitudinal strain showed good diagnostic values for the presence of flow stasis, thrombus in the LA and LAA. The LA mechanical function was independently correlated with age, left ventricular function, LA volume index, and aortic stiffness. LAA has been considered the primary site for thrombus formation in AF patients. Furthermore, cauliflower LAA morphology, characterized by extensive LAA trabeculations, and larger LAA orifice has been shown to be associated with ischemic stroke [69].

Beside structural atrial changes detected by echocardiographic or MRI studies, also ECG signs related to the left atrium have been associated with the risk of stroke, particularly of nonlacunar subtypes, even in the absence of AF. Excessive supraventricular ectopic activity (ESVEA) is linked to a high risk of AF, and it has also been associated with an increased risk of stroke [72–74]. Paroxysmal supraventricular tachycardia in AF-free patients aged >65 increase the risk of stroke [75]. P-wave indexes (P-wave terminal force in lead V1 (PTFV1) P-wave duration, maximum P-wave area) have been recognized as markers of left atrial abnormality on 12-lead ECG such as atrial dilatation, atrial muscular hypertrophy, elevated atrial pressure, and delayed intra-atrial conduction. High P wave duration (PWD) values are a marker of irregular propagation of sinus impulses and prolongation of atrial conduction time, the atrial electrophysiological substrate of paroxysmal AF. An association of P-wave indexes with stroke outcome has been documented even in the absence of AF. In the Multi-Ethnic Study of Atherosclerosis during a mean follow-up of 8.5 years, the PTFV1 was

more strongly associated with incident stroke than incident AF [76]. The ARIC study (Atherosclerosis Risk in Communities) documented an independent association between abnormal P-wave axis and ischemic stroke. The risk of ischemic stroke was increased of 1.50-fold even when AF was included in the multivariate model. The risk was higher for cardioembolic stroke than for thrombotic stroke [77]. A recent systematic review of He et al. [78] has evaluated the value of P-wave indices in predicting ischemic stroke risk. PTFV1 was found to be an independent predictor of stroke both as continuous or categorical variable. P-wave duration predicted stroke occurrence only when analyzed as a categorical variable. Maximum P-wave area also predicted the risk of stroke. An abnormally increased PTFV1 has been detected in about one-third of ESUS patients. Furthermore, in a large prospective cohort study, PTFV1 resulted significantly associated with prevalent MRI-defined infarcts and with baseline and worsening white matter disease grade supporting a causal link between atrial cardiopathy and vascular brain injury [79]. However, we should consider that these ECG measures have a low sensitivity and specificity, because ECG signals can be affected by body habitus, lead position, lung pathology (e.g., emphysema), and obesity. Moreover, the analysis of PTFV1 is not standardized and validated across different cohorts.

AF has also been linked to inflammation and cardiac serum markers. Systemic inflammation markers, such as high-sensitive C-reactive protein (hsCRP), have been associated to the development and persistence of atrial fibrillation, by contributing to atrial remodelling. Acampa et al., in their recent study, have detected in ESUS patients a positive correlation between increased hsCPR levels and high PWD [80]. Subclinical inflammation may play a role in the biology of atrial cardiopathy and the increase risk of AF among ESUS subjects [81].

Although serum biomarkers are not specific to atrial disease, various serum biomarkers have been reported to be elevated in AF or predictive of AF. Elevated levels of B-type natriuretic peptide (BNP) and of the N-terminal fragment of BNP have been associated with the risk of development AF even in the absence of left ventricular dysfunction. High plasma levels of NT-proBNP have been associated with a substantially increased risk of cardioembolic stroke, but not with other subtypes of ischemic stroke. The mechanism behind this association is not easily understandable considering that several volume and pressure loading conditions can affect natriuretic peptides synthesis and secretion and that BNP is also secreted from brain tissue and its elevation in the acute phase of stroke may be due to stroke itself. Similarly, elevated levels of cardiac troponin, a marker of myocardial cell death which may presage a reparative fibrotic process, have been associated with a higher risk of cardioembolic stroke in patients with AF [82]. Yaghy et al. have recently confirmed an association between positive cardiac troponin I level measured within 24 h from hospital arrivals and after ischemic stroke and ESUS or cardioembolic stroke subtypes [83]. If confirmed using high-sensitivity troponin assay, these findings would support the concept of possible cardiac embolic source other than AF in ESUS patients and could be used to test optimal secondary prevention strategies in these patients.

Recently, in a large prospective study, the Cardiovascular Health Study, with a median follow-up of 12.9 years, among 3723 participants, 585 subjects experienced an incident ischemic stroke. A significant association of atrial cardiopathy markers and incident ischemic stroke was confirmed for PTFV1, NT-proBNP, and incident AF but not for left atrial dimension [84].

Acampa et al. have reviewed the evidence in favor of a link between ANS dysfunction and atrial cardiopathy as a possible pathogenic factor in cryptogenic stroke. The impact of ANS on PWD has been suggested in chronic spinal cord injury and in neurally mediated syncope. The prolongation of the P wave duration in non-elite athletes has been related to an altered atrial substrate, determined by the exercise-induced atrial fibrosis, probably mediated by increased vagal tone. Finally, ANS imbalance is a well-known risk factor for alterations in atrial electrophysiology. In particular, adrenergic activation can lead to focal ectopic firing, modulating cardiac ionic

channels activity, and promoting atrial structural remodelling. Changes of ANS activity may trigger different signalling pathways that are able to determine an atrial derangement, promoting structural alteration. A sympatho-vagal imbalance may induce the expression of pro-inflammatory cytokine (TNFα, IL-1β, and IL-6) with consequent structural atrial alterations mediated by the increased release of matrix metalloproteinases and a fibroblast activation. The epicardial adipose tissue (EAT), surrounding the left atrium, has an important endocrine and inflammatory function, and it is a source of several pro-inflammatory mediators. The ANS is embedded in the epicardial fat pads forming ganglionated plexi, the EAT contains both adrenergic and cholinergic nerves which interact with the extrinsic sympathetic and parasympathetic nervous system. A sympatho-vagal imbalance has been associated to EAT activity and thickness, and an excess of EAT has been implicated in atrial remodelling and cardiac function. ANS has a well-defined role in regulating oxidative stress, and oxidative stress is a pathogenetic mechanism of atrial fibrosis and structural cardiac remodelling. Lastly, the ANS may modulate the renin-angiotensin-aldosterone system, and this system exerts a well-known role in atrial fibrosis [85].

The above findings strongly support the hypothesis of Kamal et al. [64] that systemic and atrial substrate as well as rhythm can be involved in thrombogenesis in ESUS. Age and systemic vascular risk factors can induce the development of an abnormal atrial substrate that can result in AF and thromboembolism. Atrial cardiopathy can play a role in thrombogenesis even in the absence of AF. On the other hand, when AF appears, the dysrhythmias induces contractile dysfunction and stasis which further increases the risk of thromboembolism, but over time, AF causes an atrial remodelling and consequently a worsening of atrial cardiopathy and an increasing of the risk of thromboembolism. AF can increase the risk of thromboembolism but is not necessary for its occurrence being only a secondary contributor to abnormal tissue substrate. In this model, the timing and burden of AF does not need to be coupled with the timing and burden of stroke.

Based on these evidence, two trials are actually ongoing to explore whether ESUS patients with at least one marker of atrial cardiopathy would benefit from anticoagulation compared antiplatelet therapy for prevention of stroke recurrence. In case of positive findings, benefit observed with anticoagulants in AF may be extended to at least one-fourth of patients with ESUS.

The ATTICUS trial (Apixaban for the Treatment of Embolic Stroke of Undetermined Source) [86] compares apixaban 5 mg b.i.d. versus aspirin 100 mg o.d. It is focused on a selected group of ESUS patients with at least one minor cardiac sources of embolism, such as: LA size >45 mm (parasternal axis), spontaneous echo contrast in LAA, LAA flow velocity ≤0.2 m/s, atrial high rate episodes, CHA2DS2-Vasc score ≥4, persistent foramen ovale, and with implanted insertable cardiac monitor (ICM) to detect covert AF. The main end-point is the prevention of new ischemic lesions, both symptomatic or silent. The ARCADIA trial (Atrial Cardiopathy and Antithrombotic Drugs in prevention After Cryptogenic Stroke) [87] compares Apixaban 5 mg b.i.d versus Aspirin 100 mg o.d. in ESUS patients with evidence of atrial cardiopathy. The primary outcome of the study is the incidence of recurrent stroke from any cause (ischemic, hemorrhagic of unknown).

Conclusion

The mechanistic concept of thromboembolism in AF is insufficient to completely explain the pathogenesis of embolic stroke in AF and ESUS patients. Atrial cardiopathy may be the key to explain cardiac embolism in ESUS and the lack of a temporal relationship between AF and embolism. Standardization of atrial cardiopathy markers is needed in order to translate research findings into clinical practice.

These markers should be included in stroke risk scores for cardiac embolism to improve the stratification of stroke recurrence risk and detect those patients with an embolic stroke that could benefit of oral anticoagulant therapy in the absence of AF or in presence of AFDAS.

References

1. Samuels MA. The brain-heart connection. Circulation. 2007;116:77–84.
2. Kamel H, Healey JS. Cardioembolic stroke. Circ Res. 2017;120:514–26.
3. Hart RG, Diener HC, Coutts SB, Easton JD, Granger CB, O'Donnell MJ, et al. Embolic strokes of undetermined source: the case for a new clinical construct. Lancet Neurol. 2014;13:429–38.
4. Adams HP, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, Marsh EE III. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of ORG 10172 in acute stroke treatment. Stroke. 1993;24:35–41.
5. Hart RG, Catanese L, Perera KS, Ntaios G, Connolly SJ. Embolic stroke of undetermined source: a systematic review and clinical update. Stroke. 2017;48:867–72.
6. Perera KS, Vanassche T, Bosch J, Giruparajah M, Swaminathan B, Mattina KR, et al. Embolic strokes of undetermined source: prevalence and patient features in the ESUS Global Registry. Int J Stroke. 2016;11:526–33.
7. Ntaios G, Papavasileiou V, Milionis H, Makaritsis K, Vemmou A, Koroboki E. Embolic strokes of undetermined source in the Athens Stroke Registry: an outcome analysis. Stroke. 2015;46:2087–93.
8. Ntaios G, Lip GYH, Vemmos K, Koroboki E, Manios E, Vemmou A, et al. Age- and sex-specific analysis of patients with embolic stroke of undetermined source. Neurology. 2017;89(6):532–9.
9. Ntaios G, Vemmos K, Lip GY, Koroboki E, Manios E, Vemmou A, et al. Risk stratification for recurrence and mortality in embolic stroke of undetermined source. Stroke. 2016;47(9):2278–85.
10. Molina CA, Santamarina E, Alvarez-Sabín J. Cryptogenic stroke, aortic arch atheroma and patent foramen ovale. Cerebrovasc Dis. 2007;24(Suppl 1):84–8.
11. Ryoo S, Chung JW, Lee MJ, Kim SJ, Lee JS, Kim GM, et al. An approach to working up cases of embolic stroke of undetermined source. J Am Heart Assoc. 2016;5(3):e002975.
12. Jaffre A, Guidolin B, Ruidavets JB, Nasr N, Larrue V. Non-obstructive carotid atherosclerosis and patent foramen ovale in young adults with cryptogenic stroke. Eur J Neurol. 2017;24(5):663–6.
13. Lattanzi S, Cagnetti C, Pulcini A, Morelli M, Maffei S, Provinciali L, Silvestrini M. The P-wave terminal force in embolic strokes of undetermined source. J Neurol Sci. 2017;375:175–8.
14. Brinjikji W, Huston J 3rd, Rabinstein AA, Kim GM, Lerman A, Lanzino G. Contemporary carotid imaging: from degree of stenosis to plaque vulnerability. J Neurosurg. 2016;124:27–42.
15. Bayer-Karpinska A, Schindler A, Saam T. Detection of vulnerable plaque in patients with cryptogenic stroke. Neuroimaging Clin N Am. 2016;26:97–110.
16. Gupta A, Baradaran H, Schweitzer AD, Kamel H, Pandya A, Delgado D, et al. Carotid plaque MRI and stroke risk: a systematic review and meta-analysis. Stroke. 2013;44:3071–7.
17. Bulwa Z, Gupta A. Embolic stroke of undetermined source: the role of the nonstenotic carotid plaque. J Neurol Sci. 2017;382:49–52.
18. Freilinger TM, Schindler A, Schmidt C, Grimm J, Cyran C, Schwarz F, et al. Prevalence of nonstenosing, complicated atherosclerotic plaques in cryptogenic stroke. JACC Cardiovasc Imaging. 2012;5:397–405.
19. Hyafil F, Schindler A, Sepp D, Obenhuber T, Bayer-Karpinska A, Boeckh-Behrens T, et al. High-risk plaque features can be detected in non-stenotic carotid plaques of patients with ischaemic stroke classified as cryptogenic using combined (18)F-FDG PET/MR imaging. Eur J Nucl Med Mol Imaging. 2016;43(2):270–9.
20. Li L, Yiin GS, Geraghty OC, Schulz UG, Kuker W, Mehta Z, et al. Incidence, outcome, risk factors, and long-term prognosis of cryptogenic transient ischaemic attack and ischaemic stroke: a population-based study. Lancet Neurol. 2015;14(9):903–13.
21. Truijman MT, de Rotte AA, Aaslid R, van Dijk AC, Steinbuch J, Liem MI, et al. Intraplaque hemorrhage, fibrous cap status, and microembolic signals in symptomatic patients with mild to moderate carotid artery stenosis: the plaque at RISK study. Stroke. 2014;45(11):3423–6.
22. Sanna T, Diener HC, Passman RS, Di Lazzaro V, Bernstein RA, Morillo CA, et al. Cryptogenic stroke and underlying atrial fibrillation. N Engl J Med. 2014;370:2478–86.
23. Sposato LA, Cipriano LE, Saposnik G, Ruíz Vargas E, Riccio PM, Hachinski V. Diagnosis of atrial fibrillation after stroke and transient ischaemic attack: a systematic review and meta-analysis. Lancet Neurol. 2015;14(4):377–87.
24. Kasner SE, Lavados P, Sharma M, Wang Y, Wang Y, Dávalos A, et al. Characterization of patients with embolic strokes of undetermined source in the NAVIGATE ESUS randomized trial. J Stroke Cerebrovasc Dis. 2018;27:1673–82.
25. De Meyer SF, Andersson T, Baxter B, Bendszus M, Brouwer P, Brinjikji W, et al. Analyses of thrombi in acute ischemic stroke: a consensus statement on current knowledge and future directions. Int J Stroke. 2017;12:606–14.
26. Boeckh-Behrens T, Kleine JF, Zimmer C, Neff F, Scheipl F, Pelisek J, et al. Thrombus histology suggests cardioembolic cause in cryptogenic stroke. Stroke. 2016;47:1864–71.
27. Kim SK, Yoon W, Kim TS, Kim HS, Heo TW, Park MS. Histologic analysis of retrieved clots in acute ischemic stroke: correlation with stroke etiology and gradient-echo MRI. AJNR Am J Neuroradiol. 2015;36:1756–62.
28. Cho KH, Kim JS, Kwon SU, Cho AH, Kang DW. Significance of susceptibility vessel sign on

T2*-weighted gradient echo imaging for identification of stroke subtypes. Stroke. 2005;36:2379–83.
29. Niesten JM, van der Schaaf IC, Biessels GJ, van Otterloo AE, van Seeters T, Horsch AD, et al. Relationship between thrombus attenuation and different stroke subtypes. Neuroradiology. 2013; 55(9):1071–9.
30. Sacco RL, Prabhakaran S, Thompson JL, Murphy A, Sciacca RR, Levin B, et al. Comparison of warfarin versus aspirin for the prevention of recurrent stroke or death: subgroup analyses from the warfarin-aspirin recurrent stroke study. Cerebrovasc Dis. 2006;22:4–12.
31. Homma S, Sacco RL, Di Tullio MR, Sciacca RR, Mohr JP, PFO in Cryptogenic Stroke Study (PICSS) Investigators. Effect of medical treatment in stroke patients with patent foramen ovale: patent foramen ovale in Cryptogenic Stroke Study. Circulation. 2002;105:2625–31.
32. Mas JL, Derumeaux G, Guillon B, Massardier E, Hosseini H, Mechtouff L, et al. Patent foramen ovale closure or anticoagulation vs. antiplatelets after stroke. N Engl J Med. 2017;377:1011–21.
33. The Stroke Prevention In Reversible Ischemia Trial (SPIRIT) Study Group. A randomized trial of anticoagulants versus aspirin after cerebral ischemia of presumed arterial origin. Ann Neurol. 1997;42:857–65.
34. ESPRIT Study Group, Halkes PH, van Gijn J, Kappelle LJ, Koudstaal PJ, Algra A. Medium intensity oral anticoagulants versus aspirin after cerebral ischaemia of arterial origin (ESPRIT): a randomised controlled trial. Lancet Neurol. 2007;6:115–24.
35. Caron F, Anand SS. Antithrombotic therapy in aortic diseases: a narrative review. Vasc Med. 2017;22:57–65.
36. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet. 2014; 383:955–62.
37. Hart RG, Sharma M, Mundl H, Kasner SE, Bangdiwala SI, Berkowitz SD, et al. Rivaroxaban for stroke prevention after embolic stroke of undetermined source. N Engl J Med. 2018;378:2191–201.
38. Hirsh BJ, Copeland-Halperin RS, Halperin JL. Fibrotic atrial cardiomyopathy, atrial fibrillation, and thromboembolism: mechanistic links and clinical inferences. J Am Coll Cardiol. 2015;65:2239–51.
39. Sposato LA, Klein FR, Jáuregui A, Ferrúa M, Klin P, Zamora R, et al. Newly diagnosed atrial fibrillation after acute ischemic stroke and transient ischemic attack: importance of immediate and prolonged continuous cardiac monitoring. J Stroke Cerebrovasc Dis. 2012;21:210–6.
40. Lau CP, Siu CW, Yiu KH, Lee KL, Chan YH, Tse HF. Subclinical atrial fibrillation and stroke: insights from continuous monitoring by implanted cardiac electronic devices. Europace. 2015;17(Suppl 2):ii40–6.
41. Sposato LA, Cerasuolo JO, Cipriano LE, Fang J, Fridman S, Paquet M, et al. Atrial fibrillation detected after stroke is related to a low risk of ischemic stroke recurrence. Neurology. 2018;90:e924–31.
42. Tomita H, Sasaki S, Hagii J, Metoki N. Covert atrial fibrillation and atrial high-rate episodes as a potential cause of embolic strokes of undetermined source: their detection and possible management strategy. J Cardiol. 2018;72:1–9.
43. Glotzer TV, Hellkamp AS, Zimmerman J, Sweeney MO, Yee R, Marinchak R, et al. Atrial high rate episodes detected by pacemaker diagnostics predict death and stroke: report of the Atrial Diagnostics Ancillary Study of the MOde Selection Trial (MOST). Circulation. 2003;107:1614–9.
44. Glotzer TV, Daoud EG, Wyse DG, Singer DE, Ezekowitz MD, Hilker C, et al. The relationship between daily atrial tachyarrhythmia burden from implantable device diagnostics and stroke risk: the TRENDS study. Circ Arrhythm Electrophysiol. 2009;2:474–80.
45. Van Gelder IC, Healey JS, Crijns HJGM, Wang J, Hohnloser SH, Gold MR, et al. Duration of device-detected subclinical atrial fibrillation and occurrence of stroke in ASSERT. Eur Heart J. 2017;38:1339–44.
46. Daoud EG, Glotzer TV, Wyse DG, Ezekowitz MD, Hilker C, Koehler J, et al. Temporal relationship of atrial tachyarrhythmias, cerebrovascular events, and systemic emboli based on stored device data: a subgroup analysis of TRENDS. Heart Rhythm. 2011;8:1416–23.
47. Brambatti M, Connolly SJ, Gold MR, Morillo CA, Capucci A, Muto C, et al. Temporal relationship between subclinical atrial fibrillation and embolic events. Circulation. 2014;129:2094–9.
48. Turakhia MP, Ziegler PD, Schmitt SK, Chang Y, Fan J, Than CT, et al. Atrial fibrillation burden and short-term risk of stroke: casecrossover analysis of continuously recorded heart rhythm from cardiac electronic implanted devices. Circ Arrhythm Electrophysiol. 2015;8:1040–7.
49. Cerasuolo JO, Cipriano LE, Sposato LA. The complexity of atrial fibrillation newly diagnosed after ischemic stroke and transient ischemic attack: advances and uncertainties. Curr Opin Neurol. 2017;30(1):28–37.
50. Scridon A, Şerban RC, Chevalier P. Atrial fibrillation: neurogenic or myogenic? Arch Cardiovasc Dis. 2018;111:59–69.
51. Sposato LA, Fridman S, Whitehead SN, Lopes RD. Linking stroke-induced heart injury and neurogenic atrial fibrillation: a hypothesis to be proven. J Electrocardiol. 2018. pii: S0022-0736(18)30097-9. https://doi.org/10.1016/j.jelectrocard.2018.02.006. [Epub ahead of print].
52. González Toledo ME, Klein FR, Riccio PM, Cassará FP, Muñoz Giacomelli F, Racosta JM, et al. Atrial fibrillation detected after acute ischemic stroke: evidence supporting the neurogenic hypothesis. J Stroke Cerebrovasc Dis. 2013;22:e486–91.

53. Hsieh CY, Lee CH, Wu DP, Sung SF. Characteristics and outcomes of ischemic stroke in patients with known atrial fibrillation or atrial fibrillation diagnosed after stroke. Int J Cardiol. 2018;261:68–72.
54. Bisson A, Clementy N, Bodin A, Angoulvant D, Babuty D, Lip GYH, Fauchier L. Relationship of preexisting cardiovascular comorbidities to newly diagnosed atrial fibrillation after ischemic stroke. Stroke. 2017;48:2878–80.
55. Ntaios G, Papavasileiou V, Lip GY, Milionis H, Makaritsis K, Vemmou A, et al. Embolic stroke of undetermined source and detection of atrial fibrillation on follow-up: how much causality is there? J Stroke Cerebrovasc Dis. 2016;25:2975–80.
56. Kim Y, Lee SH. Embolic stroke and after-admission atrial fibrillation. Int J Cardiol. 2016;222:576–80.
57. Scheitz JF, Erdur H, Haeusler KG, Audebert HJ, Roser M, Laufs U, et al. Insular cortex lesions, cardiac troponin, and detection of previously unknown atrial fibrillation in acute ischemic stroke: insights from the troponin elevation in acute ischemic stroke study. Stroke. 2015;46:1196–201.
58. Rizos T, Bartsch AJ, Johnson TD, Dittgen F, Nichols TE, Malzahn U, Veltkamp R. Voxelwise distribution of acute ischemic stroke lesions in patients with newly diagnosed atrial fibrillation: trigger of arrhythmia or only target of embolism? PLoS One. 2017;12:e0177474.
59. Paquet M, Cerasuolo JO, Thorburn V, Fridman S, Alsubaie R, Lopes RD, et al. Pathophysiology and risk of atrial fibrillation detected after ischemic stroke (PARADISE): a translational, integrated, and transdisciplinary approach. J Stroke Cerebrovasc Dis. 2018;27:606–19.
60. Gorenek B, Bax J, Boriani G, Chen SA, Dagres N, Glotzer TV, et al. Device-detected subclinical atrial tachyarrhythmias: definition, implications and management-an European Heart Rhythm Association (EHRA) consensus document, endorsed by Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS) and Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología (SOLEACE). Europace. 2017;19:1556–78.
61. Lopes RD, Alings M, Connolly SJ, Beresh H, Granger CB, Mazuecos JB, et al. Rationale and design of the Apixaban for the reduction of thromboembolism in patients with device-detected subclinical atrial fibrillation (ARTESiA) trial. Am Heart J. 2017;189:137–45.
62. Kirchhof P, Blank BF, Calvert M, Camm AJ, Chlouverakis G, Diener HC, et al. Probing oral anticoagulation in patients with atrial high rate episodes: rationale and design of the non-vitamin K antagonist oral anticoagulants in patients with atrial high rate episodes (NOAH-AFNET 6) trial. Am Heart J. 2017;190:12–8.
63. Zimetbaum P, Waks JW, Ellis ER, Glotzer TV, Passman RS. Role of atrial fibrillation burden in assessing thromboembolic risk. Circ Arrhythm Electrophysiol. 2014;7:1223–9.
64. Kamel H, Okin PM, Elkind MS, Iadecola C. Atrial fibrillation and mechanisms of stroke: time for a new model. Stroke. 2016;47:895–900.
65. Goldberger JJ, Arora R, Green D, Greenland P, Lee DC, Lloyd-Jones DM, et al. Evaluating the atrial myopathy underlying atrial fibrillation: identifying the arrhythmogenic and thrombogenic substrate. Circulation. 2015;132:278–91.
66. Fonseca AC, Alves P, Inácio N, Marto JP, Viana-Baptista M, Pinho-E-Melo T, et al. Patients with undetermined stroke have increased atrial fibrosis: a cardiac magnetic resonance imaging study. Stroke. 2018;49:734–7.
67. Tsang TS, Barnes ME, Bailey KR, Leibson CL, Montgomery SC, Takemoto Y, et al. Left atrial volume: important risk marker of incident atrial fibrillation in 1655 older men and women. Mayo Clin Proc. 2001;76:467–75.
68. Benjamin EJ, D'Agostino RB, Belanger AJ, Wolf PA, Levy D. Left atrial size and the risk of stroke and death. The Framingham Heart Study. Circulation. 1995;92:835–41.
69. Yaghi S, Moon YP, Mora-McLaughlin C, Willey JZ, Cheung K, Di Tullio MR, et al. Left atrial enlargement and stroke recurrence: the Northern Manhattan Stroke Study. Stroke. 2015;46:1488–93.
70. Yaghi S, Song C, Gray WA, Furie KL, Elkind MS, Kamel H. Left atrial appendage function and stroke risk. Stroke. 2015;46:3554–9.
71. Kim D, Shim CY, Hong GR, Kim MH, Seo J, Cho IJ, et al. Clinical implications and determinants of left atrial mechanical dysfunction in patients with stroke. Stroke. 2016;47:1444–51.
72. Larsen BS, Kumarathurai P, Falkenberg J, Nielsen OW, Sajadieh A. Excessive atrial ectopy and short atrial runs increase the risk of stroke beyond incident atrial fibrillation. J Am Coll Cardiol. 2015;66:232–41.
73. Marinheiro R, Parreira L, Amador P, Sá C, Duarte T, Caria R. Excessive atrial ectopic activity as an independent risk factor for ischemic stroke. Int J Cardiol. 2017;249:226–30.
74. Pinho J, Braga CG, Rocha S, Santos AF, Gomes A, Cabreiro A, et al. Atrial ectopic activity in cryptogenic ischemic stroke and TIA: a risk factor for recurrence. J Stroke Cerebrovasc Dis. 2015;24:507–10.
75. Kamel H, Elkind MS, Bhave PD, Navi BB, Okin PM, Iadecola C, et al. Paroxysmal supraventricular tachycardia and the risk of ischemic stroke. Stroke. 2013;44:1550–4.
76. Kamel H, Soliman EZ, Heckbert SR, Kronmal RA, Longstreth WT Jr, Nazarian S, Okin PM. P-wave morphology and the risk of incident ischemic stroke in the multi-ethnic study of atherosclerosis. Stroke. 2014;45:2786–8.
77. Maheshwari A, Norby FL, Soliman EZ, Koene RJ, Rooney MR, O'Neal WT, et al. Abnormal P-wave axis and ischemic stroke: the ARIC Study (atherosclerosis risk in communities). Stroke. 2017;48:2060–5.

78. He J, Tse G, Korantzopoulos P, Letsas KP, Ali-Hasan-Al-Saegh S, Kamel H, et al. P-wave indices and risk of ischemic stroke: a systematic review and meta-analysis. Stroke. 2017;48:2066–72.
79. Kamel H, Bartz TM, Longstreth WT Jr, Okin PM, Thacker EL, Patton KK, et al. Association between left atrial abnormality on ECG and vascular brain injury on MRI in the Cardiovascular Health Study. Stroke. 2015;46:711–6.
80. Acampa M, Lazzerini PE, Guideri F, Tassi R, Lo Monaco A, Martini G. Inflammation and atrial electrical remodeling in patients with embolic strokes of undetermined source. Heart Lung Circ. 2018. pii: S1443-9506(18)30465-7. https://doi.org/10.1016/j.hlc.2018.04.294. [Epub ahead of print].
81. Jalife J, Kaur K. Atrial remodeling, fibrosis, and atrial fibrillation. Trends Cardiovasc Med. 2015;25:475–84.
82. Akoum N. New perspectives on atrial fibrillation and stroke. Heart. 2016;102:1788–92.
83. Yaghi S, Chang AD, Ricci BA, Jayaraman MV, McTaggart RA, Hemendinger M, et al. Early elevated troponin levels after ischemic stroke suggests a cardioembolic source. Stroke. 2018;49:121–6.
84. Kamel H, Bartz TM, Elkind MSV, Okin PM, Thacker EL, Patton KK, et al. Atrial cardiopathy and the risk of ischemic stroke in the CHS (Cardiovascular Health Study). Stroke. 2018;49:980–6.
85. Acampa M, Lazzerini PE, Martini G. Atrial cardiopathy and sympatho-vagal imbalance in cryptogenic stroke: pathogenic mechanisms and effects on electrocardiographic markers. Front Neurol. 2018;9:469.
86. Geisler T, Poli S, Meisner C, Schreieck J, Zuern CS, Nägele T, et al. Apixaban for treatment of embolic stroke of undetermined source (ATTICUS randomized trial): rationale and study design. Int J Stroke. 2017;12(9):985–90.
87. Eklind MS et al. Atrial cardiopathy and antithrombotic drugs in prevention after cryptogenic stroke (ARCADIA) https://clinicaltrials.gov/ct2/show/study/NCT03192215?show_locs=Y#locn. Accessed 06 July 2018.

The Heart-Brain Connection in Patients with Disorders of Consciousness

29

Francesca Pistoia, Simona Sacco, Marco Sarà, and Antonio Carolei

Contents

Abstract

Recently, there has been a growing emphasis on better understanding how the brain-heart axis works and in which way the brain may influence cardiac performances both in physiological and in pathological conditions. A new research field, named as *neurocardiology*, investigates the whole spectrum of cardiac syndromes, which arise as a result of a widespread or a strategic brain injury in the absence of a real ischemic heart disease. Disorders of consciousness, such as coma, vegetative state and minimally conscious state, have been recently reported to be associated with multiple medical comorbidities, also including cardiovascular manifestations like arrhythmias, arterial hypertension, and conditions of myocardial stunning. There is growing evidence that such clinical events are the consequence of an autonomic imbalance within the autonomic

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*, https://doi.org/10.1007/978-3-030-28008-6_34

nervous system, with the sympathetic activation outweighing the parasympathetic one. Either a widespread anoxic brain injury or a vascular/traumatic damage in specific cortical areas, which usually slow down the activity of the sympathetic branch, may produce a wide pattern of cardiac manifestations ultimately interfering with the prognosis of patients. Investigating the cardiac behavior in patients with disorders of consciousness is mandatory in order to avoid further medical complications, prevent the secondary injury occurring in the minutes to months following the primitive brain damage, and improve survival and long-term outcomes. Moreover, the study of the brain-heart interface offers a window for a better understanding of the natural history of disorders of consciousness and the identification of chances for recovery. This is because the heart behavior, with its physiological fluctuations, may represent an indirect sign of the residual complexity of cortical-subcortical networks responsible for consciousness recovery.

Keywords

Coma · Vegetative state · Unresponsive wakefulness syndrome · Minimally conscious state · Comorbidities · Heart

Introduction

Disorders of consciousness (coma, vegetative state, and minimally conscious state) are the result of a severe acquired brain injury, which is classified as a damage leading to consciousness impairment and vital parameter instability. Patients suffering from a severe acquired brain injury usually show widespread bihemispheric damage or a selective brainstem lesion, which interferes with survival, so that nursing and medical care are necessary to maintain the patients alive. They are managed within intensive care units and may have different outcomes and a variable degree of functional impairment depending on the extent of the primitive damage. Recent evidence shows that multiple medical comorbidities, also including the whole spectrum of cardiac syndromes, may be associated with the brain damage [1]. However, it is not clear whether these syndromes arise autonomously or, on the other hand, they are the result of the brain's effects on the heart. Recently, a fascinating field of study, named *neurocardiology*, was developed in the attempt of investigating the heart's effect on the brain and the brain's effect on the heart in all patients with nervous system's diseases, especially those potentially interfering with the cardiovascular control. According to the most accredited theory, neurocardiac syndromes following a severe brain damage may be the result of a generalized autonomic storm having both sympathetic and parasympathetic effects [2]. This condition may produce, in patients with disorders of consciousness, asymptomatic electrocardiographic (ECG) changes, or clinical cardiac disorders, which are reminiscent of a coronary disease, even in the absence of a real ischemic heart disease.

Classification of Disorders of Consciousness

Disorders of consciousness include a wide spectrum of neurological syndromes such as coma, vegetative state (VS), also named as unresponsive wakefulness syndrome (UWS), and minimally conscious state (MCS). Although patients showing a disorder of consciousness may appear similar from a behavioral point of view, they are deeply different from each other with respect to the underlying brain injury and the degree of residual behavioral responsiveness they show. Patients in coma are neither awake nor aware [3]: they are confined to bed, have closed eyes, do not have spontaneous breathing, so that mechanical ventilation is usually needed, and are fed by parenteral nutrition. On the other hand, patients in VS/UWS show recovered wakefulness in the absence of self- and environmental awareness, so they have open eyes and normal sleep-wake cycles but are completely unable to interact with the environment through purposeful behaviors [4, 5]. As a consequence they are completely depended on others in all self-care activities including toileting and feeding, so they need

continuous assistance and are fed through a feeding tube or a percutaneous endoscopic gastrostomy. The ability for functional communication is completely lacking, and there is no way to establish a communication channel with the patients. Finally patients in MCS are those showing a partial recovery of consciousness, being again able to carry out basic purposeful movements: however, in MCS, the behavioral evidence of consciousness is considered clearly discernible but inconsistent, and the patients can remain in such state for an indefinite time [6]. The recovery of functional object use and of functional communication, as assessed by the Coma Recovery Scale (Revised), denotes the emergence from minimally conscious state to a condition of completely restored consciousness [7, 8].

Medical Complications in Disorders of Consciousness

Recent evidence revealed that multiple medical comorbidities might be detected in patients with disorders of consciousness [1]. Patients in coma are, by definition, unstable as the acute brain injury, together with a condition of severe edema, may cause a progressive rostral-caudal neurologic deterioration, which may be fatal for the patients. Moreover, in the acute stage, patients show medical and surgical complications, including cardiac, hemodynamic, and vascular disorders, and require full life support within intensive care units until the condition improves and wakefulness and spontaneous breathing are recovered. On the other hand, patients in VS and MCS have spontaneous breathing and are considered stable from a medical perspective, with a normal life expectancy if immobilization-related complications are avoided through standard medical and nursing care. However, recent literature findings show that medical comorbidities may also be present in patients in VS and MCS, thus interfering with the natural course of their disease and the likelihood of a further recovery. These comorbidities include respiratory diseases, arrhythmias without organic heart diseases, arterial hypertension, anemia, diabetes, ischemic or organic heart diseases, kidney and urinary tract diseases, peripheral artery and venous diseases, gastrointestinal and hepatobiliary disorders, cerebrovascular events, musculoskeletal disorders, and malignancies [1]. Particular attention has been paid to the occurrence of arrhythmias not supported by organic heart diseases: the pathological effects of the initial brain injury on the heart might explain arrhythmias through a mechanism of autonomic imbalance. In fact, it is not rare that patients in VS develop a paroxysmal sympathetic hyperactivity even many months after the primitive brain injury, which was responsible for the consciousness impairment [9]. Arrhythmias without organic heart diseases have been recognized in patients with disorders of consciousness following a brain damage of different etiologies: they have been frequently found not only in patients in whom the condition of VS/UWS was the result of a stroke or of a postanoxic encephalopathy due to a cardiac arrest but also in patients with a traumatic injury caused by external circumstances. While in the former cases, arrhythmias could be somehow expected, especially in the patients with a cardiac arrest or a cardioembolic stroke, they were less expected in patients with a damage of traumatic nature. Moreover, arrhythmias without organic heart diseases have been shown to be negative predictors of full recovery of consciousness in severely brain-injured patients [1]: this prompts reflections on the usefulness of investigating the brain-heart interface as potential marker of the brain network derangement associated with the persistence of the loss of consciousness.

Empirical Evidence About Cardiovascular Dysfunctions in Disorders of Consciousness

One of the first descriptions of ECG changes in patients with disorders of consciousness was provided by Harold Levine who described a 69-year-old woman showing a condition of coma as a result of a subarachnoid hemorrhage caused by a ruptured aneurysm [2]. Two days following the brain damage, the patient's ECG showed a pattern

suggestive of myocardial infarction (ST segment elevation), which was not confirmed by later autopsy [2]. This description was followed by multiple observations from other researchers suggesting the presence of ECG changes (long QT intervals, large inverted T waves, and U waves) in patients with severe brain damage, mainly of hemorrhagic nature [2]. In all the cases, postmortem examination excluded the presence of ischemic heart diseases, just endorsing the view of a visceral organ dysfunction directly linked to the primitive brain damage. In the same venue, research in animal models revealed that the occurrence of cardiac syndromes following a severe brain injury might be favored by the development of an autonomic dysregulation. Specifically, it seems that a sympathetic hyperactivity associated with catecholamine increasing and toxicity may lead to several cardiac dysfunctions. Moreover, the described cardiac disorders cannot be prevented by adrenalectomy, thus suggesting that a direct neural connection between the brain and the heart rather than a blood-borne route is more likely to be responsible for the final cardiac effects [2]. The autonomic storm ultimately resulting in cardiac disorders may arise as a consequence of strategic brain lesions, which involve areas and structures normally contributing to the cardiovascular control. These structures, which represent the cortical inhibitory centers for sympathetic tone, include the Brodmann areas n.13 and n. 24, respectively, located in the orbitofrontal cortex and in the anterior cingulate gyrus, the anterolateral portion of the hypothalamus, and the insular cortex. After a widespread brain injury, the above cortical inhibitory centers might be functionally disconnected from the hypothalamic, diencephalic, and brainstem hubs that are responsible for the supraspinal control of sympathetic tone, thus leading to the so-known paroxysmal sympathetic hyperactivity (PSH) syndrome. This syndrome is characterized by the sudden onset, in patients with apparently stationary conditions, of tachycardia, arterial hypertension, tachypnea, hyperthermia, and decerebrate posturing following stimulation. A mechanism of allodynia underlies the occurrence of these paroxysms, as normally non-noxious stimuli such as mild pain, urinary retention, or simple movements may trigger a condition of hyperresponsiveness, resulting in sympathetic storms [10]. The prevalence of PSH ranges from 8% to 33% across different studies and countries, with the higher prevalence being recognized after a traumatic brain injury [10]. As concerns the effects of PSH on outcomes of patients, there are some discrepancies across literature findings, with some studies reporting PSH as an independent risk factor for mortality or poor clinical outcome and others excluding the effects of PSH on long-term neurological outcomes of patients [10].

Protecting the Heart from the Severely Injured Brain

Although the effects of a severe brain injury on the cardiovascular system are only partially understood, there is much evidence that they can have a profound impact on the short- and long-term recovery of patients. Arrhythmias and ECG abnormalities may occur, in the absence of a previous or a concomitant structural heart disease, in the whole spectrum of the central nervous system (CNS) diseases, including ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage, traumatic brain injury, meningitis and encephalitis, epilepsy, and neurodegenerative diseases [11]. Especially in CNS diseases with an acute onset and a rapidly progressive course, including those leading to consciousness impairment, a closed cardiac monitoring of patients is mandatory in order to properly identify and manage any unexpected cardiovascular dysfunction, which may affect survival and outcomes. The most frequently encountered cardiac abnormalities in acquired severe brain injuries include arrhythmias, stress cardiomyopathy (also known as Takotsubo syndrome), myocardial infarction, paroxysmal arterial hypertension, and autonomic dysfunction in ischemic stroke; arrhythmias, stress cardiomyopathy, heart failure, systolic dysfunction, myocardial infarction, and wall motion abnormalities in intracerebral hemorrhage; asymptomatic ECG abnormalities or arrhythmias, heart failure,

systolic and diastolic dysfunction, stress cardiomyopathy, myocardial infarction, and pulmonary hypertension in subarachnoid hemorrhage; and arrhythmias, sudden cardiac death, stress cardiomyopathy, myocardial infarction, systolic dysfunction, heart failure, arterial hypertension, and autonomic dysfunction in traumatic brain injury [11]. Arrhythmias cover a heterogeneous spectrum of conditions, ranging from asymptomatic ECG changes to life-threatening conditions like ventricular runs, torsades de pointes, and sustained ventricular tachycardias. In the presence of any ECG changes, it is important to exclude the presence of concomitant cardiovascular causes by evaluating serum cardiac enzymes, echocardiography, and, when necessary, coronary angiography. Electrolyte abnormalities have to be promptly reversed, and medications causing a QT prolongation (such as antipsychotics) should be avoided [12]. Another harmful condition, following a severe brain injury, is represented by the stress cardiomyopathy/Takotsubo syndrome, which is characterized by the occurrence of a neurogenic myocardial stunning triggered by a catecholamine storm: although catecholamine usually have a positive inotropic effect on the heart, a catecholamine excess during an acute brain injury may result in a myocardial stunning and require active management [13]. The prognosis is usually good, but no data are available on the effects of this additional complication on brain injury-related outcomes.

The risk of developing arrhythmias after a severe brain injury seems to be higher in patients with right-sided lesions as compared to those with left-sided lesions [14]. Of note, right insular cortical lesions have been frequently associated with the development of ECG abnormalities and increased 3-month mortality rates following the primitive brain injury. This suggests that the right insula plays a dominant role in the modulation of the autonomic nervous system, through the hyperactivation of the sympathetic branch ("fight or flight system") over the parasympathetic ("rest and digest" system) one. The recent research has been mainly focused on the identification of biomarkers denoting an overactivity of the sympathetic system after a traumatic brain injury: increased plasma and urinary catecholamine levels have been reported being associated with the occurrence and the severity of the primitive brain injury, with high levels of epinephrine and norepinephrine being found to be independent predictors of the need of mechanical ventilation, the length of hospital stay, and the in-hospital mortality [15]. Moreover, various catecholamine levels have been detected across brain injuries of different severity: patients with a consciousness impairment following a severe acquired brain injury, as denoted by a Glasgow Coma Scale score of 3–4, have been reported to have epinephrine and norepinephrine levels four to five times above the normal values, whereas patients with a mild brain injury had only slightly elevated levels [16]. In this view, the use of beta-adrenergic blockers after TBI has been considered useful in controlling the effects of the sympathetic system overactivity, thus improving the global outcomes of patients. Many studies investigated the impact of the beta-adrenergic blockers use on early survival and long-term functional outcomes and quality of life of patients, all reporting a beneficial effect of beta-blockers [17]. The mechanism by which these drugs, particularly propranolol, exert their beneficial effects seems to be linked to an improvement of cerebral perfusion and microcirculation and a decrease of secondary brain injury of anoxic nature [17]. The decreasing adrenergic or sympathetic hyperactivity after severe traumatic brain injury (DASH After TBI Study) trial recently investigated the effects of combined propranolol and clonidine on the outcomes of severely brain-injured patients: the study was structured as a single-center, randomized, double-blinded, placebo-controlled, two-arm trial where patients with a severe acquired brain injury, as defined by a Glasgow Coma Scale ≤ 8, were divided in two groups, one receiving a combination of propranolol (1 mg intravenously every 6 h for 7 days) and clonidine (0.1 mg per tube every 12 h for 7 days) and the other receiving double placebo [18]. The main outcomes explored included the norepinephrine plasma level reduction; the heart rate variability pattern; the occurrence of arrhythmias, infections, and agitation; the medication profile; the extent of coma-free days

and ventilator-free days; the length of stay; and the mortality. Although the recruitment of patients has been completed, the definitive results are still awaited. They will allow us a better comprehension of the sympathetic overactivity-related injury in traumatic brain damage and the potential benefits arising from the use of drugs acting by controlling the sympathetic branch of the autonomic nervous system [18].

Quantifying the Cardiac Dysfunction After a Severe Brain Injury

The prerequisite to carry out effective treatments to control cardiac dysfunctions in widespread brain injury is the proper identification of patients who, as a result of specific brain lesions, are more likely to develop a cardiac disorder even in the absence of a previous or concomitant direct myocardial injury. For this aim, a series of clinical parameters and biomarkers should be identified and investigated in all the patients at risk of experiencing a sympathetic storm-related damage. Serum troponin and creatine kinase levels are certainly the ideal biomarkers to promptly evaluate any cardiac disorder, whether a primitive damage linked to atherosclerotic coronary artery diseases or a secondary cardiac dysfunction triggered by a brain injury, which affects the brain-heart interface. High troponin and creatine kinase levels have been recognized in multiple cardiac manifestations following a cerebral damage of traumatic or vascular nature and have been reported to be predictive of later functional outcomes [17]. Similarly, the plasma levels of the N-terminal probrain natriuretic peptide may be higher in patients with a severe brain injury, especially when the size of the brain parenchymal damage is relevant or when the contribution of edema to the whole damage increases [17]. Moreover, the assessment of hemodynamic parameters, such as the heart rate variability and the baroreflex sensitivity, may be a reliable method to indirectly investigate the autonomic dysfunction associated with the underlying brain damage. In fact, intracranial pressure, mean arterial pressure, and heart rate are mutually interconnected with the consequence that the heart rate and the blood pressure profile, in patients with a severe brain damage and an increased intracranial pressure, may show pathological changes. Moving from the assumption that the autonomic, the cardiovascular, and the cerebrovascular system have a physiologic dynamic interdependence, TBI may be classified as a multisystem disease, where cerebral perturbations manifest extra-cranially by affecting the normal fluctuations of measured physiological parameters such as blood pressure and heart rate [19]. In this respect, a lower complexity of the patterns of heart rate, mean arterial pressure, and intracranial pressure, as expressed by a reduction of the nonlinear parameter approximate entropy, has been related to unfavorable outcomes in severely brain-injured patients [20]. Specifically, the lower ApEn intracranial pressure has been interpreted as a sign of the primary cranial insult occurring at the moment of the impact, while the lower ApEn mean arterial pressure and ApEn heart rate have been postulated to reflect the secondary additional injury, which also contributes to mortality and disability [20]. In these terms, ApEn and other complexity indexes might be used as indicators of the residual health of the brain-heart axis, in order to stratify patients on the basis of their chances for recovery and to plan a more adequate management.

The Heart Behavior as a Prognostic Window in Disorders of Consciousness

The most relevant challenge in patients with disorders of consciousness is trying to establish a prognosis. Notwithstanding the recent developments in medicine, we are still unable to establish whether a patient in VS of MCS will recover consciousness or not. This causes great psychological distress for families and caregivers and practical difficulties in establishing which patients may benefit more from resource allocation in this field. In this light, we recently proposed a new prognostic approach in patients with disorders of consciousness, based on the analysis of the nonlinear dynamics of ECG and electroencephalographic (EEG) signals [21–24]. This approach

moves from the assumption that formulating a prognosis in such patients remains challenging as a consequence of the lack of an univocal definition of consciousness, the missing knowledge of its neural correlates and the extreme heterogeneity of patients with respect to the extent and severity of brain damage, the underlying mechanism of injury, and the presence of additional comorbidities [23]. The proposed approach is an "edgeshot" research method, which goes beyond the definition and localization of consciousness, by considering the brain as a complex system and consciousness as an emergent phenomenon whose peripheral outputs show a nonlinear behavior [24]. A system is defined as complex when the whole is more than the sum of its single parts, thus showing emergent properties or behaviors, which arise as a result of the interaction among the single parts. Therefore, an emergent phenomenon is a large-scale group behavior of a system, which doesn't seem to have any clear explanation in terms of the system's constituent parts [25]. An example of emergent phenomenon is a flock, where the single constituent parts (birds) carry out basic behaviors and give rise to a more complex compound group behavior, which is unpredictable on the basis of the single parts' behavior. In these terms, the brain may be considered as a complex system, showing large-scale connections within its cortical and subcortical loops, and consciousness may be labeled as one of its emergent unpredictable phenomena. This is also in line with the most accredited definition of VS according to which VS is a disconnection syndrome with frontoparietal networks being functionally disconnected from thalamic structures [26].

Each complex system (including the brain) has peripheral outputs (blood pressure dynamics, heart rate dynamics, ECG and EEG dynamics) showing a nonlinear unpredictable behavior. When nonlinearity and unpredictability of blood pressure, heart rate, and EEG time series are preserved, this denotes that the complex system, from which they arise, is properly working. On the other hand, when the complex is injured, with some of its parts being functionally disconnected from the others, this results in a loss of unpredictability of its outputs' behaviors. As the degree of unpredictability may be stated as a complexity-related parameter (whose reduction reflects the system "decomplexification"), we can assume that a reduction of nonlinear behavior of one or more physiological measures in a patient with disorder of consciousness may indicate a reduced brain complexity and, consequently, a poor outcome [21]. Therefore, the nonlinear analysis of heart rate and EEG signal may be a promising way to investigate the residual complexity of a severely injured brain as a prerequisite to establish the prognosis of patients. In this venue, we recently investigated the heart rate (HR) nonlinear pattern, through a specific parameter known as approximate entropy (ApEn), in 15 patients with a persistent VS as compared to 15 matched healthy control subjects. The findings showed that mean ApEn values of patients were significantly lower than those recognized in healthy control subjects, thus demonstrating that patients had a reduced unpredictability of fluctuations in HR time series, as a possible sign of their neural networks derangement (Fig. 1). The same was applied later to a combination of ECG and EEG signals in order to confirm that ApEn is able to indicate decreased brain complexity and to discriminate patients with VS from healthy control subjects [22]. Interest findings also come from a recent study, which demonstrated that patients in MCS, as compared to VS/UWS patients, have more complex heart rate variability (HRV) patterns, as estimated through the complexity index (CI) [27]. Moreover, a positive correlation was found between the CI and the connectivity in several brain areas belonging to the central autonomic network and the autonomic nervous system [27]. However, the main limitation of using HR time series to investigate the degree of the neural derangement lies with the possible presence of cardiac comorbidities or other concomitant medical conditions, which can interfere with the analysis. Obviously, all the patients suffering from such concomitant conditions are not the ideal candidates to be selected for prognostic studies on this issue and should be necessarily excluded. This represents a relevant restriction if we consider that a high proportion of patients with a VS/

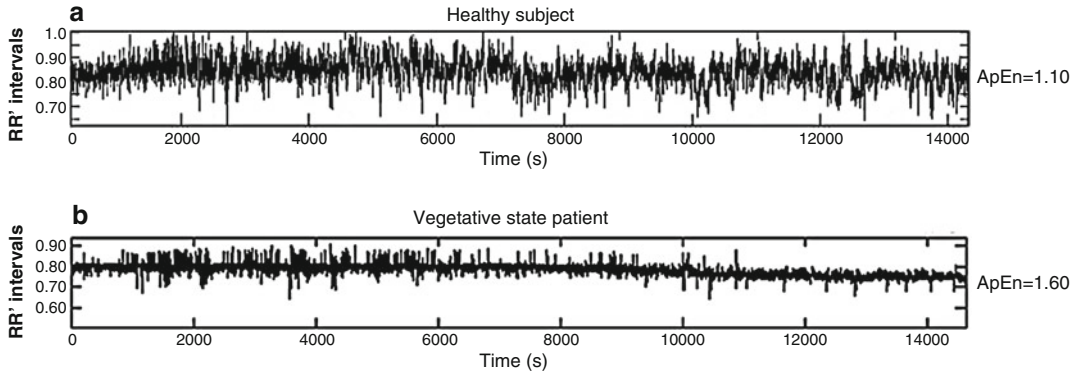

Fig. 1 RR time series in a patient and in the healthy matched control subject

UWS shows a postanoxic disorder of consciousness due to a primitive cardiac arrest: moreover, it is well known that the above patients are those showing the worst prognosis in terms of consciousness recovery, with all the ensuing doubts and controversies about the possibility of late recoveries. Therefore, this might lead to the paradox that the patients who would benefit more from an innovative prognostic approach are the same who cannot be included in prognostic studies. For this reason, much attention has been recently paid to the EEG (rather to the ECG) nonlinear dynamics as prognostic indicator for recovery: it has been reported that ApEn, when applied to EEG time series analysis, has a strong discriminative and prognostic validity as it is able to discriminate patients from healthy controls and correlate significantly with the extent of recovery or the persistence of a condition of VS/UWS [28].

In the same venue, other recent studies, focusing on the relevance of the brain-heart research in prognostic studies on disorders of consciousness, investigated the occurrence of stereotyped cardiac and autonomic changes associated with the recovery of sustained focused attention in severely brain-injured patients. Particular attention has been paid to the phenomena of anticipatory bradycardia and pupillary dilatation, which seem to precede attentional task performances, and may be of help in discriminating even minimal attentional efforts in apparently behaviorally unresponsive patients [29]. Stereotyped cardiac responses, including anticipatory bradycardia, have been recently assessed in a patient with a diagnosis of posttraumatic persistent minimally conscious state, as a consequence of a severe closed head injury following a blunt trauma to the right frontal lobe occurred 6 years earlier. The patient underwent a stimulation protocol based on the implantation of deep brain stimulation (DBS) electrodes in the anterior intralaminar thalamic nuclei, which resulted in a marked improvement in behavioral responsiveness. The improvement was explained by considering the hypothesis that DBS could have partially reversed the depressed cerebral global metabolism previously measured in the patient through fluorodeoxyglucose positron emission tomography (FDG-PET) [29]. What's of note here is that the arousal improvement, most likely due to DBS, was associated with consistently produced marked changes in heart rate and audible modulations of heart rhythm during interactions with the patient. Specifically, a nearly 50% increase in heart rate was detected and interpreted as the result of an increase in cardiac output demand in order to meet the progressively increasing cerebral metabolic rates. Moreover, the above pattern was occasionally reversed, with audible signs of cardiac deceleration being detected, when the patient was engaged in cognitive tasks requiring attentional efforts. This finding, although confined to a single subject and deserving further confirmation, sheds light on the possibility of indirectly monitoring the cerebral demand of patients during recovery of consciousness by easily tracking their patterns of

heart rate variation. This would be another opportunity to use the heart window as a prognostic indicator in disorders of consciousness [29].

Conclusions

The assessment of the brain-heart axis in patients with a disorder of consciousness, as a result of a severe acquired brain injury, may have multiple implications from a prognostic and a therapeutic perspective. First, a better understanding of the mutual interactions which occur when the brain and the heart are, respectively, damaged may allow us to characterize the mechanisms of myocardial injury following a primitive damage and, conversely, the effects of an impaired cardiac performance on the brain. This may contribute to avoid the occurrence of any secondary damage, which frequently occurs in the minutes to months following the primary injury, through the development of biochemical and metabolic changes and the activation of inflammatory and immune processes [30]. Moreover, the heart window may represent an easily accessible way to investigate the residual complexity of the interconnected brain networks, which are responsible for the consciousness recovery. Quantifying the heart nonlinear dynamics may improve our ability to discriminate the patients who are more likely to recover, even some months or years after the cerebral injury, from those whose chances for recovery are extremely poor. This might allow us to overcome the most relevant difficulty we have when establishing a prognosis in patients with a disorders of consciousness, which lies with our actual inability to localize the consciousness into the brain within well-established brain areas or networks.

Cross-References

- Brain-Heart Afferent-Efferent Traffic
- Brain-Heart Communication
- Genetic Determinants Affecting the Relationship Between the Autonomic Nervous System and Sudden Death
- Heart Activity and Cognition

References

1. Pistoia F, Sacco S, Franceschini M, Sarà M, Pistarini C, Cazzulani B, Simonelli I, Pasqualetti P, Carolei A. Comorbidities: a key issue in patients with disorders of consciousness. J Neurotrauma. 2015;315(32):682–8.
2. Samuels MA. The brain-heart connection. Circulation. 2007;116(1):77–84.
3. Plum F, Posner JB. The diagnosis of stupor and coma. Contemp Neurol Ser. 1972;10:1–286.
4. The Multi-Society Task Force on PVS. Medical aspects of the persistent vegetative state: first of two parts. N Engl J Med. 1994;1994(330):1499–508.
5. The Multi-Society Task Force on PVS. Medical aspects of the persistent vegetative state: second of two parts. N Engl J Med. 1994;330(22):1572–9.
6. Giacino JT, Ashwal S, Childs N, Cranford R, Jennett B, Katz DI, Kelly JP, Rosenberg JH, Whyte J, Zafonte RD, Zasler ND. The minimally conscious state: definition and diagnostic criteria. Neurology. 2002;58:349–53.
7. Kalmar K, Giacino JT. The JFK coma recovery scale – revised. Neuropsychol Rehabil. 2005;15(3–4):454–60.
8. Lombardi F, Gatta G, Sacco S, Muratori A, Carolei A. The Italian version of the Coma Recovery Scale-Revised (CRS-R). Funct Neurol. 2007;22(1):47–61.
9. Levy ER, McVeigh U, Ramsay AM. Paroxysmal sympathetic hyperactivity (sympathetic storm) in a patient with permanent vegetative state. J Palliat Med. 2011;14 (12):1355–7.
10. Meyfroidt G, Baguley IJ, Menon DK. Paroxysmal sympathetic hyperactivity: the storm after acute brain injury. Lancet Neurol. 2017;16(9):721–9.
11. Finsterer J, Wahbi K. CNS-disease affecting the heart: brain-heart disorders. J Neurol Sci. 2014;345 (1–2):8–14.
12. Tahsili-Fahadan P, Geocadin RG. Heart-brain axis: effects of neurologic injury on cardiovascular function. Circ Res. 2017;120(3):559–72.
13. Murthy SB, Shah S, Venkatasubba Rao CP, Suarez JI, Bershad EM. Clinical characteristics of myocardial stunning in acute stroke. J Clin Neurosci. 2014;21 (8):1279–82.
14. Daniele O, Caravaglios G, Fierro B, Natalè E. Stroke and cardiac arrhythmias. J Stroke Cerebrovasc Dis. 2002;11(1):28–33.
15. Woolf PD, Hamill RW, Lee LA, Cox C, McDonald JV. The predictive value of catecholamines in assessing outcome in traumatic brain injury. J Neurosurg. 1987;66(6):875–82.
16. Hamill RW, Woolf PD, McDonald JV, Lee LA, Kelly M. Catecholamines predict outcome in traumatic brain injury. Ann Neurol. 1987;21(5):438–43.
17. El-Menyar A, Goyal A, Latifi R, Al-Thani H, Frishman W. Brain-heart interactions in traumatic brain injury. Cardiol Rev. 2017;25(6):279–88.
18. Patel MB, McKenna JW, Alvarez JM, Sugiura A, Jenkins JM, Guillamondegui OD, Pandharipande PP. Decreasing adrenergic or sympathetic hyperactivity after severe traumatic brain injury using propranolol

and clonidine (DASH after TBI study): study protocol for a randomized controlled trial. Trials. 2012;13:177. https://doi.org/10.1186/1745-6215-13-177.
19. Gao L, Smielewski P, Czosnyka M, Ercole A. Early asymmetric cardio-cerebral causality and outcome after severe traumatic brain injury. J Neurotrauma. 2017;34(19):2743–52.
20. Gao L, Smielewski P, Czosnyka M, Ercole A. Cerebrovascular signal complexity six hours after intensive care unit admission correlates with outcome after severe traumatic brain injury. J Neurotrauma. 2016;33 (22):2011–8.
21. Sarà M, Sebastiano F, Sacco S, Pistoia F, Onorati P, Albertini A, Carolei A. Heart rate non linear dynamics in patients with persistent vegetative state: a preliminary report. Brain Inj. 2008;22:33–7.
22. Sarà M, Pistoia F. Complexity loss in physiological time series of patients in vegetative state: a pilot study. Nonlinear Dynamics Psychol Life Sci. 2010;14:1–13.
23. Sarà M, Pistoia F. Defining consciousness: lessons from patients and modern techniques. J Neurotrauma. 2010;27:771–3.
24. Sarà M, Onorati P, Albertini G, Pistoia F. Consciousness: no matter what is, no matter where is – an edge shot approach. J Policy Pract Intellect Disabil. 2010;7: 231–2.
25. Daley V. Emergent phenomena and complexity. In: Brooks R, Maes P, editors. Artificial life IV, Proceedings of the Fourth International Workshop on the Synthesis and Simulation of Living Systems. Cambridge, MA: The MIT Press; 1994.
26. Laureys S. The neural correlate of (un)awareness: lessons from the vegetative state. Trends Cogn Sci. 2005;9(12):556–9.
27. Riganello F, Larroque SK, Bahri MA, Heine L, Martial C, Carrière M, Charland-Verville V, Aubinet C, Vanhaudenhuyse A, Chatelle C, Laureys S, Di Perri C. A heartbeat away from consciousness: heart rate variability entropy can discriminate disorders of consciousness and is correlated with resting-state fMRI brain connectivity of the central autonomic network. Front Neurol. 2018;9:769.
28. Sarà M, Pistoia F, Pasqualetti P, Sebastiano F, Onorati P, Rossini PM. Functional isolation within the cerebral cortex in the vegetative state: a nonlinear method to predict clinical outcomes. Neurorehabil Neural Repair. 2011;25(1):35–42.
29. Schiff ND. Recovery of consciousness after severe brain injury: the role of arousal regulation mechanisms and some speculation on the heart-brain interface. Cleve Clin J Med. 2010;77(Suppl 3):S27–33.
30. Degan D, Ornello R, Tiseo C, Carolei A, Sacco S, Pistoia F. The role of inflammation in neurological disorders. Curr Pharm Des. 2018;24(14):1485–501.

Epilepsy and Cardiovascular Function 30

Seizures and Antiepileptic Drugs Effects

Raffaele Manni, Gianpaolo Toscano, and Michele Terzaghi

Contents

Abstract

Epilepsy is a chronic neurological disorder, characterized by predisposition to recurrent seizures. Epilepsy patients show an increased mortality rate, and cardiovascular disease is a significant cause of death.

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*,
https://doi.org/10.1007/978-3-030-28008-6_30

The interrelationship between epilepsy and hearth is complex and many physiopathological aspects still remain unclear. Epilepsy may induce both acute and chronic cardiac changes.

The Central Autonomic Network (CAN) includes cortical, subcortical, hypothalamic, and subthalamic regions which control the activity of preganglionic sympathetic and parasympathetic neurons; activation or deactivation of CAN may be responsible for cardiac changes related to seizures. Acute cardiac effects of seizures include ictal tachycardia, ictal bradycardia syndrome (including bradycardia and asystole), postictal asystole, postictal atrial, and ventricular fibrillation; periictal QT changes, cardiac ischemia, and acute stress cardiomyopathy are also described.

Chronic cardiac changes include reduced interictal heart rate variability and QT interval modifications. Both acute and chronic factors may be involved in the pathogenesis of SUDEP.

Many drugs, i.e., Phenitoin, Carbamazepine, Lamotrigine, Lacosamide, have been associated with cardiac side effects. Levetiracetam, Valproic Acid, and other AEDs are relatively free of any untoward cardiac effect.

Keywords

Epilepsy · Epilepsy and heart · Cardiovascular comorbidity · SUDEP · AEDs · Ictal bradycardia · Ictal tachycardia · Ictal asystole · Heart rate variability

Introduction

Epilepsy is a chronic neurological disorder characterized by predisposition to recurrent seizures [1]. Epidemiological studies have reported for epilepsy patients an increased mortality, compared with general population, and cardiovascular disease is a significant cause of death. The association between epilepsy and cardiovascular morbidity and mortality is not clearly defined; people with epilepsy may report more cardiovascular disease than people without epilepsy because of behavioral risk factors, genetic predisposition, seizure-related damage to the heart, or medication effect. Epilepsy, antiepileptic drugs (AEDs), and cardiac arrhythmias may be all involved in the pathogenesis of Sudden Unexpected Death in Epilepsy (SUDEP) in such patients [2].

The relation between epilepsy and heart is complex and reciprocal. True epileptic seizures could occur in the course of a syncopal attack caused by a cardiac arrhythmia, but also epileptic seizures could provoke severe cardiac arrhythmias [3]. Epilepsy is frequently associated with ictal tachycardia or bradycardia, which sometimes precedes the onset of seizures [4], suggesting an important role of brain in cardiac autonomic control. The peri-ictal changes can lead to short term alteration of cardiac functions in patients with seizures, while long lasting epilepsy may lead to a chronic dysfunction of the autonomic nervous system [5].

Since many AEDs may exert effects on heart, the choice of AEDs should be accurately evaluated based on patient profile and the cardiovascular risk.

Central Control of Cardiac Function

The autonomic nervous system is fundamental for body homeostasis. Cardiac control results from integration between parasympathetic and sympathetic reflex centers; medullary reflexes are then influenced by cerebral cortex [5].

Parasympathetic output travels from the medullary nuclei DMN (Dorsal Motor Nucleus) and NA (Nucleus Ambiguus), through the vagus nerve. According to the "polyvagal theory," NA can be considered the origin of the more recently phylogenetically developed "smart" vagus, reflecting the vagal phasic output of the heart, while the DMN is part of the more primitive "vegetative" vagus, showing only more tonic effects on heart rate [6]. Vagal efferent activity causes a slowing of heart rate, a depression of left ventricular contractility, and a reduction of the ventricular conduction system.

The sympathetic output to the heart is mediated by preganglionic neurons from the intermediolateral column of the spinal cord, extending from the first through fifth thoracic segments [4], resulting in an increased automatism of the sinus node, increase in atrioventricular conduction and ventricular excitability and contractility.

Visceromotor, neuroendocrine, and behavioral responses are mediated through a Central Autonomic Network (CAN) which controls the activity of preganglionic sympathetic and parasympathetic neurons, but also neuroendocrine, respiratory, and sphincter neurons. The central autonomic network includes the insular cortex, anterior cingulate cortex, amygdala, hypothalamus, periaqueductal gray, parabrachial nucleus, nucleus of the solitary tract, ventrolateral reticular formation of the medulla, and medullary raphe [7].

Both the insular and infralimbic cortices have been implicated as critical sites for the

generation of autonomic or cardiovascular responses [8]. In the rat, the stimulation of caudal posterior insular cortex generates increases in heart rate and blood pressure, while the same stimula applied on rostral posterior insula results in decreases in heart rate and blood pressure [9]. The stimulation of infralimbic cortex is responsible for changes in blood pressure, heart rate, baroreceptor gain, and even an influence on chronic hypertension [10, 11].

The left insula is responsible for parasympathetic cardiovascular effects; damages in this cortex could lead to increased sympathetic tone and thus to a pro-arrhythmic condition [12]. In stimulation studies, electrical stimulation of left insula more often produces bradycardia, while stimulation of right insula tends to produce tachycardia [13].

Effects of Seizures on Heart

Rhythm Disturbances Related to Seizures

During seizures, ictal autonomic changes and thus cardiovascular or pulmonary dysfunction may occur. These cardiorespiratory complications are suspected to be a significant risk factor for Sudden Unexpected Death in Epilepsy (SUDEP) [14]. Sympathetic responses are common during most seizures, causing tachycardia and hypertension. It is also possible that ictal parasympathetic activity or sympathetic inhibition occurs, leading to bradycardia and hypotension.

Seizures of temporal lobe onset are more likely to show heart rate changes compared to extratemporal epilepsies [15, 16]. The occurrence of early ictal heart decrease is mainly reported in seizures of temporal origin [17]. Even though events with increase in heart rate seem to be more influenced by right anatomic structures than by left ones, more recent studies have demonstrated a less evident lateralization of cardiovascular effects [18]. Heart rate changes prior to seizure onset are reported in several studies; recently, suppressed parasympathetic activity at seizure onset has been described, suggesting the possibility of predicting seizures by heart rate variability analysis, shortly before seizure onset [19].

The following cardiac autonomic changes have been reported to occur during seizures [20]:

Ictal tachycardia: Sympathetic responses, and thus tachycardia, are the most common changes occurring during seizures. In patients with epilepsy, ictal discharges that occur in or propagate to anterior cingulate, insular, posterior orbitofrontal, prefrontal cortices, amygdala, and hypothalamus, can lead to increased sympathetic outflows, impacting autonomic function.

- *Ictal sinus tachycardia*: it is usually defined as heart rate exceeding 100 beats per minute (bpm). Ictal tachycardia can be defined as the occurrence of sinus tachycardia either prior to, during or shortly after the onset of ictal discharges. It is the most frequent cardiac dysrhythmia during epileptic seizures, occurring in >90% of seizures and usually without any consequence [21]. Its occurrence ranges from 4% to 41% of subclinical seizures, from 32.9% to 100%, with a weighted average of 71%, of partial seizures (with or without generalization), from 48% to 100% with a weighted average of 64% of generalized seizures.
- *Ictal atrial flutter/fibrillation (AF)*: both ictal and postictal tachyarrhythmias are reported [22].
- *Ventricular fibrillation (VF)*: in all the described cases, VF is preceded by a convulsive seizure [22].

Ictal bradycardia syndrome. Bradycardia and asystole during an epileptic seizure are defined as "ictal bradycardia syndrome" [23].

- *Ictal bradycardia (IB)*: This is considered a rare event, affecting <5% of epileptic patients [18]. A progressive decrease in heart rate from normal sinus rhythm to atrial paced rhythm with subsequent development of AV block has been described. It has been hypothesized that IB could be the consequence of central autonomic network activation, with consequent increase of parasympathetic activity or disruption of sympathetic activity [24, 18]. This syndrome is mainly described in seizures involving the temporal lobe (67%),

but it has also been reported in frontal lobe seizures (33%) involving the insular cortex. The original Oppenheimer hypothesis about left-sided stimulation of insular cortex causing bradycardia and right-sided stimulation causing tachycardia is not completely reflected in clinical practice; no clear lateralizing value of bradycardia in localizing seizure onset has been proved, since ictal bradycardia most often occurs in association with bilateral hemispheric seizure activity.

- *Ictal asystole (IA)*: IA has been reported in 0.22–0.4% of monitored patients, although an underdetection of this phenomenon is possible [25]. Predominantly focal seizures result in asystole; in a minority of cases, asystole appears after a secondary generalization to GTCS. Regarding seizure onset zone and seizure activity at asystole beginning, significant temporal predominance has been detected; in a minority of cases, extratemporal (mostly frontal) localization can be detected. When lateralized, left hemispheric predominance can be observed; however, many cases show bilateral seizure activity. Conflicting opinions are available regarding the overall nature of IA, since some suggest its connection to SUDEP and others argue for its benign nature. It is anyway considered a rare cause of cardiac arrest [26].

IB or IA should be considered in patients with unusual or refractory episodes of syncope. Sudden loss of consciousness, falls, and trauma due to this subtype of complex partial seizures are similar to those observed in nonepileptic vasovagal syncope; this suggests that cerebral hypoperfusion secondary to asystole, rather than seizure-induced stimulation of cortical regions, is responsible for the clinical manifestation of IA or symptomatic IB [27].

Regarding management of patients presenting with ictal asystole and bradycardia, AEDs, and epilepsy surgery may lead to sustained freedom of seizures and ictal syncope; in drug-resistant patients not suitable for epilepsy surgery, pacemaker implantation should be considered (Fig. 1) [28].

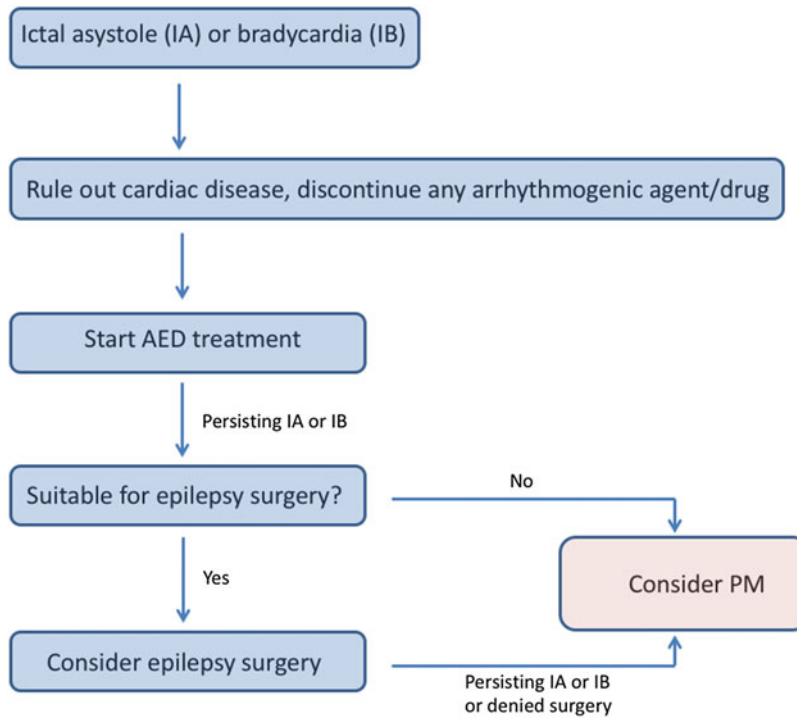

Fig. 1 Clinical algorithm for management of ictal asystole and symptomatic ictal bradycardia. AED: Anti-epileptic drug; PM: Pace-maker. (Modified from Ref. [28])

The following cardiac autonomic changes have been reported to occur after seizures:

Postictal asystole. It is associated with convulsive rather than focal dyscognitive temporal lobe seizures; the association with SUDEP is strong [22]. Prolonged apnea, activating the carotid chemoreceptors, causes arousal and eventually vagally mediated bradycardia or cardiac arrest [29].

Postictal AF and VF. They have been detected in the context of convulsive seizures. Convulsive seizures cause an activation of sympathetic nervous system, which is considered a trigger for both AF and VF. Postictal VF is always classified as (near-)SUDEP [22].

Cardiac Dysregulation Related to Chronic Epilepsy

The association between uncontrolled epilepsy and cardiac dysregulation has gained prominence in recent years. Respiratory depression occurs both during and between seizures, resulting in oxygen desaturation, while heart rate variability is diminished in patients suffering from chronic epilepsy. Permanent alteration in cardiac electrophysiology has been observed in chronic epilepsy, leading to the development of arrhythmias, bradycardia, and asystole [30].

Pathophysiology. In rat models, chronic epilepsy causes electrophysiological changes and thus a secondary cardiac channelopathy. A number of groups of ion channels are expressed in both brain and heart, and are implicated in the dual pathologies of both epilepsy and cardiac dysrhythmias. For example, hyperpolarization-activated cyclic nucleotide-gated (HCN) channels are expressed in both brain, where they promote normal neuronal excitability, and in heart, where they contribute to the maintenance of pacemaker activity in the sinoatrial node. HCN channel genes could be implicated in both pathophysiology of arrhythmias and seizures [31].

Interictal heart rate variability. Epileptic patients show cardiac dysfunction similar to patients at risk of sudden cardiac death in general population; modifications in cardiac electrophysiology induced by epilepsy may be also responsible for SUDEP. Interictal heart rate variability (HRV), determined by cyclical variations in sympathetic and parasympathetic inputs to the SA node, is significantly decreased in patients with chronic temporal lobe epilepsy [32]. HRV is heavily dependent on the vagus nerve, modulating heart rate in response to inspiration, expiration, wake and sleep states, levels of activity. Low HRV may be a risk factor for SUDEP [24].

Other Cardiac Effects of Epilepsy

QT modifications due to epilepsy. Seizures have been associated with QT prolongation and QT shortening [33]. Potential factors leading to periictal QT prolongation are cerebral dysregulation, cardiorespiratory interactions, release of stress hormones during seizures. Data about the role of acquired QTc shortening, induced or not by drugs, in epilepsy patients are ambiguous. Some drugs, such as primidone, have been proved to shorten QTc. Finally, epilepsy patients show an increased QT dispersion (i.e., the difference between the longest and the shortest QT intervals), which is a marker for spatial distribution of cardiac repolarization [34].

Prolongation or shortening of QT intervals as well as increased QT dispersion are established risk factors for life-threatening tachyarrhythmia and sudden cardiac death. QT prolongation can cause a delayed ventricular repolarization, leading to polymorphic ventricular tachycardia and sudden cardiac death. QT shortening is associated with abbreviation of refractory period that, when combined with an increase in dispersion of repolarization, may lead to ventricular fibrillation and sudden cardiac death [24].

Cardiac ischemia. Rarely, individuals with underlying coronary artery disease may have significant cardiac ischemia and myocardial infarction during seizures, due to physiologic stress and adrenergic surge associated with a seizure [35].

Cardiomyopathy. Stress-induced cardiomyopathy or Takotsubo cardiomyopathy, resulting in transient dilatation of ventricular walls

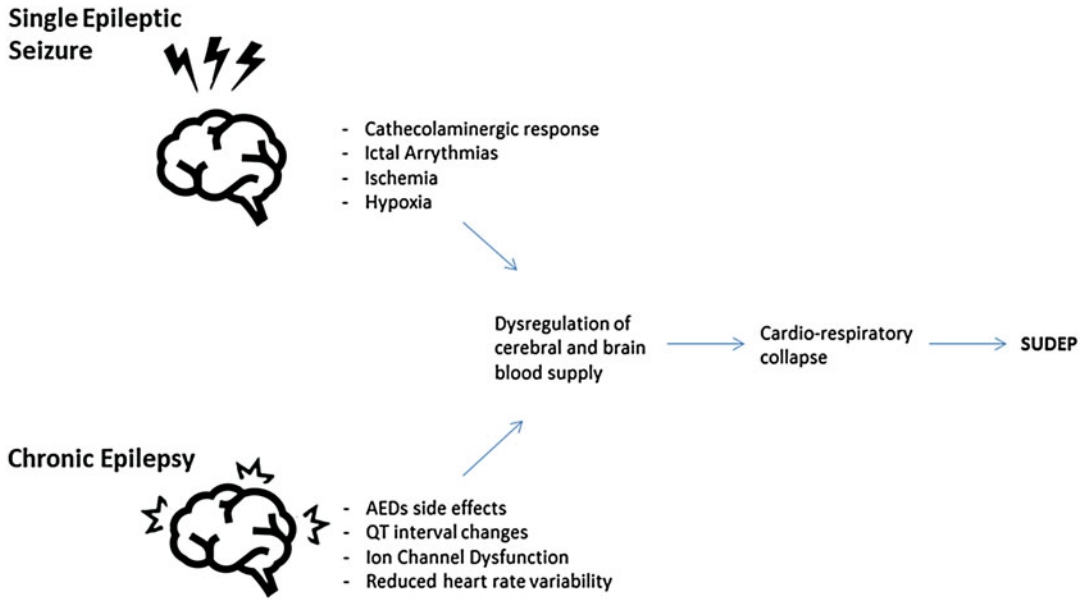

Fig. 2 Brain and heart mechanisms potentially involved in the genesis of SUDEP. (Modified from Ref. [24])

associated with left ventricular dysfunction, have analogously been reported due to high levels of sympathetic activity [36].

SUDEP

SUDEP is defined as "sudden, unexpected, nontraumatic, witnessed or unwitnessed death in patients with epilepsy, with or without evidence for a seizure and excluding documented status epilepticus, in which postmortem examination does not reveal a toxicologic or anatomic cause of death" [37]. SUDEP is a major clinical problem in epileptic patients, especially those with chronic and uncontrolled epilepsy. The role of rhythm disturbances in SUDEP (tachyarrhythmia, bradyarrhythmia, asystole, atrial fibrillation, supraventricular tachycardia, and atrioventricular blocks), commonly reported during ictal, interictal, and postictal phase, is unclear.

SUDEP accounts for 8–17% of deaths in people with epilepsy [38], with an incidence 2–10 per 1000 person years in population-based studies [39].

The pathogenesis of SUDEP is multifactorial, including changes in cardiac functions during seizures, neurogenic pulmonary edema, and respiratory factors (ictal respiratory suppression, central or obstructive apnea) [5]. The role of potential cardiac factors contributing to SUDEP is summarized in Fig. 2.

Effects of AEDs on Heart

AEDs may exert both beneficial and adverse cardiovascular effects [2].

Metabolic effects. Valproic acid (VPA), carbamazepine (CBZ), pregabalin, gabapentin (GBP), vigabatrin (VIG) have been associated with weight gain [40], probably due to interference with leptin release, insulin resistance, hyperinsulinemia, and increased food intake. Nonalcoholic fatty liver disease has been documented in 60.9%, 22.7%, and 8.7% patients on VPA, CBZ, and lamotrigine (LTG) monotherapy, respectively [41]. Weight gain, metabolic syndrome, and nonalcoholic fatty liver disease are linked to increased cardiovascular risk [2].

Enzyme-inducers AEDs (phenytoin (PHT), fenobarbital (PB), primidone, CBZ) enhance P450 cytochrome system activity, leading to increased cholesterol synthesis; enzyme

inhibitors (VPA, LTG, levetiracetam (LEV)) exert the opposite action [42]. For example, significantly increased levels of total and LDL cholesterol and triglycerides have been reported in patients treated with PHT and CBZ, while VPA-treated patients are reported to have lower total, LDL, and HDL-cholesterol compared with nonepileptic patients.

Lifestyle measures and the use of lipid lowering drugs may be useful in patients with epilepsy, since lipid abnormalities are associated with increased cardiovascular risk.

Many AEDs (CBZ, oxarbazepine (OXC), VPA, PHT, PB, LEV, topiramate (TPM)) have been associated with elevated serum homocysteine levels. Since hyperhomocysteinemia is a risk factor for hypercoagulability and vascular diseases and can also enhance seizure activity, screening for homocysteine concentrations before and during antiepileptic therapy is recommended [2]. The mechanism leading to hyperhomocysteinemia may involve depletion of folate, B6 and B12 vitamins; a decrease of cofactor molecules has been outlined for CBZ and PHT, while for VPA the changes are unrelated to the alteration in the levels of cofactors. It is unknown whether AEDs-induced changes on vitamin levels could be translated to a real higher risk of cardiovascular events [2].

Cardiac Rhythm effects. Many AEDs exert their effect by binding electrolyte channels, which could induce effects on cardiac rhythm. PHT, CBZ, LTG, LAC have been associated with cardiac side effects. LEV, VPA, and other AEDs are relatively free of any untoward cardiac effect.

- **Phenytoin**. PHT is an effective drug in the treatment of acute seizures and status epilepticus, with a less sedative effect than benzodiazepines. Serious adverse effects of IV PHT, such as cardiac arrhythmias, hypotension, respiratory arrest, and related deaths, were historically reported.
  PHT is a class IB antiarrhythmic drug; increasing the conduction in myocardial junctions, shortening the duration of action potential in injured cardiac tissue, and raising the threshold of ventricular fibrillation [43], it was used in the past in the treatment of digoxin intoxication and atrial fibrillation. Particularly during rapid intravenus infusion, PHT can lead to AV block and QT prolongation and consequent death of patients [2]. It also induces peripheral vasodilatation and negative inotropic effect, leading to a lowering in blood pressure [44]. Phenytoin preparations contain propylene glycol to increase water solubility, which may cause bradycardia and asystole in toxic dosages. Phosphenytoin is a pro-drug of PHT lacking propylene glycol, but it may cause hypotension and arrhythmia in rapid infusion rates.
  PHT is now considered safe in oral administration; IV administration is considered safe at a maximum infusion rate of 50 mg/min in young patients and 25 mg/min in patients over 50 years old [45].
- **Carbamazepine**. CBZ is a widely diffused AED, used for partial and generalized seizures, trigeminal neuralgia, as a mood stabilizer and for neuropathic pain syndromes. Sodium channel inhibition is the primary mechanism of CBZ; this causes reduction of phase 4 of depolarization, affecting the automaticity of pacemaker cells of the heart. CBZ may suppress the AV node and aggravate a bradycardia to complete heart block.

  Based on a review of the evidence, CBZ may worsen preexisting heart blocks at low and therapeutic doses may induce de novo AV conduction delay at higher concentrations in otherwise normal-aged subjects [46]. The latter effect is reversible after drug discontinuation. Abrupt withdrawal of CBZ can lead to a decrease in total heart rate variability and predominance of sympathetic activity during sleep [2].
- **Lamotrigine**. No elevated risk of clinically relevant cardiac side effects on LTG treatment is reported. PR interval may be slightly prolonged, especially at high doses of LTG; post-marketing safety surveillance proved this not to be a clinically relevant adverse effect [47]. Lamotrigine exerts an effect neuronal sodium channels within cardiac fibers; as slight sodium channel block tends to shorten action potential duration before affecting the rate

of rise, Lamotrigine may cause a small reduction in QTcF; the clinical consequences of QT shortening are unclear. Lamotrigine overdose has been reported to cause complete hearth block.

– **Lacosamide**. LAC is a new AED with demonstrated efficacy for partial-onset seizures in adults with epilepsy. CBZ, LTG and LAC all inhibit the cardiac voltage-gated sodium channel (SCN5A). In vivo studies showed that lacosamide acts as a cardiac depressant, with decreased systolic left ventricular pressure, transient increases in PR interval, and QRS complex duration [48]. Phase III epilepsy trials and postmarketing studies have observed a dose-dependent increase in PR interval of patients taking lacosamide [49]; this prolongation is within the range caused by moderate doses of LTG, PRG, CBZ and its clinical relevance is unknown. Recent case reports are available about conduction disturbances and arrhythmias associated with lacosamide treatment.

Conclusions/Summary

Epilepsy and AEDs may exert strong effects on cardiovascular function.

Since insular and infralimbic cortices have been implicated as critical sites for the generation of autonomic or cardiovascular responses, seizures of temporal lobe onset are more likely to show heart rate changes compared to extratemporal epilepsies. Ictal tachycardia (sinus or aritmic tachycardia) and ictal bradycardia syndrome have been reported during seizures; postictal asystole and atrial/ventricular fibrillation have been reported following seizures. Other effects of epilepsy include QT modifications, cardiac ischemia, and stress-induced cardiomyopathy.

AEDs influence cardiac function through metabolic and cardiac rhythm effects. The first include weight gain, hypercholesterolemia, hyperomocysteinemia. Effects on heart rhythm include AV block and QT prolongation (PHT) and AV conduction delay (CBZ, LTG, LAC). The knowledge of these side effects could help to tailor the therapy according to patient's characteristic and comorbidities, and to avoid unexpected cardiac side effects.

References

1. Fisher R, van Emde Boas W, Blume W, Elger C, Genton P, Lee P, et al. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau For Epilepsy (IBE). Epilepsia. 2005;46(4):470–2.
2. Katsiki N, Mikhailidis D, Nair D. The effects of antiepileptic drugs on vascular risk factors: a narrative review. Seizure. 2014;23(9):677–84.
3. Jallon P. Epilepsy and the heart. Rev Neurol (Paris). 1997;153(3):173–84.
4. Sevcencu C, Struijk J. Autonomic alterations and cardiac changes in epilepsy. Epilepsia. 2010;51(5):725–37.
5. Jansen K, Lagae L. Cardiac changes in epilepsy. Seizure. 2010;19(8):455–60.
6. Berntson GG, Cacioppo JT, Grossman P. Whither vagal tone. Biol Psychol. 2007;74:295–300.
7. Benarroch E. The central autonomic network: functional organization, dysfunction, and perspective. Mayo Clin Proc. 1993 Oct;68(10):988–1001.
8. Cechetto DF. Cortical control of the autonomic nervous system. Exp Physiol. 2014;99(2):326–31.
9. Yasui Y, Breder CD, Saper CB, Cechetto DF. Autonomic responses and efferent pathways from the insular cortex in the rat. J Comp Neurol. 1991;303(3):355–74.
10. Verberne A, Lewis S, Worland P, Beart P, Jarrott B, Christie M, et al. Medial prefrontal cortical lesions modulate baroreflex sensitivity in the rat. Brain Res. 1987;426(2):243–9.
11. Verberne A. Medullary sympathoexcitatory neurons are inhibited by activation of the medial prefrontal cortex in the rat. Am J Phys. 1996;270(4 Pt 2):R713–9.
12. Oppenheimer SM, Kedem G, Martin WM. Left-insular cortex lesions perturb cardiac autonomic tone in humans. Clin Auton Res. 1996;6(3):131–40.
13. Oppenheimer S, A G GJ, Hachinski V. Cardiovascular effects of human insular cortex stimulation. Neurology. 1992;42(9):1727–32.
14. Kothare SV, Singh K. Cardiorespiratory abnormalities during epileptic seizures. Sleep Med. 2014;15(12):1433–9.
15. Garcia M, D'Giano D, Estellés S, Leiguarda R, Rabinowicz A. Ictal tachycardia: its discriminating potential between temporal and extratemporal seizure foci. Seizure. 2001;10(6):415–9.
16. Leutmezer F, Schernthaner C, Lurger S, Pötzelberger K, Baumgartner C. Electrocardiographic changes at the onset of epileptic seizures. Epilepsia. 2003;44(3):348–54.

17. Galimberti C, Marchioni E, Barzizza F, Manni R, Sartori I, Tartara A. Partial epileptic seizures of different origin variably affect cardiac rhythm. Epilepsia. 1996;37(8):742–7.
18. Serafini A, Gelisse P, Reana V, Crespel A. Cardiac asystole during a cluster of right temporo-parietal seizures. Seizure. 2011;20(2):181–3.
19. Eggleston K, Olin B, Fisher R. Ictal tachycardia: the head–heart connection. Seizure. 2014;23(7):496–505.
20. Moseley B, Wirrel E, Nickels K, Johnson J, Ackerman M, Britton J. Electrocardiographic and oximetric changes during partial complex and generalized seizures. Epilepsy Res. 2011;95:237–45.
21. Allana S, Ahmed H, Shah K, Kelly A. Ictal bradycardia and atrioventricular block: a cardiac manifestation of epilepsy. Oxf Med Case Reports. 2014;2014 (2):33–5.
22. van der Lende M, Surges R, Sander J, Thijs R. Cardiac arrhythmias during or after epileptic seizures. J Neurol Neurosurg Psychiatry. 2016;87(1):69–74.
23. Reeves A, Nollet K, Klass D, Sharbrough F, So E. The ictal bradycardia syndrome. Epilepsia. 1996;37(10):983–7.
24. Velagapudi P, Turagam M, Laurence T, Kocheril A. Cardiac arrhythmias and sudden unexpected death in epilepsy (SUDEP). Pacing Clin Electrophysiol. 2012;35(3):363–70.
25. Tényi D, Gyimesi C, Kupó P, Horváth R, Bóné B, Barsi P, et al. Ictal asystole: a systematic review. Epilepsia. 2017;58(3):356–62.
26. Larsen D, Agmed A. Ictal asystole: a rare cause of cardiac arrest. JAAPA. 2013;26(9):30–2.
27. Ghearing G, Munger T, Jaffe A, Benarroch E, Britton J. Clinical cues for detecting ictal asystole. Clin Auton Res. 2007a;17:221–6.
28. Strzelczyk A, Cenusa M, Bauer S, Hamer H, Mothersill I, Grunwald T, et al. Management and long-term outcome in patients presenting with ictal asystole or bradycardia. Epilepsia. 2011;52(6): 1160–7.
29. Paton j B p, Pickering A, Nalivaiko E. The yin and yang of cardiac autonomic control: vago-sympathetic interactions revisited. Brain Res Brain Res Rev. 2005;49(3):555–65.
30. Ravindran K, Powell K, Todaro M, O'Brien T. The pathophysiology of cardiac dysfunction in epilepsy. Epilepsy Res. 2016;127:19–29.
31. Ludwig A, Budde T, Stieber J, Moosmang S, Wahl C, Holthoff K, et al. Absence epilepsy and sinus dysrhythmia in mice lacking the pacemaker channel HCN2. EMBO J. 2003;22(2):216–24.
32. Tomson T, Ericson M, Ihrman C, Lindblad L. Heart rate variability in patients with epilepsy. Epilepsy Res. 1998;30(1):77–83.
33. Natelson B, Suarez R, Terrence C, Turizo R. Patients with epilepsy who die suddenly have cardiac disease. Arch Neurol. 1998;55:857–60.
34. Neufeld G, Lazar J, Chari G, Kamran H, Akajagbor E, Salciccioli K, et al. Cardiac repolarization indices in epilepsy patients. Cardiology. 2009;114(4):255–60.
35. Chin P, Branch K, Becker K. Myocardial infarction following brief convulsive seizures. Neurology. 2004;63(12):2453–4.
36. Akashi Y, Goldstein D, Barbaro G, Ueyama T. Takotsubo cardiomyopathy: a new form of acute, reversible heart failure. Circulation. 2008;118:2754–62.
37. Nashef L. Sudden unexpected death in epilepsy: terminology and definitions. Epilepsia. 1997;38(suppl 11): S6–8.
38. Tomson T, Nashef L, Ryvlin P. Sudden unexpected death in epilepsy: current knowledge and future directions. Lancet Neurol. 2008;7(11):1021–31.
39. Ficker D, So E, Shen W, Annegers J, O'Brien P, Cascino G, et al. Population-based study of the incidence of sudden unexplained death in epilepsy. Neurology. 1998;51(5):1270–4.
40. Ben-Menachem E. Weight issues for people with epilepsy: a review. Epilepsia. 2007;48(Suppl 9):42–5.
41. Luef G, Rauchenzauner M, Waldmann M, Sturm W, Sandhofer A, Seppi K, et al. Non-alcoholic fatty liver disease (NAFLD), insulin resistance and lipid profile in antiepileptic drug treatment. Epilepsy Res. 2009;86(1):42–7.
42. Lopinto-Khoury C, Mintzer S. Antiepileptic drugs and markers of vascular risk. Curr Treat Options Neurol. 2010;12(4):300–8.
43. York R, Coleridge S. Cardiopulmonary arrest following intravenous phenytoin loading. Am J Emerg Med. 1988;6:255–9.
44. Conn R, Kennedy J, Blackmon J. The hemodynamic effects of diphenylhydantoin. Am Heart J. 1967;73:500–5.
45. Guldiken B, Rémi J, Noachtar S. Cardiovascular adverse effects of phenytoin. J Neurol. 2016;263(5):861–70.
46. Kasarskis E, Kuo C, Berger R, Nelson K. Carbamazepine-induced cardiac dysfunction. Characterization of two distinct clinical syndromes. Arch Intern Med. 1992;152(1):186–91.
47. Dixon R, Alexander S, Brickel N. Effect of lamotrigine on the PR interval in healthy subjects. Br J Clin Pharmacol. 2011;71(6):961–2.
48. Beyreuther B, Freitag J, Heers C. Lacosamide: a review of preclinical properties. CNS Drug Rev. 2007;13:21–42.
49. Rosenfeld W, Fountain N, Kaubrys G. lacosamide: an interim evaluation of long-term safety and efficacy as oral adjunctive therapy in subjects with partial-onset seizures. Epilepsia. 2007;48(Suppl. 6):318.

Headache and the Heart

31

A Controversial Relationship

Cristina Tassorelli, Roberto De Icco, Daniele Martinelli, and Michele Viana

Contents

Abstract

The general term headache indicates a pain localized in the cranial region, associated with a variety of different signs and symptoms. A headache can be a primary condition, when no organic cause can be identified, or it can represent symptom of an underlying condition, being in this latter case defined as secondary.

In this chapter the intricate relation between the heart and brain is depicted in relation to the different types of existing headaches, based on

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*,
https://doi.org/10.1007/978-3-030-28008-6_31

the most recent diagnostic criteria and available scientific evidence.

Primary headaches, with migraine in particular, represent a risk factor for heart diseases and heart defects: the decision on how to treat these conditions, such as patent foramen ovale, will be therefore properly addressed. Moreover, as different categories of pharmacological treatments for migraine prevention derive from the cardiovascular pharmacopeia, the rationale behind their use will be further elucidated. Finally, among secondary headaches, we will describe the causative relationship due to hypertension, cervical artery dissection, and angina pectoris.

The pathways leading to the relationship between the heart and brain are multifold in number and nature: this chapter highlights the variety of connections between them through the experience in the headache field.

Keywords

Primary headaches · Migraine · Cluster headache · Nytroglicerin · Heart defects · Secondary headaches · Hypertension · Cervical artery dissection · Angina cephalgia

Generalities on Headache: Classification

Headache is a general term that indicates pain localized in the cranial region. Several types of headaches are nowadays recognized and identified with precise diagnostic criteria in the International Classification of Headache Disorders (ICHD), recently published in its 3rd edition [1].

Classifications are extremely important because they offer a common framework on which to conceptualize knowledge and research and, at the same time, ensure standardized communication among the scientific community.

ICHD subdivides headaches into "primary," when no organic cause can be identified and the headache is actually the disease, and "secondary," where headache is a symptom of an underlying condition.

Primary headaches are represented by migraine, tension-type headache, trigeminal autonomic cephalalgias, and other primary headache disorders.

Table 1 Diagnostic criteria of the International Classification of Headache Disorders for "migraine without aura" (2018)

A. At least five attacks fulfilling criteria B–D
B. Headache attacks lasting 4–72 h (when untreated or unsuccessfully treated)
C. Headache has at least two of the following four characteristics:
1. Unilateral location
2. Pulsating quality
3. Moderate or severe pain intensity
4. Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
D. During headache at least one of the following:
1. Nausea and/or vomiting
2. Photophobia and phonophobia
E. Not better accounted for by another ICHD-3 diagnosis

Migraine is a common disabling condition with an estimated 1-year prevalence in the general population that varies from 12% to 42% [2]. Many epidemiological studies have documented its high prevalence and socioeconomic and personal impacts. In the *Global Burden of Disease Survey 2010* (GBD2010), it was ranked as the third most prevalent disorder in the world. In the *2015 edition of the same survey* (GBD2015), it was ranked third-highest cause of disability worldwide in both males and females under the age of 50 years.

Migraine has two major types: *migraine without aura* is a clinical syndrome characterized by headache with specific features and associated symptoms (see Table 1), and *migraine with aura* is primarily characterized by the occurrence of transient focal neurological symptoms that usually precede or sometimes accompany the headache (see Table 2).

Relationship Between Migraine and the Heart

The association between migraine and cardiovascular events has been a field of ongoing interest, but the data available do not allow, so far, any strong conclusive indications.

Migraine headache, especially migraine with aura, has been linked to cerebral hypoperfusion,

Table 2 Diagnostic criteria of the International Classification of Headache Disorders for "migraine with aura" (2018)

A. At least two attacks fulfilling criteria B and C
B. One or more of the following fully reversible aura symptoms:
1. Visual
2. Sensory
3. Speech and/or language
4. Motor
5. Brainstem
6. Retinal
C. At least three of the following six characteristics:
1. At least one aura symptom spreads gradually over ≥5 min
2. Two or more aura symptoms occur in succession
3. Each individual aura symptom lasts 5–60 min
4. At least one aura symptom is unilateral
5. At least one aura symptom is positive
6. The aura is accompanied, or followed within 60 min, by headache
D. Not better accounted for by another ICHD-3 diagnosis

systemic vasculopathy, endothelial dysfunction, and a hypercoagulable state. It is hypothesized that these factors may increase the risk of various adverse cardiovascular and cerebrovascular events. However, studies that investigated an association between migraine and cardiovascular and cerebrovascular outcomes demonstrated inconsistent associations [3].

A recent large meta-analysis involving 16 observational cohort studies including over 1.1 million subjects and an extended follow-up duration up to 26 years showed that subjects with migraine are at increased risk of myocardial infarction at a follow-up of 8.8 years [4]. However, no apparent influence emerges in the meta-analysis as regards the type of migraine (with/without aura) or gender.

In a previous analysis, Sacco et al. reported an increased risk of myocardial infarction in migraine with aura [5] but no increased risk of ischemic heart disease and coronary revascularization. It must be noted that the Authors reported quite a high variability of data in the evaluation of the different studies.

Taken these findings altogether, it seems reasonable to state that in general there is some signal that migraine sufferers may be more exposed to coronary heart disease. One piece of the picture may be represented by the increased number of risk factors for migraineurs. Indeed, the GEM (Genetic Epidemiology of Migraine) population-based study showed that compared to controls, migraineurs have a higher number of risk factors for myocardial infarction: they are more likely to smoke, to have a parental history of early myocardial infarction, an unfavorable cholesterol profile and elevated blood pressure.

Contrarily to what has been proposed for stroke, where evidence is in favor of an increased risk for women suffering from migraine with aura using combined hormonal contraception, no evidence was found on risk of myocardial infarction [6].

Patent Foramen Ovale

Multiple studies have reported a significant association between migraine, in particular migraine with aura, and the presence of a patent foramen ovale (PFO) [7]. The foramen ovale serves the purpose of physiologic right-to-left shunting of blood circulation until the pulmonary circulation is established after birth. It remains patent after birth in approximately 20% of the general population, while this percentage rises from 41% to 48% in patients with migraine with aura [8]. Reports suggesting an association of PFO and migraine have been published after observational studies in migraine patients undergoing device closure of PFO and experiencing an alleviation of migraine symptoms after the procedure. With migraine without aura, the association with PFO seems to be weaker [9].

Several pathophysiological mechanisms may be invoked to explain the association of PFO with migraine with aura: platelet activation, aggregation, and embolism [10] and paradoxical gas embolism across atrial shunts (with the severity of an episode of migraine related to the amount of bubbles crossing the defect) [11]. A genetic mechanism has also been proposed, with dominant inheritance of atrial shunts, linked to inheritance of migraine with aura in some families that

may be explained by the common development of endocardium, endothelium, and platelets.

It must be however noted that, at variance with the first positive results obtained in open or retrospective studies, several controlled studies aimed at evaluating the efficacy of PFO closure on migraine disease failed to reach the primary endpoints, although they report a partial improvement [12] or were totally negative [13]; consequently up to now, FDA has not approved closure devices for treating migraine.

Other Heart Defects

An *atrial septal aneurysm* (ASA) consists of redundant atrial septal tissue bulging into the right or left atrium. A high prevalence of isolated ASA was described in a small group of patients with migraine with aura without cerebral and cardiovascular disease; the probability of having ASA seems to be higher in patients with ischemic stroke, PFO, and comorbid migraine [14].

Mitral valve prolapse (MVP) is definitely associated with migraine as suggested by convincing evidence in favor of a bilateral relationship: subjects with migraine bear MVP more frequently than the general population, and subjects with MVP prolapse more frequently suffer from migraine [15].

The shared pathogenetic mechanisms are elusive; thus it seems reasonable to hypothesize a role for serotonin release by platelets that are damaged by the MVP regurgitant jet. Furthermore, MVP may be a source of small emboli due to myxomatous degeneration of the prolapsing mitral valve leaflets, which in turn may cause platelet aggregation. The subsequent thrombi formation may therefore result in transient cerebral ischemia [16].

The Human Migraine Model: Nitroglycerin

Another area of contact of migraine and the heart is nitroglycerin, a well-known vasodilator used for coronary heart disease. Researchers in the headache field were attracted by nitroglycerin (NTG) headache attacks that bear migraine-like features.

Sicuteri first described a segregation in the headache response to NTG in healthy subjects and migraineurs [17]. Healthy controls develop an immediate, low-intensity headache that resolves within a few minutes; at variance subjects with migraine develop a headache attack with migraine-like features after several minutes or hours and may have a long duration. The specificity of the headache response has been tested on large population [18].

A striking similarity exists between spontaneous migraine attacks and NTG-induced headache attacks in migraineurs: NTG-induced headache fulfils the IHS diagnostic criteria for migraine in a very high percentage of migraineurs [18], responds to triptans, and is prevented by migraine-preventive drug valproate.

Several studies from our group, confirmed and expanded by other groups, have shown that the mechanism linking a vasodilating drug like NTG to migraine is much more complex than the simple effect on the endothelial cells as it involves different targets: multiple lines of evidence suggest that NTG generates peripheral and central sensitization via a cascade of events that encompass the accumulation of nitric oxide and the activation of ion channels in the brain, the activation of the inflammatory cascade, and the release of neurotransmitters and vasoactive peptides (i.e., calcitonin gene-related peptide) in the meninges and in central trigeminal areas [19].

Preventive Drugs for Migraine

Patients affected by frequent migraine attacks may need preventive treatment in order to reduce the frequency and severity of attacks. A number of oral pharmacological treatments have been evaluated and are recommended for migraine prevention [20, 21]. Among them we find beta-blockers (propranolol, metoprolol), calcium antagonist (flunarizine), and angiotensin inhibitors. These substances belong to pharmacologically unrelated drug which seems to suggest that headache

prevention is due to the reduction in blood pressure per se [22]. Data from the literature at variance suggest several possible mechanisms of actions that are analyzed in the following paragraphs.

Beta-Blockers

ß-Adrenergic blockers (ß-blockers) are competitive inhibitors of ß-receptors, but they differ with regard to receptor binding (i.e., ß1-selectivity and partial agonistic activity) and pharmacokinetic properties. ß-Blockers with intrinsic sympathomimetic activity (e.g., acebutolol, alprenolol, oxprenolol, and pindolol) are not effective for migraine prevention. Clinical studies support instead the efficacy of propranolol, timolol, and metoprolol in migraine-preventive treatment [23]. Atenolol and nadolol also have a moderate effect in reducing migraine attack frequency.

The mechanisms of action of ß-blockers in migraine prevention are not completely understood, although it seems that the most relevant activity in this regard is the inhibition of $ß_1$-mediated effects. Indeed, blockade of $ß_1$ receptors may inhibit noradrenaline release and the activity of tyrosine hydroxylase, the rate-limiting synthetic step. Propranolol reduces the neuronal firing rate of noradrenergic neurons of the locus coeruleus and the firing rate of periaqueductal grey matter (PAG) neurons via a GABA-mediated action. Recent findings in an animal model of trigeminovascular activation showed that propranolol exerts its prophylactic action, at least in part, by interfering with the chronic sensitization processes in the rostral ventromedial medulla and locus coeruleus and by counteracting the facilitation of trigeminovascular transmission within the trigeminocervical complex [24].

It is also possible that some ß-blockers interact with the serotonergic system, a key player in the pathophysiology of migraine, by blocking 5-HT_{2C} and 5-HT_{2B} receptors [25]. Furthermore, propranolol inhibits nitric oxide production by blocking inducible nitric oxide synthase (NOS). Propranolol also inhibits kainite-induced currents and is synergistic with N-methyl-D-aspartate blockers, which reduce neuronal activity and have membrane-stabilizing properties and may therefore attenuate cortical excitability.

Cortical spreading depression (CSD) could also represent a target for ß-blockers in migraine. In an experimental model, it was observed that treatment with propranolol suppressed retinal spreading depression. Moreover, treatment with propranolol blocked CSD in rats, without altering regional cerebral blood flow and systemic arterial blood pressure [26].

Finally, it has also been hypothesized that ß-blockers exert some of their therapeutic effects in migraine through an action at the ventroposteromedial thalamic nucleus, which represents a relay of trigeminal sensory input to the primary somatosensory cortex.

Calcium Antagonists

Several calcium antagonists (Ca-antagonists) are used for migraine prevention since the 1980s. Flunarizine is the best studied compound and licensed for this indication in many countries (although it is not available in the USA). Verapamil and the antihistaminergic drug cinnarizine are alternatives (e.g., in refractory migraine cases or when flunarizine is not available) that also act at calcium channels. However, both latter drugs are off-label for migraine treatment, and the evidence in terms of efficacy is scarce.

As regards the potential mechanism of action of these ca-antagonists in migraine, flunarizine is a nonselective calcium antagonist, which also blocks voltage-gated sodium channels [27]. Via these two mechanisms, flunarizine may reduce neuronal excitability and normalize cortical hyperexcitability in migraine. Furthermore, flunarizine acts as a dopamine antagonist on D2 receptors, and dopamine has been invoked as an important mediator in migraine pathophysiology. Finally, flunarizine attenuates in terms of number and duration of the waves of cortical spreading depression in the animal laboratory setting and alleviates mitochondrial injury caused by cortical spreading depression waves [28].

ACE Inhibitors and Angiotensin Receptor Blockers

Lisinopril, an angiotensin-converting enzyme inhibitor (ACE-I), has been shown to be prophylactically effective at a dose of 10 mg twice daily in a small, double-blind, placebo-controlled crossover trial [29]. ACE-Is modulate vasoreactivity, alter sympathetic tone, and promote degradation of proinflammatory factors, such as substance P, enkephalin, and bradykinin. An additional mechanism of action for ACE-I in migraine could be modulation of the endogenous opioid system. Indeed the effect of this class of drugs has been reported to be blocked by antagonizing opioid receptors. In addition to its traditional role as a circulating hormone, angiotensin is also involved in local functions through activity of tissue renin-angiotensin system that occur in many organs, including the brain (both systemic and presumptive neurally derived angiotensin). Angiotensin II receptors are located on neurones, astrocytes, and endothelium, and the hormonal effect is mainly mediated through the angiotensin II type 1 receptor. Brain angiotensin II type 2 receptors are located in areas predominantly involved in sensory processing, but their function remains to be clarified [30]. Renin-angiotensin system is present in the brain where it modulates cerebrovascular flow and influences fluid and electrolyte homeostasis, autonomic pathways, and neuroendocrine systems. Angiotensin II modulates potassium channels and calcium activity in cells, increases the concentration of dopamine and of the main serotonin metabolite, 5-hydroxyindoleacetic acid, and activates nuclear factor kB, which is associated with increased expression of inducible nitric oxide synthase [31].

Candesartan is an angiotensin II receptor that showed an efficacy comparable to propranolol in migraine prevention. By blocking angiotensin receptor, candesartan provokes several effects that may be relevant to migraine, such as direct vasoconstriction, increased sympathetic discharge, and adrenal medullary catecholamine release.

Taken together the multiple biological activities of cardiovascular drugs that proved effective in migraine prophylaxis suggest that, rather than purely vascular, their mechanism of action may involve neuronal and astrocytic activities. A possible explanation may reside in a shared genetic comorbidity at the basis of the association of migraine with cardiovascular disease and the beneficial effect of "cardiovascular" drugs. In this frame, it is worth mentioning that in non-Caucasian population, an increased risk of migraine with aura was detected in subjects bearing the methylenetetrahydrofolate reductase 677C > T polymorphism with migraine, while the ACE II genotype was protective against both migraine with and without aura [32].

The importance of these polymorphisms in explaining the link between migraine and cardiovascular disease remains uncertain, and specifically targeted studies are necessary to address the issue.

Cluster Headache

Cluster headache (CH) is an infrequent primary headache belonging to the group of trigeminal autonomic cephalalgias whose attacks are characterized by the strict unilaterality of pain and the activation of the trigeminal autonomic reflex leading to ipsilateral lacrimation, rhinorrhea, partial ptosis, miosis, and conjunctival injection, as manifestation of increased parasympathetic and diminished sympathetic outflow to the cranial anatomy.

Several lines of evidence suggest that cardiac autonomic control is subclinically affected in CH sufferers. Several studies suggested an association between CH and obstructive sleep apnea [33], which is a risk factor for developing hypertension [34]. Furthermore, CH patients present a dysregulated systemic BP in the form of increased variability and an attenuation of the normal decrease in nocturnal blood pressure, known as nocturnal dipping [35]. This seems important since the absence/reduction of nocturnal dipping is a strong and independent predictor of cardiovascular risk. Indeed, in normotensive patients, the prevalence of non-dippers has been estimated to range from 10% to 20% [36], while it is as high as 84% in CH patients.

It is also true that cardiovascular risk factors, namely, cigarette smoking, seem to be more prevalent in these patients [37]. In analogy to migraine, CH-like attacks can be brought about by NTG. Ekbom described that the CH attack typically occurred 30–50 min after administration of the NTG [38]. Another similarity and link with cardiovascular function is the effect of a calcium antagonist, in this case verapamil, in the prevention of CH attacks. Once again, the mechanism involved for the biological activity of verapamil in CH is not the purely vascular but rather seems linked to the modulation of hypothalamic activity. The hypothalamus plays a leading role in the pathophysiology of CH [39] possibly through destabilization of descending antinociceptive control [40]. Of course, the hypothalamus is also a central control hub for the autonomic function.

Secondary Headache Associated with a Cardiovascular Disorder

Hypertension

Elevated blood pressure (BP) and headache have long been linked in the medical literature, although data on association are conflicting. International guidelines stipulate that headache should be attributed to elevated BP if the systolic BP (SBP) rises rapidly to 180 mmHg or higher, or if the diastolic BP rises to 120 mmHg or higher, and if the headache resolves with normalization of BP [1] (Table 3). This guideline statement is supported by ambulatory BP-monitoring studies in hypertensive patients, which demonstrate that, in general, routine headache is not preceded by atypical fluctuations in BP [41]. Left unclear by these data is the role of elevated BP in headaches of sufficient intensity to warrant a visit to a medical provider, a not uncommon scenario, and the question of how to manage patients with both an acute headache, such as migraine, and elevated BP.

A recent study that analyzed two distinct and large datasets regarding patients seeking medical help at the emergency department because of headache or arterial hypertension found that (i) elevated BP is common among patients who present with a chief complaint of headache; (ii) patients with headache are more likely to have elevated BP than are patients with other complaints; and (iii) among patients who presented with migraine and an elevated BP, there is no correlation between improvement in headache and improvement in systolic or diastolic blood pressure [42].

Therefore, if the association hypertension-headache seems in fact genuine, its directionality is not clear. Indeed, one may actually hypothesize that elevated blood pressure is causing headache, but it is just as likely that headache is causing elevated blood pressure.

Table 3 Diagnostic criteria of the International Classification of Headache Disorders for "headache attributed to arterial hypertension" (2018)

A. Any headache fulfilling criterion C
B. Hypertension, with systolic pressure $\geq$ 180 mmHg and/or diastolic pressure $\geq$ 120 mmHg, has been demonstrated
C. Evidence of causation demonstrated by either or both of the following:
1. Headache has developed in temporal relation to the onset of hypertension
2. Either or both of the following:
a) Headache has significantly worsened in parallel with worsening hypertension
b) Headache has significantly improved in parallel with improvement in hypertension
D. Not better accounted for by another ICHD-3 diagnosis

Spontaneous Cervical Artery Dissection

Cervical artery dissection is a serious but treatable cause of headache that may be misdiagnosed as recent onset migraine. Risk factors include neck trauma, recent infection, family history, smoking, hypertension, oral contraceptives, and connective tissue disease [43].

Most of the times, patients cannot recall an injury, and thus the dissection is presumed to be spontaneous. Spontaneous cervical artery dissection typically occurs in young adults before 45 years and is a common cause of stroke in the young population [44]. Typical clinical features

include ipsilateral headache preceding an abrupt neurologic deficit. Incomplete Horner syndrome (oculosympathetic paresis without facial anhidrosis) due to disruption of branches of the superior cervical ganglion is also common [45]. The diagnostic criteria of the International Classification of Headache Disorders are illustrated in Table 4. The diagnostic confirmation can be performed noninvasively with CT/CT angiography scan, MRI/MRI angiography, and ultrasonography, but angiography is the gold standard for the diagnosis [46]. Medical treatment with either antiplatelets or anticoagulants is the mainstay of treatment to prevent thromboembolic complications. Endovascular and surgical approaches, though effective, bear a greater risk for hazardous complication than medical management. No treatment guidelines have favored anticoagulation over antiplatelet agents, and the choice of management remains in the discretion of the treating physician.

Table 4 Diagnostic criteria of the International Classification of Headache Disorders for "headache attributed to acute headache or facial or neck pain attributed to cervical carotid or vertebral artery dissection" (2018)

A. Any new headache and/or facial or neck pain fulfilling criteria C and D
B. Cervical carotid or vertebral dissection has been diagnosed
C. Evidence of causation demonstrated by at least two of the following:
1. Pain has developed in close temporal relation to other local signs of the cervical artery dissection or has led to its diagnosis
2. Either or both of the following:
a) Pain has significantly worsened in parallel with other signs of the cervical artery dissection
b) Pain has significantly improved or resolved within 1 month of its onset
3. Either or both of the following:
a) Pain is severe and continuous for days or longer
b) Pain precedes signs of acute retinal and/or cerebral ischemia
4. Pain is unilateral and ipsilateral to the affected cervical artery
D. Either of the following:
1. Headache has resolved within 3 months
2. Headache has not yet resolved, but 3 months has not yet passed
E. Not better accounted for by another ICHD-3 diagnosis

Anticoagulation using intravenous heparin followed by warfarin constitutes one end of the treatment spectrum, while antiplatelet agents such as aspirin and clopidogrel represent the other commonly used strategy. Even aspirin alone has been shown to be effective in treating cerebrovascular dissections [47]. Most of the data available on the medical management of arterial dissections have come from observational studies, but recently the randomized trial CADISS (Cervical Arterial Dissection in Stroke Study) [48] did not show any difference in the efficacy of antiplatelet and anticoagulant drugs in the prevention of stroke and death in patients with symptomatic carotid and vertebral artery dissection. This finding was confirmed in a subsequent observational study on a large population, where new or recurrent ischemic and hemorrhagic events recurred in 9.6% of patients treated with antiplatelets, 10.4% of patients on anticoagulation, and 13.3% of patients on combined treatment [49].

Cardiac Cephalalgia

Cardiac cephalalgia is a migraine-like headache, usually but not always aggravated by exercise, occurring during an episode of myocardial ischemia and relieved by nitroglycerine. The diagnostic criteria are illustrated in Table 5.

In 1997, Lipton et al. described two cases and summarized five previous cases of an exertional headache complicated with acute coronary syndrome, discovering that the headache was relieved by the administration of nitroglycerine and/or surgical interventions including coronary artery bypass grafting or percutaneous angioplasty [50].

The diagnosis requires a careful documentation of headache and of the simultaneous cardiac ischemia during treadmill or nuclear cardiac stress testing. Failure to recognize and correctly diagnose it may have serious consequences. Therefore, distinguishing this disorder from 1.1 migraine without aura is of crucial importance, particularly since vasoconstrictor medications (e.g., triptans) are indicated in the treatment of migraine but absolutely contraindicated in patients with ischemic heart disease. Both

Table 5 Diagnostic criteria of the International Classification of Headache Disorders for "cardiac cephalalgia" (2018)

A. Any headache fulfilling criterion C
B. Acute myocardial ischemia has been demonstrated
C. Evidence of causation demonstrated by at least two of the following:
1. Headache has developed in temporal relation to the onset of acute myocardial ischemia
2. Either or both of the following:
a) Headache has significantly worsened in parallel with worsening of the myocardial ischemia
b) Headache has significantly improved or resolved in parallel with improvement in or resolution of the myocardial ischemia
3. Headache has at least two of the following four characteristics:
a) Moderate to severe intensity
b) Accompanied by nausea
c) Not accompanied by phototophia or phonophobia
d) Aggravated by exertion
4. Headache is relieved by nitroglycerine or derivatives of it
D. Not better accounted for by another ICHD-3 diagnosis

disorders can produce severe head pain accompanied by nausea, and both can be triggered by exertion.

The pathogenesis remains unclear and three hypotheses have been proposed along the years: (i) convergence of nerve fibers within the spinal cord, (ii) increased intracranial pressure secondary to decreased venous return from the brain, and (iii) increased inflammatory mediators causing vasodilation. In a recent case report, the Authors reported cortical hypoperfusion during headache attack in a patient with cardiac cephalalgia. This observation paves the way to an additional pathological hypothesis: the vessel constriction hypothesis. Two possible physiological mechanisms may be implicated in the hypothesis: one is represented by the activation of the sympathetic system by the myocardial ischemia, with the consequent small intracranial arteries constriction and subsequent headache, in analogy to the mechanisms of reversible cerebral vasoconstriction syndrome; the other considers that hypoperfusion might induce cortical spreading depression, which might then initiate the headache [51].

Conclusions

In the intimate and underestimated relation between the heart and the brain, headache may represent both a symptom and a comorbid condition. The pathways leading to this relationship are multifold in number and nature and comprise the autonomic nervous system, commanded by the brain and innervating the heart; the blood vessels' state of constriction/dilatation; the substances that can be released from nervous terminals near the blood vessels; the mechanic obstacles created by heart structure that may lead to the formation of microembolisms, a possible genetically based link; and most likely many others, yet to be described – but definitely worth studying – mechanisms.

References

1. Headache Classification Committee of the International Headache Society (IHS). The international classification of headache disorders, 3rd edition. Cephalalgia. 2018;38(1):1–211.
2. Allena M, Steiner TJ, Sances G, Carugno B, Balsamo F, Nappi G, Andrée C, Tassorelli C. Impact of headache disorders in Italy and the public-health and policy implications: a population-based study within the Eurolight project. J Headache Pain. 2015;16:100.
3. Rambarat CA, Elgendy IY, Johnson BD, et al. Migraine headache and long-term cardiovascular outcomes: an extended followup of the women's ischemia syndrome evaluation. Am J Med. 2017;130:738–43.
4. Mahmoud AN, Mentias A, Elgendy AY, Qazi A, Barakat AF, Saad M, Mohsen A, Abuzaid A, Mansoor H, Mojadidi MK, Elgendy IY. Migraine and the risk of cardiovascular and cerebrovascular events: a meta-analysis of 16 cohort studies including 1 152 407 subjects. BMJ Open. 2018;8(3):e020498.
5. Sacco S, Ornello R, Ripa P, Tiseo C, Degan D, Pistoia F, Carolei A. Migraine and risk of ischaemic heart disease: a systematic review and meta-analysis of observational studies. Eur J Neurol. 2015;22 (6):1001–11.
6. Tepper NK, Whiteman MK, Zapata LB, Marchbanks PA, Curtis KM. Safety of hormonal contraceptives among women with migraine: a systematic review. Contraception. 2016;94(6):630–40.
7. Takagi H, Umemoto T. A meta-analysis of case control studies of the association of migraine and patent foramen ovale. J Cardiol. 2016;67:493–503.
8. Lip PZY, Lip GYH. Patent foramen ovale and migraine attacks: a systematic review. Am J Med. 2014;127:411–20.

9. Dalla Volta G, Guindani M, Zavarise P, Griffini S, Pezzini A, Padovani A. Prevalence of patent foramen ovale in a large series of patients with migraine with aura, migraine without aura and cluster headache, and relationship with clinical phenotype. J Headache Pain. 2005;6(4):328–30.
10. Schwedt TJ, Dodick DW. Patent foramen ovale and migraine–bringing closure to the subject. Headache. 2006;46(4):663–71.
11. Nozari A, Dilekoz E, Sukhotinsky I, et al. Microemboli may link spreading depression, migraine aura, and patent foramen ovale. Ann Neurol. 2010;67(2):221–9.
12. Dowson A, Mullen MJ, Peatfield R, et al. Migraine intervention with starflex technology (MIST) trial: a prospective,multicenter, double-blind, sham-controlled trial to evaluate the effectiveness of patent foramen ovale closure with STARFlex septal repair implant to resolve refractory migraine headache. Circulation. 2008;117(11):1397–404.
13. Jasper R, Blankenship JC. Patent foramen ovale closure to prevent secondary neurologic events. Eur J Intern Med. 2017;44:1–11.
14. Carerj S, Narbone MC, Zito C, et al. Prevalence of atrial septal aneurysm of the interatrial septum in the general population and in patients with a recent episode of cryptogenic ischemic stroke: an echocardiographic study. Headache. 2003;43(7):725–8.
15. Amat G, Louis PJ, Loisy C, Centonze V, Pelage S. Migraine and the mitral valve prolapse syndrome. Adv Neurol. 1982;33:27–9.
16. Termine C, Trotti R, Ondei P, Gamba G, Montani N, Gamba A, et al. Mitral valve prolapse and abnormalities of haemostasis in children and adolescents with migraine with aura and other idiopathic headaches: a pilot study. Acta Neurol Scand. 2010;122(2):91–6.
17. Sicuteri F, Del Bene E, Poggioni M, Bonazzi A. Unmasking latent dysnociception in healthy subjects. Headache. 1987;27(4):180–5.
18. Sances G, Tassorelli C, Pucci E, Ghiotto N, Sandrini G, Nappi G. Reliability of the nitroglycerin provocative test in the diagnosis of neurovascular headaches. Cephalalgia. 2004;24:110–9.
19. Demartini C, Greco R, Zanaboni AM, Sances G, De Icco R, Borsook D, et al. Nitroglycerin as a comparative experimental model of migraine pain: from animal to human and back. Prog Neurobiol. 2019;177:15–32.
20. Sprenger T, Viana M, Tassorelli C. Current prophylactic medications for migraine and their potential mechanisms of action. Neurotherapeutics. 2018;15 (2):313–23.
21. Evers S, Afra J, Frese A, Goadsby PJ, Linde M, May A, et al. EFNS guideline on the drug treatment of migraine–revised report of an EFNS task force. Eur J Neurol. 2009;16(9):968–81.
22. Law M, Morris JK, Jordan R, Wald N. Headaches and the treatment of blood pressure. Results from a meta-analysis of 94 randomized placebo-controlled trials with 24000 participants. Circulation. 2005;112:2301–6.
23. Linde K, Rossnagel K. Propranolol for migraine prophylaxis. Cochrane Database Syst Rev. 2017;2: CD003225.
24. Boyer N, Signoret-Genest J, Artola A, Dallel R, Monconduit L. Propranolol treatment prevents chronic central sensitization induced by repeated dural stimulation. Pain. 2017;158(10):2025–34.
25. Chugani DC, Niimura K, Chaturvedi S, Muzik O, Fakhouri M, Lee ML, et al. Increased brain serotonin synthesis in migraine. Neurology. 1999;53(7):1473–9.
26. Richter F, Mikulik O, Ebersberger A, Schaible HG. Noradrenergic agonists and antagonists influence migration of cortical spreading depression in rat-a possible mechanism of migraine prophylaxis and prevention of postischemic neuronal damage. J Cereb Blood Flow Metab. 2005;25(9):1225–35.
27. Ye Q, Wang Q, Yan LY, Wu WH, Liu S, Xiao H, et al. Flunarizine inhibits sensory neuron excitability by blocking voltage-gated Na+ and Ca2+ currents in trigeminal ganglion neurons. Chin Med J. 2011;124 (17):2649–55.
28. Li F, Qiu E, Dong Z, Liu R, Wu S, Yu S. Protection of flunarizine on cerebral mitochondria injury induced by cortical spreading depression under hypoxic conditions. J Headache Pain. 2011;12(1):47–53.
29. Schrader H, Stovner LJ, Helde G, Sand T, Bovim G. Prophylactic treatment of migraine with angiotensin converting enzyme inhibitor (lisinopril): randomised, placebo controlled, crossover study. BMJ. 2001;322 (7277):19–22.
30. Saavedra JM. Brain angiotensin II: new developments, unanswered questions and therapeutic opportunities. Cell Mol Neurobiol. 2005;25(3–4):485–512.
31. Reuter U, Chiarugi A, Bolay H, Moskowitz MA. Nuclear factor-kappaB as a molecular target for migraine therapy. Ann Neurol. 2002;51(4):507–16.
32. Schürks M, Rist PM, Kurth T. MTHFR 677C>T and ACE D/I polymorphisms in migraine: a systematic review and meta-analysis. Headache. 2010;50 (4):588–99.
33. Evers S, Barth B, Frese A, Husstedt IW, Happe S. Sleep apnea in patients with cluster headache: a case-control study. Cephalalgia. 2014;34(10):828–32.
34. Metoki H, Ohkubo T, Kikuya M, et al. Prognostic significance for stroke of a morning pressor surge and a nocturnal blood pressure decline. The Ohasama study. Hypertension. 2006;47:149–54.
35. Santos S, Navarro J, Vel_azquez A. Pe´ rez C. Nighttime blood pressure in cluster headache. Headache. 2011;51:1445–9.
36. Kario K. Nocturnal hypertension: new technology and evidence. Hypertension. 2018;71(6):997–1009.
37. Manzoni GC. Cluster headache and lifestyle: remarks on a population of 374 male patients. Cephalalgia. 1999;19(2):88–94.
38. Ekbom K. Heart rate, blood pressure, and electrocardiographic changes during provoked attacks of cluster headache. Acta Neurol Scand. 1970;46:215–224. 27.

39. Stillman M, Spears R. Endocrinology of cluster headache: potential for therapeutic manipulation. Curr Pain Headache Rep. 2008;12:138–44.
40. Holland PR, Goadsby PJ. Cluster headache, hypothalamus, and orexin. Curr Pain Headache Rep. 2009;13:147–54.
41. Gus M, Fuchs FD, Pimentel M, Rosa D, Melo AG, Moreira LB. Behavior of ambulatory blood pressure surrounding episodes of headache in mildly hypertensive patients. Arch Intern Med. 2001;161:252–5.
42. Friedman BW, Mistry B, West JR, Wollowitz A. The association between headache and elevated blood pressure among patients presenting to an ED. Am J Emerg Med. 2014;32(9):976–81.
43. Lee VH, Brown RD Jr, Mandrekar JN, Mokri B. Incidence and outcome of cervical artery dissection: a population-based study. Neurology. 2006;67(10):1809–12.
44. Schievnik WI, Mokri B, Piepgras DG. Spontaneous dissection of the cervicocephalic arteries in childhood and adolescence. Neurology. 1994;44:1607–12.
45. Laing C, Thomas DJ, Mathias CJ, Unwin RJ. Headache, hypertension and horner's syndrome. J R Soc Med. 2000;93:535–6.
46. Hanning U, Sporns PB, Schmiedel M, Ringelstein EB, Heindel W, Wiendl H, Niederstadt T, Dittrich R. CT versus MR techniques in the detection of cervical artery dissection. J Neuroimaging. 2017;27(6):607–12.
47. Georgiadis D, Arnold M, von Buedingen HC, et al. Aspirin vs anticoagulation in carotid artery dissection: a study of 298 patients. Neurology. 2009;72(21):1810–5.
48. The CADISS trial investigators. Antiplatelet treatment compared with anticoagulation treatment for cervical artery dissection (CADISS): a randomised trial. Lancet Neurol. 2015;14(4):361–7.
49. Daou B, Hammer C, Mouchtouris N, Starke RM, Koduri S, Yang S, Jabbour P, Rosenwasser R, Tjoumakaris S. Anticoagulation vs antiplatelet treatment in patients with carotid and vertebral artery dissection: a study of 370 patients and literature review. Neurosurgery. 2017;80(3):368–79.
50. Lipton RB, Lowenkopf T, Bajwa ZH, Leckie RS, Ribeiro S, Newman LC, Greenberg MA. Cardiac cephalgia: a treatable form of exertional headache. Neurology. 1997;49(3):813–6.
51. Wang M, Wang L, Liu C, Bian X, Dong Z, Yu S. Cardiac cephalalgia: one case with cortical hypoperfusion in headaches and literature review. J Headache Pain. 2017;18(1):24.

Multiple Sclerosis and the Heart

32

Camilla Rocchi, Giorgia Mataluni, and Doriana Landi

Contents

Abstract

The ability of the central nervous system (CNS) to damage the heart depends on the physiological link between the brain and cardiovascular system. The latter is under control of interconnected areas of CNS belonging to the central autonomic network (CAN) and of two different pathways: the sympathetic and the parasympathetic nervous system. Neurological disorders that disrupt this complex system at various levels can lead to cardiovascular dysfunction. Multiple sclerosis (MS) is an inflammatory disorder of the central nervous system leading to focal and diffuse demyelination of neurons and ultimately to neurodegeneration and accumulation of disability. Recently, attention has been paid to the study of autonomic dysfunction and of cardiovascular complications of MS, as they may impact on MS prognosis and long-term disability. Acute cardiac events have been also reported in MS patients associated with inflammatory relapses. Nevertheless, treatments for MS, such as mitoxantrone or

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*,
https://doi.org/10.1007/978-3-030-28008-6_32

fingolimod, may impact on cardiovascular functioning via autonomic system-dependent or autonomic system-independent mechanism of action. Therefore, accurate and periodic monitoring of heart and cardiovascular system is required during disease-modifying treatments. This chapter will provide an overview of the available evidence on the role of the autonomic system in MS, to describe clinical and prognostic features of cardiac events in MS and to describe the main cardiovascular complications of disease-modifying treatments in MS.

Keywords

Multiple sclerosis · Cardiovascular reflexes · Autonomic nervous system · Heart rate variability · Fingolimod · Mitoxantrone

Introduction

Multiple sclerosis (MS) is an inflammatory disorder of the central nervous system (CNS) leading to focal and diffuse demyelination of neurons and ultimately to neurodegeneration and accumulation of disability. MS was traditionally considered to be an autoimmune disease mediated by autoreactive T helper (Th)1 and Th17 cells releasing pro-inflammatory cytokines allowing Th cells to enter the CNS and induce focal damage. Recently, B cells are increasingly recognized as main players in the MS pathogenesis, particularly after the discovery of B-cell follicles in the meninges and the encouraging results of clinical trials using B-cell-depleting agents to treat MS [1].

MS typically affects patients between 20 and 40 years of age, and it is one of the world's leading causes of disability in young adults with a prevalence that varies between 50 and 300 per 100,000 people [2]. The risk of developing MS is higher in women (female-to-male ratio about 3:1) and in northern countries. The two main clinical courses of MS are relapsing-remitting and progressive, although many overlaps exist between the two forms. Relapsing-remitting MS (RRMS) is characterized by the occurrence of subacute neurological deficits ("relapses") undergoing complete or incomplete remission in days to weeks, which are usually subtended by new focal demyelinating lesions in the brain or spinal cord. In progressive MS, slow disability accumulation occurs over time due to progressive neuronal loss. In order to provide a standardized definition of MS subtypes and to unify terminology, in 1996, it was proposed to classify MS subtypes in relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), and primary progressive MS (PPMS) [3]. In 2013, an updated revision of this classification was made [4], introducing new disease courses (radiological and clinically isolated syndromes) and adding to the established MS phenotypes two disease modifiers, activity and progression, to better define individual clinical course.

The diagnosis of MS is based on a combination of clinical, imaging, and laboratory evidence and on the exclusion of alternative explanations. The most updated revision of the McDonald diagnostic criteria has been made in 2017 and can be used as guidance for diagnosis [5].

Clinical symptoms of MS may involve several functional systems, most commonly visual, pyramidal, sensitive, cerebellar, and urogenital. Cardiovascular and autonomic involvement, both at onset and during the disease course, is more rarely investigated and described, and it is reliably underestimated. It is dependent on brain and spinal cord inflammatory lesions or may occur as complication of treatments.

As of June 2019, 15 disease-modifying treatments have been approved for the treatment of MS, with very different mechanisms of action and side effect profile. With the development of disease-modifying therapies (DMTs), patients and health-care providers now have multiple options and improved flexibility in managing MS.

This chapter will provide an overview of the available evidence on the role of the cardiovascular autonomic system in MS, of clinical and prognostic features of cardiac events in MS, and of the main cardiovascular complications of disease-modifying treatments in MS.

Cardiovascular Autonomic Dysfunction in Multiple Sclerosis

Autonomic nervous system (ANS) impairment frequently occurs in MS [6], although it is rarely explored. Anatomic and functional organization of ANS is very complex, and the effector organ of ANS and the sympathetic and parasympathetic system are under the control of the central autonomic network (CAN). The latter is distributed throughout the neuraxis and is involved in visceromotor, neuroendocrine, complex motor, and pain modulating control mechanisms essential for adaptation and survival [7]. With regard to cardiovascular function, the CAN receives inputs, from baroreceptors, cardiac receptors, and chemoreceptors, which are carried by the glossopharyngeal and vagus nerves and relay on the nucleus of the tractus solitarius (NTS) in the medulla. NTS and ventrolateral medulla contain a network of respiratory, cardiovagal, and vasomotor neurons implicated in the control of cardiovascular function. The physiologic control of the cardiovascular system results from a balance between sympathetic and parasympathetic activity regulated by the medullary reflexes and by descending influences from other areas of CAN. The parasympathetic system decreases the heart rate, atrioventricular conduction, and ventricular excitability, via the vagus nerve through a direct input of the NTS to a group of preganglionic cholinergic neurons located in the ventrolateral portion of the nucleus ambiguus, while the sympathetic system produces the reverse effects through noradrenergic postganglionic neurons activated by the preganglionic sympathetic neurons located in the intermediolateral columns in the upper thoracic segments of the spinal cord [8]. Via the NTS, the baroreflex also suppresses the secretion of vasopressin by magnocellular neurons of the supraoptic and paraventricular nuclei of the hypothalamus by inhibiting noradrenergic cells of the A1 group [9]. As a consequence, the involvement of all the aforementioned areas by pathological processes can lead to dysfunctions of the autonomic cardiovascular system. MS is considered a secondary cause for autonomic cardiovascular dysfunction [10]; indeed, there has been an upsurge in cardiovascular ANS investigations, involving patients with MS. Autonomic symptoms can be evaluated with clinimetric scores as the Composite Autonomic Scoring Scale (CASS) [11] or the more recent Composite Autonomic Symptom Score (COMPASS-31) [12]. The neurophysiological assessment of ANS integrity is usually indirectly achieved by measuring the reflex responses of the target organs to physiological and pathological stimuli [13]. The cardiovascular reflex tests (head-up tilt test, Valsalva maneuver, handgrip, deep breathing, and cold face) assess heart rate (HR) and blood pressure changes in response to certain particular maneuvers, with the aim of disclosing a dysfunction of the autonomic control of the cardiovascular system and assessing the integrity of the parasympathetic and the sympathetic branch and baroreflex [13]. Another method for evaluating sympathetic or parasympathetic cardiac control is the spectral analysis of HR variability (HRV), calculated from the interval between two consecutive R-waves of QRS complexes in the ECG trace. The power spectrum of HRV comprises high-frequency (HF), respiratory-linked component (centered 0.16–0.4 Hz) reflecting mostly vagal activity, and a low-frequency (LF) component (0.04–0.15 Hz) reflecting mostly sympathetic activity [14]. As early as 1985, Sterman et al. [15] proved significant differences in the heart rate and blood pressure change in two or more out of six cardiovascular function tests in half of MS patients studied, with lack of clinical correlation to patients' disability or MS type. Single patients showed diverse abnormality patterns, and this heterogeneity has been attributed to the difference plaques dissemination. The correlation of cardiovascular dysfunction with demyelinating lesions in the brainstem has been proved through magnetic resonance imaging, supporting the anatomical origin of cardiovascular impairment [16]. The abovementioned correlation was also found by other authors [10, 17, 18]. Nevertheless, another study has shown the impairment of cardiovascular reflexes correlated also with parietal MS

lesions [19]; hence, also hemispherical lesions can be involved in cardiovascular autonomic dysregulation.

While the anatomical origin of autonomic impairment is certainly proved, this probably does not fully explain the cardiovascular dysfunction. In any case, inflammatory processes most likely have a role in cardiovascular dysfunction. The release of catecholamines caused by the inflammatory lesions in the central nervous system can alter cardiovascular function. Th 1-type cytokines have pro-inflammatory effects in MS and activate the sympathetic nervous system; on the other side, the activation of the sympathetic nervous system produces changes in the immune system [20]. Moreover, previous studies have demonstrated an enhanced expression of beta-adrenergic receptor density on peripheral blood mononuclear cells in MS patients, associated with an increase in interleukin 2 receptors that are largely engaged in pro-inflammatory pathways [21]. The beta-adrenergic receptors involved in the inflammatory process also regulate the sympathetic cardiovascular function, which, as a consequence, may undergo alterations. Conversely, the parasympathetic system plays an anti-inflammatory role warning the central nervous system on the presence of inflammation via afferent signals transmitted by the vagus nerve. These signals trigger an anti-inflammatory response named "cholinergic anti-inflammatory pathway" that culminate activating the alpha-7 subunit on nicotinic acetylcholine receptors expressed in immune and nonimmune cells [20, 22]. Both parasympathetic and sympathetic cardiovascular components are impaired selectively in different stages in MS, and the sympathetic-vagal imbalance may be implicated in heart events.

Epidemiology and Prognostic Value of Cardiovascular Dysfunction in MS

Cardiovascular dysfunction in MS has been less frequently described and is less well understood than other neurological manifestations of MS. However, it is well known that MS can affect cardiovascular function in a variety of ways ranging from abnormalities in blood pressure response, heart rate, heart rhythm, and left ventricular systolic function to acute dramatic cases of sudden unexpected death in MS (SUDIMS). Among cardiovascular autonomic dysfunction in MS patients, there is emerging evidence suggesting that certain disorders may even serve as prognostic markers of severity and progression of the disease. There seems to exist a distinct pattern of dysautonomia, which depends on different phases of the disease. Orthostatic hypotension and postural orthostatic tachycardia syndrome (POTS) have both been reported in MS patients [23]. POTS diagnosis result as a significant predictor of conversion from clinical isolated syndrome (CIS) to defined MS [24]. Several studies, using the cardiovascular autonomic function tests (heart rate and blood pressure responses to Valsalva maneuver and heart rate response to deep breathing), have suggested a distinct pattern of autonomic dysfunction in different phases of the disease. In the CIS stage, there is predominant sympathetic dysfunction with sparing of the parasympathetic system [25]. A similar finding was observed in RRMS, where adrenergic sympathetic dysfunction was higher in patients with active MS compared to healthy controls or stable patients [26]. Further, sympathetic dysfunction was associated with the clinical activity of the disease [27] and thus may be related to inflammatory mechanisms in MS.

In contrast, parasympathetic, but not sympathetic dysfunction, increases with disease duration significantly correlating with an increase in clinical disability [26]. These results were confirmed in a recent study prospectively designed to assess differences in autonomic dysfunction between RRMS and PMS [28]. Specifically, differences in total composite autonomic scoring scale, as well as adrenergic, cardiovagal, and sudomotor indices, were assessed for the two groups. The study has shown similar results for RRMS, with autonomic involvement being present in the majority of patients. Sympathetic dysfunction was noted in 35.9% and cardiovagal in 2.5% of patients. The HRV analysis in the same study has shown that PMS have an overall decrease of HRV

with a reduction of cardiovagal activity, as well as combined sympathetic and parasympathetic cardiac activity. These results are in concordance with CASS results in PMS, which also show a higher degree of both adrenergic and cardiovagal dysfunction, compared to RR phenotype. Consistently with these results, other authors described an altered HRV in progressive patients with respect to healthy controls and RR patients. In PMS a higher low frequency power at rest, reflecting parasympathetic outflow and a lack of the expected increase of low frequency power, during the head-up tilt test were found. The authors hypothesized that patient-specific autonomic balance could reflect an endogenous inhibitory signal inefficiency against overshooting inflammation in RR phase of the disease. Accordingly, hyperactivity of the sympathetic system could be protective against neuroinflammation, and neurodegeneration and progressive disease could be the price for the continuous autonomic control of acute inflammatory reactivation in MS [29]. As to what, studies that have investigated longitudinal evolution of cardiovascular dysfunction in MS showed a worsening of different measures of parasympathetic function, while there was no substantial change in the results of adrenergic sympathetic function tests [26, 30, 31].

A critical revision of the results of published studies on cardiovascular dysfunction in MS patients suggests that the active inflammatory stage of the disease could lead to an initial sympathetic activation and a subsequent progressive sympathetic dysfunction with a relative sparing of the parasympathetic system. Parasympathetic dysfunction correlates with progression of clinical disability, resulting more likely from structural CNS damage in MS.

The abnormalities of the cardiovascular autonomic system described in MS patients might be related to epidemiological studies showing that MS patients may have an increased risk of ischemic heart disease and congestive heart failure when compared with the general population [32] and they have a markedly increased risk of myocardial infarction in the first year after the MS diagnosis [33]. A recently published retrospective study found that MS patients have adrenergic hyperactivity, expressed as an increase in adrenergic baroreflex sensitivity, compared with healthy controls [34]. In the same study, the authors also observed a positive correlation between in adrenergic baroreflex sensitivity and systolic blood pressure at head-up tilt test [34]. These results are meaningful knowing that adrenergic hyperactivity can predispose to arterial hypertension [35] and may contribute to the increased risk of ischemic heart disease and congestive heart failure in MS patients, impacting on global clinical outcome. An impairment of the cardiac autonomic reflexes, described so far, may cause an inadequate cardiac autonomic control during endurance exercise in MS patients [36]. The importance of physical activity, even high-intensity and resistance training in global outcome of MS, has been established [37]. Therefore, limited exercise capacity in individuals with MS, due to disturbed cardiovascular autonomic reflexes, can severely affect patients' abilities to properly perform physical rehabilitation – an essential aspect of MS treatment.

Acute Cardiac Events in MS Patients

Although autonomic dysfunction frequently impairs the patient's quality of life, autonomic dysregulation and its prognostic value are still poorly addressed in the clinical evaluation of MS patients. Acute cardiovascular emergencies are rarely recognized as manifestation of MS, probably because cardiologists and neurologists are unaware of this phenomenon. The important role of the CNS in the regulation of normal cardiovascular and pulmonary functions is well known. Several nuclei of the central autonomic network, in the diencephalon, brainstem, and spinal cord, as well as areas within the insular cortex, are critical for modulation of cardiac function, systemic blood pressure, and pulmonary hydrostatic pressure. Acute interruption of the function of these regions may cause symptomatic, sometimes fatal, cardiopulmonary syndromes [38]. Neurogenic pulmonary edema and neurogenic stunned myocardium are both described as

possible dramatic clinical expression of acute brainstem demyelinating lesions in MS patients. This condition shares a common catecholamine-mediated pathophysiology [39]. The reason why patients with MS exacerbations and lesions in similar locations develop predominantly neurogenic pulmonary edema or predominantly myocardial dysfunction remains unclear. Two different mechanisms may trigger the sympathetic overactivation: a sudden increase in intracranial pressure with global decrease in brain perfusion and a localized insult in suspected brain vasomotor centers [40].

Thirty-one case reports of acute cardiopulmonary events in patients with RRMS associated with MS exacerbations have been recently revised [38]. In 12 patients, these events represented the clinical onset of the disease. MS lesions located in the dorsomedial medulla can cause damage to the nucleus tractus solitarius and result in baroreflex failure and loss of regulation of the excess sympathetic activity. A reliable mechanism is a loss of inhibition of the neurons in the rostral ventrolateral medulla and loss of activation of the cardioinhibitory outflow from the nucleus ambiguus [8].

Neurogenic myocardial dysfunction described in MS patients has been identified as Takotsubo-like cardiomyopathy. Takotsubo is a reversible but potentially life-threatening left ventricular dysfunction, also known as stress-induced cardiomyopathy, neurogenic stunned myocardium, and broken heart syndrome [41]. The pathogenic mechanism of this disease is still unclear, but it could be linked to catecholamine release and cardiotoxicity. Diagnostic criteria for Takotsubo syndrome include presence of a transient abnormality in the left ventricular wall motion beyond a single epicardial coronary artery perfusion territory, absence of obstructive coronary artery disease, presence of new electrocardiographic abnormalities or elevation in cardiac troponin levels, and absence of pheochromocytoma and myocarditis [42, 43].

In all case reports of acute cardiopulmonary events described in MS patients, a clear temporal relationship between cardiac event and a newly formed demyelinating lesion was detected, as well as a significant improvement of neurological and cardiac symptoms after the administration of corticosteroids. These evidences strongly argue in favor of a causal association between the two entities. Due to their complexity, autonomic cardiovascular dysfunctions in MS patients remain often overlooked. Although they are mostly described as subclinical, they include clinical manifestations with potentially strong impact on quality of life and global disability of MS patients.

A deeper understanding of the pathogenic mechanisms of autonomic unbalance occurring in MS is needed; in this perspective, a systematic investigation of cardiovascular autonomic dysfunction in MS patients could potentially serve for clinicians as warning signs of disease activity and progression.

Cardiovascular Complications of MS Treatments

Cardiovascular complications are not commonly associated with MS treatments. However, for some treatments, cardiovascular effects are known, and they do involve both autonomic system dysregulation and structural heart damage and require specific monitoring (Kaplan et al.). Among those we find mainly mitoxantrone, fingolimod, teriflunomide, and others.

Mitoxantrone

Mitoxantrone is an analog of doxorubicin; both are anthracenedione derivative, originally used as antineoplastic agents. Mitoxantrone is an inhibitor of RNA synthesis, so, due to its antiproliferative properties, it was considered a suitable agent to treat chronic autoimmune disorders [44]. Its efficacy in MS was demonstrated by a phase III clinical trial conducted by the mitoxantrone in Multiple Sclerosis (MIMS) Study Group [45] and by additional smaller studies [46–48]. In December 2000, the US Food and Drug Administration (FDA) approved mitoxantrone hydrochloride as the first non-biological treatment for worsening relapsing-remitting MS, progressive-relapsing MS, or secondary progressive MS.

Originally developed to be less cardiotoxic compared to doxorubicin, over the last decade, several acute and chronic cardiac complications such as acute cardiac failure, arrhythmias, cardiomyopathy, reduced left ventricular ejection fraction (LVFE), and congestive heart failure have been associated with mitoxantrone [44]. Based on all the available evidence in MS patients, the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology has reported that overall systolic dysfunction occurs in approximately 12% of patients and congestive heart failure in approximately 0.4% [49]. The exact mechanism by which mitoxantrone induces cardiotoxicity is not known, although free radical formation and oxidative stress have been claimed as main factors. Pathological studies found profound structural abnormalities of myocytes including myofibrillar loss and swelling of mitochondria, sarcoplasmic reticulum, and T tubules. The main prognostic factor for cardiotoxicity development seems to be the cumulative dose of treatment received. In particular, congestive heart failure increases significantly (>5%) beyond a cumulative dose of 160 mg/m^2; therefore, the ceiling dose for mitoxantrone has been initially set at 140 mg/m^2. Later some evidences have suggested that initial cardiac damage may be seen also at lower dosage [44]. The last revision of product labels indicates that MS patients candidate to mitoxantrone need to be screened for cardiac dysfunction by echocardiogram or multiple-gated acquisition (MUGA) prior to administration of the initial dose, prior to each dose, and yearly for up to 5 years after the end of therapy. It cannot be administered to patients with LVFE<50%, and a maximum cumulative dose of 100 mg/m^2 can be reached [Novantrone SPmC].

Due to the high risk of cardiotoxicity, but also of treatment-related acute leukemia and amenorrhea, mitoxantrone is now rarely used in MS.

Fingolimod

Fingolimod (FTY720) has been approved in 2012 as the first oral -1-phosphate (S1P) receptor modulator for treatment of relapsing-remitting multiple sclerosis (MS). Fingolimod is licensed as a first-line treatment in the USA, Canada, Australia, New Zealand, Switzerland, and Russia while in the European Union for highly active MS. It is a structural analog of intracellular sphingosine, and it acts as functional antagonist of S1P receptors (S1P1R, S1P3R, S1P4R, S1P5R) that are ubiquitously expressed in human tissues [50]. By modulating S1P1R receptors on lymphocytes, FTY is able to reduce the trafficking of autoreactive lymphocytes and inhibit their infiltration into the central nervous system, reducing local inflammation and neurodegeneration. Nevertheless, it may also have several non-immunological effects in humans, such as ocular or cardiovascular effects by modulating other receptor subtypes. Transient agonistic activation of S1P1R expressed on myocytes leads to activation of G protein-gated cholinergic potassium channels, eliciting an inwardly rectifying potassium current, membrane hyperpolarization, reduced cell excitability, and decreased firing rate that determine negative chronotropic effects on the SA node and the upper fibers of the AV node [51]. Patients may develop transient bradycardia or, more rarely, delay or blockade of atrioventricular conduction during the administration of first dose, which returns to baseline in few hours. In phase III of the clinical trials (TRANSFORMS, FREEDOM, FREEDOM II) [52–54] heart rate average decrease of 8.1 beats/min, starting from the 1–2 h after the first dose and reaching the maximum after 4–5 h. Heart rate returned to normal after the first dose and during prolonged treatment due to internalization of S1P1R. According to pooled analysis of phase III trials, PR interval decreased to 4.5 ms, while first-degree AV block was observed in 4.7% of the cases (Mobitz type I second-degree AV block in 0.2%) of the study participants during the first dose [55]. Several observational studies (FIRST, EPOC) [56, 57] including also patients with cardiac comorbidities or taking calcium antagonist or beta-blockers have further investigated cardiovascular safety of fingolimod, confirming previous findings [58]. Based on pre- and post-marketing evidence, and according to the summary of product characteristics (Gilenya SpMC), ECG and blood pressure measurements are required prior to and 6 h

after the first dose of fingolimod, and continuous monitoring during the first 6 h is recommended. The same monitoring procedures are recommended if the treatment is interrupted for one or several days during the first 2 weeks of treatment, for more than 7 days during the third and fourth weeks of treatment, and for more than 2 weeks after 1 month of treatment. Moreover, fingolimod is contraindicated in patients who in the previous 6 months had myocardial infarction, unstable angina pectoris, stroke/transient ischemic attack, decompensated heart failure, or New York Heart Association (NYHA) class III/IV heart failure, with severe cardiac arrhythmias requiring anti-arrhythmic treatment with class Ia or class III anti-arrhythmic medicinal products, with second-degree Mobitz type II atrioventricular (AV) block or third-degree AV block, or sick sinus syndrome, if they do not wear a pacemaker, with a baseline QTc interval $\geq$500 ms. In MS patients with no cardiovascular diseases, baseline individual sympathetic and parasympathetic regulation may predict cardiac effects after the first fingolimod dose [59]. In particular, higher heart rate response to deep breathing and Valsalva maneuver, which measure parasympathetic activity, seems to be correlated with a lower nadir heart rate and to predict the risk of significant bradycardia after the first dose. PR prolongation, instead, is associated with reduced sympathetic tone, unveiling the importance of the sympathetic system in limiting the negative dromotropic effects of fingolimod [59]. S1P signaling, particularly through the S1PR1–3 subtypes, has emerged also as an important regulator of vascular development and stability, angiogenesis, permeability, and vascular tone. Clinical trials in MS have reported an average increase of approximately 3 mmHg in systolic pressure, and approximately 1 mmHg in diastolic pressure, first detected approximately 1 month after treatment initiation, and persisting with continued treatment. In the 2-year placebo-controlled study, hypertension was reported as an adverse event in 6.5% of patients on fingolimod 0.5 mg and in 3.3% of patients on placebo [53] (Gilenya SPmC 2015). Animal models have shown, instead, that fingolimod treatment increases blood pressure in control mice, exacerbates hypertension, and impairs endothelial-dependent vasodilation [58, 60]. Therefore, monitoring of blood pressure is recommended during treatment, in particular in patients with cardiovascular risk factors.

To minimize cardiovascular risk of fingolimod, over the past decade, several new S1P1 modulators were developed with increased receptor binding selectivity, such as siponimod and ozanimod, which are S1P1,5 functional antagonist, and ponesimod, which is reversible S1P1 functional antagonist. Siponimod has been already approved in the USA for the treatment of MS, while ozanimod and ponesimod are in phase III trials.

Results of clinical trials (BOLD and BOLD extension study) exploring the safety of siponimod have shown a better cardiac safety profile, also thanks to availability of dose titration [61].

Increased cardiac safety of siponimod is of paramount importance considering that it is indicated for patients with secondary progressive MS that are usually older and show higher prevalence of cardiovascular comorbidities.

Teriflunomide

Teriflunomide is an oral agent available in two different dosages – 7 and 14 mg – approved for the treatment of relapsing-remitting MS. It inhibits the synthesis of pyrimidine in activated and proliferating B and T lymphocytes by selectively and reversibly blocking the mitochondrial enzyme dihydroorotate dehydrogenase DHODH. Treatment with teriflunomide is not associated with cardiac diseases, but increase in blood pressure has been reported. The risk of hypertension in treated patients varies from 9.2% to 4.5%, and it is dose dependent (14 vs. 7 mg) and amplified by pre-existing hypertension [62]. The time of onset of hypertension is not established, but there is a trend for a gradual increase during treatment, which is reverted by treatment interruption. Usually, blood pressure values are mildly elevated and well controlled by antihypertensive treatment. Incidental hypertension has been also observed in patients with rheumatoid arthritis taking

leflunomide, which is the precursor of teriflunomide, after few weeks of treatment [63, 64]. All these evidences support a causal relationship between inhibitors of DHODH and hypertension; nevertheless, the mechanisms subtending this side effect remain unknown. Sympathetic modulation by leflunomide has been postulated, but no evidence is available so far. According to teriflunomide SmPC, blood pressure has to be checked before starting treatment and periodically thereafter.

Cladribine

Cladribine tablets are the last oral agent approved for treatment of relapsing-remitting MS. It is a synthetic analog of chlorinated deoxyadenosine: it is actively transported into cells where it undergoes phosphorylation by deoxycytidine kinase (dCK). It is then incorporated into nuclear DNA, altering the double helix structure and leading to a failure of DNA repair and synthesis. Cells containing a high deoxycytidine kinase, such as B and T lymphocytes, accumulate deoxynucleotides to toxic concentrations, resulting in cell death. Cardiac effects of cladribine on heart rate, AV conduction, and cardiac repolarization in patients with MS have been explored by a sub-study of the multicenter CLARITY phase III trial (Hermann et al. [65]). No effect of cladribine has been observed on cardiac functions, including QT prolongation. The integrated analysis of clinical trials and follow-up in patients with MS [66] reported four cases of cardiac death in young MS patients previously treated with cladribine; however, due to the long time from the last administration and death, they were considered unrelated to treatment. In one case, cardiorespiratory arrest was ascribed to a large MS brain stem lesion [66].

Others

No special warning exists for other MS treatments (IFN, glatiramer acetate, dimethyl fumarate, natalizumab, ocrelizumab, alemtuzumab).

Conclusions

Cardiovascular dysfunction in multiple sclerosis may be the result of the disruption of central autonomic network depending on demyelinating lesion distribution. Nevertheless, diffuse neuroinflammation may induce cardiovascular impairment in MS via sympathetic activation and consequent catecholamine release. Cardiovascular autonomic dysregulation has an important yet underrecognized prognostic value both regarding long-term disability and side effects of treatments, such as fingolimod. Moreover, it can be associated with acute clinical syndromes, like Takotsubo syndrome, in MS that should be promptly identified and managed.

References

1. Hauser SL, Bar-Or A, Comi G, Giovannoni G, Hartung H-P, Hemmer B, et al. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. N Engl J Med. 2017;376:221–34.
2. Li H, Hu F, Zhang Y, Li K. Comparative efficacy and acceptability of disease-modifying therapies in patients with relapsing–remitting multiple sclerosis: a systematic review and network meta-analysis. J Neurol [Internet]. 2019 [citato 9 giugno 2019]; Recuperato da: http://link.springer.com/10.1007/s00415-019-09395-w
3. Lublin FD, Reingold SC, National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis∗. Defining the clinical course of multiple sclerosis: results of an international survey. Neurology. 1996;46:907–11.
4. Lublin FD. New multiple sclerosis phenotypic classification. Eur Neurol. 2014;72(Suppl 1):1–5.
5. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018;17:162–73.
6. Racosta JM, Kimpinski K, Morrow SA, Kremenchutzky M. Autonomic dysfunction in multiple sclerosis. Auton Neurosci. 2015;193:1–6.
7. Benarroch EE. The central autonomic network: functional organization, dysfunction, and perspective. Mayo Clin Proc. 1993;68:988–1001.
8. Palma J-A, Benarroch EE. Neural control of the heart: recent concepts and clinical correlations. Neurology. 2014;83:261–71.
9. Benarroch EE. The arterial baroreflex: functional organization and involvement in neurologic disease. Neurology. 2008;71:1733–8.
10. Acevedo AR, Nava C, Arriada N, Violante A, Corona T. Cardiovascular dysfunction in multiple sclerosis. Acta Neurol Scand. 2000;101:85–8.

11. Low PA. Composite autonomic scoring scale for laboratory quantification of generalized autonomic failure. Mayo Clin Proc. 1993;68:748–52.
12. Sletten DM, Suarez GA, Low PA, Mandrekar J, Singer W. COMPASS 31: a refined and abbreviated composite autonomic symptom score. Mayo Clin Proc. 2012;87:1196–201.
13. Mathias CJ. Autonomic diseases: clinical features and laboratory evaluation. J Neurol Neurosurg Psychiatry. 2003;74(3):iii31–41.
14. Electrophysiology TF of the ES. Heart rate variability: standards of measurement, physiological interpretation, and clinical use. Circulation. 1996;93:1043–65.
15. Sterman AB, Coyle PK, Panasci DJ, Grimson R. Disseminated abnormalities of cardiovascular autonomic functions in multiple sclerosis. Neurology. 1985;35:1665–8.
16. Vita G, Carolina Fazio M, Milone S, Blandino A, Salvi L, Messina C. Cardiovascular autonomic dysfunction in multiple sclerosis is likely related to brainstem lesions. J Neurol Sci. 1993;120:82–6.
17. McLeod JG, Tuck RR. Disorders of the autonomic nervous system: Part 1. Pathophysiology and clinical features. Ann Neurol. 1987;21:419–30.
18. Thomaides TN, Zoukos Y, Chaudhuri KR, Mathias CJ. Physiological assessment of aspects of autonomic function in patients with secondary progressive multiple sclerosis. J Neurol. 1993;240:139–43.
19. Saari A, Tolonen U, Pääkkö E, Suominen K, Pyhtinen J, Sotaniemi K, et al. Cardiovascular autonomic dysfunction correlates with brain MRI lesion load in MS. Clin Neurophysiol. 2004;115:1473–8.
20. Racosta JM, Kimpinski K. Autonomic dysfunction, immune regulation, and multiple sclerosis. Clin Auton Res. 2016;26:23–31.
21. Zoukos Y, Kidd D, Woodroofe MN, Kendall BE, Thompson AJ, Cuzner ML. Increased expression of high affinity IL-2 receptors and β-adrenoceptors on peripheral blood mononuclear cells is associated with clinical and MRI activity in multiple sclerosis. Brain. 1994;117:307–15.
22. Habek M. Immune and autonomic nervous system interactions in multiple sclerosis: clinical implications. Clin Auton Res. 2019;29:267–75.
23. Kanjwal K, Karabin B, Kanjwal Y, Grubb BP. Autonomic dysfunction presenting as postural orthostatic tachycardia syndrome in patients with multiple sclerosis. Int J Med Sci. 2010;7:62–7.
24. Habek M, Krbot Skorić M, Crnošija L, Gabelić T, Barun B, Adamec I. Postural orthostatic tachycardia predicts early conversion to multiple sclerosis after clinically isolated syndrome. Eur Neurol. 2017;77:253–7.
25. Crnošija L, Adamec I, Lovrić M, Junaković A, Krbot Skorić M, Lušić I, et al. Autonomic dysfunction in clinically isolated syndrome suggestive of multiple sclerosis. Clin Neurophysiol. 2016;127:864–9.
26. Flachenecker P, Reiners K, Krauser M, Wolf A, Toyka KV. Autonomic dysfunction in multiple sclerosis is related to disease activity and progression of disability. Mult Scler J. 2001;7:327–34.
27. McDougall AJ, McLeod JG. Autonomic nervous system function in multiple sclerosis. J Neurol Sci. 2003;215:79–85.
28. Adamec I, Crnošija L, Junaković A, Krbot Skorić M, Habek M. Progressive multiple sclerosis patients have a higher burden of autonomic dysfunction compared to relapsing remitting phenotype. Clin Neurophysiol. 2018;129:1588–94.
29. Studer V, Rocchi C, Motta C, Lauretti B, Perugini J, Brambilla L, et al. Heart rate variability is differentially altered in multiple sclerosis: implications for acute, worsening and progressive disability. Mult Scler J Exp Transl Clin. 2017;3:205521731770131.
30. Nasseri K, TenVoorde BJ, Adèr HJ, Uitdehaag BM, Polman CH. Longitudinal follow-up of cardiovascular reflex tests in multiple sclerosis. J Neurol Sci. 1998;155:50–4.
31. Nasseri K, Uitdehaag BM, van Walderveen MA, Ader HJ, Polman CH. Cardiovascular autonomic function in patients with relapsing remitting multiple sclerosis: a new surrogate marker of disease evolution? Eur J Neurol. 1999;6:29–33.
32. Marrie RA, Reider N, Cohen J, Stuve O, Trojano M, Cutter G, et al. A systematic review of the incidence and prevalence of cardiac, cerebrovascular, and peripheral vascular disease in multiple sclerosis. Mult Scler J. 2015;21:318–31.
33. Christiansen CF, Christensen S, Farkas DK, Miret M, Sørensen HT, Pedersen L. Risk of arterial cardiovascular diseases in patients with multiple sclerosis: a population-based cohort study. Neuroepidemiology. 2010;35:267–74.
34. Habek M, Mutak T, Nevajdić B, Pucić D, Crnošija L, Krbot Skorić M. Adrenergic hyperactivity: a missing link between multiple sclerosis and cardiovascular comorbidities? Acta Neurol Belg [Internet]. 2018 [citato 17 giugno 2019]; Recuperato da. http://link.springer.com/10.1007/s13760-018-1051-4
35. Grassi G, Seravalle G, Brambilla G, Pini C, Alimento M, Facchetti R, et al. Marked sympathetic activation and baroreflex dysfunction in true resistant hypertension. Int J Cardiol. 2014;177:1020–5.
36. Dominique H, Inez W, Paul D, Eijnde BO. Exercise-onset heart rate increase is slowed in multiple sclerosis patients: does a disturbed cardiac autonomic control affect exercise tolerance? NeuroRehabilitation. 2013;33:139–46.
37. Zaenker P, Favret F, Lonsdorfer E, Muff G, de Seze J, Isner-Horobeti M-E. High-intensity interval training combined with resistance training improves physiological capacities, strength and quality of life in multiple sclerosis patients: a pilot study. Eur J Phys Rehabil Med [Internet]. 2018 [citato 17 giugno 2019]; Recuperato da: https://www.minervamedica.it/index2.php?show=R33Y2018N01A0058
38. Valencia-Sanchez C, Goodman BP, Carter JL, Wingerchuk DM. The spectrum of acute cardiopulmonary

events associated with multiple sclerosis exacerbations. Mult Scler J. 2019;25:758–65.
39. Biso S, Wongrakpanich S, Agrawal A, Yadlapati S, Kishlyansky M, Figueredo V. A review of neurogenic stunned myocardium. Cardiovasc Psychiatry Neurol. 2017;2017:5842182.
40. Baumann A, Audibert G, McDonnell J, Mertes PM. Neurogenic pulmonary edema. Acta Anaesthesiol Scand. 2007;51:447–55.
41. Watanabe M, Izumo M, Akashi YJ. Novel understanding of Takotsubo syndrome. Int Heart J. 2018;59:250–5.
42. Templin C, Ghadri JR, Diekmann J, Napp LC, Bataiosu DR, Jaguszewski M, et al. Clinical features and outcomes of Takotsubo (stress) cardiomyopathy. N Engl J Med. 2015;373:929–38.
43. Lyon AR, Bossone E, Schneider B, Sechtem U, Citro R, Underwood SR, et al. Current state of knowledge on Takotsubo syndrome: a position statement from the taskforce on Takotsubo syndrome of the heart failure association of the European Society of Cardiology: current state of knowledge on Takotsubo syndrome. Eur J Heart Fail. 2016;18:8–27.
44. Kingwell E, Koch M, Leung B, Isserow S, Geddes J, Rieckmann P, et al. Cardiotoxicity and other adverse events associated with mitoxantrone treatment for MS. Neurology. 2010;74:1822–6.
45. Hartung H-P, Gonsette R, König N, Kwiecinski H, Guseo A, Morrissey SP, et al. Mitoxantrone in progressive multiple sclerosis: a placebo-controlled, double-blind, randomised, multicentre trial. Lancet. 2002;360:2018–25.
46. Millefiorini E, Gasperini C, Pozzilli C, D'Andrea F, Bastianello S, Trojano M, et al. Randomized placebo-controlled trial of mitoxantrone in relapsing-remitting multiple sclerosis: 24-month clinical and MRI outcome. J Neurol. 1997;244:153–9.
47. Bastianello S, Pozzilli C, D'Andrea F, Millefiorini E, Trojano M, Morino S, et al. A controlled trial of mitoxantrone in multiple sclerosis: serial MRI evaluation at one year. Can J Neurol Sci. 1994;21:266–70.
48. Edan G, Miller D, Clanet M, Confavreux C, Lyon-Caen O, Lubetzki C, et al. Therapeutic effect of mitoxantrone combined with methylprednisolone in multiple sclerosis: a randomised multicentre study of active disease using MRI and clinical criteria. J Neurol Neurosurg Psychiatry. 1997;62:112–8.
49. Marriott JJ, Miyasaki JM, Gronseth G, O'Connor PW. Evidence report: the efficacy and safety of mitoxantrone (Novantrone) in the treatment of multiple sclerosis: report of the therapeutics and technology assessment subcommittee of the American Academy of Neurology. Neurology. 2010;74:1463–70.
50. Landi D, Vollaro S, Pellegrino G, Mulas D, Ghazaryan A, Falato E, et al. Oral fingolimod reduces glutamate-mediated intracortical excitability in relapsing-remitting multiple sclerosis. Clin Neurophysiol. 2015;126:165–9.
51. Kovarik JM, Lu M, Riviere G-J, Barbet I, Maton S, Goldwater DR, et al. The effect on heart rate of combining single-dose fingolimod with steady-state atenolol or diltiazem in healthy subjects. Eur J Clin Pharmacol. 2008;64:457–63.
52. Calabresi PA, Radue E-W, Goodin D, Jeffery D, Rammohan KW, Reder AT, et al. Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Neurol. 2014;13:545–56.
53. Kappos L, Antel J, Comi G, Montalban X, O'Connor P, Polman CH, et al. Oral Fingolimod (FTY720) for relapsing multiple sclerosis. N Engl J Med. 2006;355:1124–40.
54. Cohen JA, Barkhof F, Comi G, Hartung H-P, Khatri BO, Montalban X, et al. Oral Fingolimod or intramuscular interferon for relapsing multiple sclerosis. N Engl J Med. 2010;362:402–15.
55. Kaplan TB, Berkowitz AL, Samuels MA. Cardiovascular dysfunction in multiple sclerosis. Neurologist. 2015;20:108–14.
56. For the FIRST Study Investigators, Gold R, Comi G, Palace J, Siever A, Gottschalk R, et al. Assessment of cardiac safety during fingolimod treatment initiation in a real-world relapsing multiple sclerosis population: a phase 3b, open-label study. J Neurol. 2014;261:267–76.
57. Hughes B, Cascione M, McCague K, Pestreich L, Schofield L, Kim E, et al. Cardiac effects of fingolimod after first dose administration and therapy change in patients with multiple sclerosis (P01.170). Neurology. 2013;80:P01.170.
58. Meissner A, Miro F, Jiménez-Altayó F, Jurado A, Vila E, Planas AM. Sphingosine-1-phosphate signalling – a key player in the pathogenesis of Angiotensin II-induced hypertension. Cardiovasc Res. 2017;113:123–33.
59. Rossi S, Rocchi C, Studer V, Motta C, Lauretti B, Germani G, et al. The autonomic balance predicts cardiac responses after the first dose of fingolimod. Mult Scler J. 2015;21:206–16.
60. Cantalupo A, Gargiulo A, Dautaj E, Liu C, Zhang Y, Hla T, et al. S1PR1 (sphingosine-1-phosphate receptor 1) signaling regulates blood flow and pressure. Hypertension. 2017;70:426–34.
61. Kappos L, Li DKB, Stüve O, Hartung H-P, Freedman MS, Hemmer B, et al. Safety and efficacy of siponimod (BAF312) in patients with relapsing-remitting multiple sclerosis: dose-blinded, randomized extension of the phase 2 BOLD study. JAMA Neurol. 2016;73:1089.
62. Comi G, Freedman MS, Kappos L, Olsson TP, Miller AE, Wolinsky JS, et al. Pooled safety and tolerability data from four placebo-controlled teriflunomide studies and extensions. Mult Scler Relat Disord. 2016;5:97–104.
63. Baker JF, Sauer B, Teng C-C, George M, Cannon GW, Ibrahim S, et al. Initiation of disease-modifying therapies in rheumatoid arthritis is associated with changes in blood pressure. JCR: Journal of Clinical Rheumatology. 2018;24:203–9.

64. Rozman B. Leflunomide and hypertension. Ann Rheum Dis. 2002;61:567–9.
65. Hermann R, Litwin JS, Friberg LE, Dangond F, Munafo A. Effects of cladribine tablets on heart rate, atrio-ventricular conduction and cardiac repolarization in patients with relapsing multiple sclerosis. Br J Clin Pharmacol [Internet]. 2019 [citato 16 giugno 2019]; Recuperato da: https://onlinelibrary.wiley.com/doi/abs/10.1111/bcp.13919
66. Cook S, Leist T, Comi G, Montalban X, Giovannoni G, Nolting A, et al. Safety of cladribine tablets in the treatment of patients with multiple sclerosis: an integrated analysis. Mult Scler Relat Disord. 2019;29:157–67.

The Heart-Brain Connection in Patients with Duchenne Muscular Dystrophy

33

Claudia Bearzi and Roberto Rizzi

Contents

Abstract

Duchenne muscular dystrophy (DMD) is a progressive form of muscular dystrophy that occurs primarily in males and though in rare cases may affect females. It is caused by mutations in the *DMD* gene, which result in the completely lack of the related protein dystrophin (Dp427). Absence of Dp427 causes progressive weakening and degeneration of muscles. In addition, beyond skeletal muscle, these mutations alter the respiratory and heart

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*,
https://doi.org/10.1007/978-3-030-28008-6_64

performances, representing the leading causes of death in these patients. Furthermore, certain neuronal populations express Dp427, whose perturbation is correlated with several neural disorders in DMD patients. Recently, it has been hypothesized that dystrophin could play a fundamental role also in the axonal growth mediated by the nerve growth factor (NGF). Indeed, different studies have shown that in a dystrophic scenario, different neural populations exhibit reduced responsiveness to NGF stimulation, compared to controls. Parameters, such as number and length of neurites, growth cone advancement, and receptor ligand responsiveness (NGF/TrkA), are significantly reduced in neurons deriving from DMD patients or dystrophin-deficient (*mdx*) mice, a murine dystrophic model. Remarkably, the reduced sympathetic innervation affects even more distal districts, such as the heart, disturbing electrophysiology, beating, and contraction force. A deepen analysis of the relationship between the heart and brain in the context of DMD offers a new strategy for patient stratification and knowledge of the pathology that could open up new therapeutic scenarios.

Keywords

Heart · Brain · Innervation · Duchenne muscular dystrophy · Nerve growth factor · Sympathetic nervous system · Fibrosis · Postganglionic adrenergic neurons

Introduction

Cardiac innervation originates from the sympathetic nervous system (SNS), and it occurs in the late stages of embryogenesis. SNS is able to condition cardiac activity throughout life, modulating rhythm and contractility based on emotional and physical stresses. The sympathetic neurons (SNs) are capable to regulate the contractility, frequency, and electrical conductivity of the entire cardiac system, releasing specific neurotransmitters, such as norepinephrine (NE). On the other hand, cardiac cells are able to guide the innervation and guarantee the survival of the afferent neurons through the secretion of specific molecules. The main molecule that guides the distribution of sympathetic synapses is the nerve growth factor (NGF).

The topology of innervation is generated over a fine balance between chemoattracting and chemorepellent cardiac signals, which allow or repel penetration of the nerve endings within the myocardium. Some areas of the heart are differentially innervated, such as the subendocardial and subepicardial regions, because of the function that the SNS must exercise in that particular area. Although cardiac innervation density reflects in general the levels of NGF produced by the heart, some myocardial elements, such as the sinoatrial node, are more intensely innervated, in line with the specific physiologic role of the SNS in controlling heart rhythm in response to stimuli related to fight-or-flight response. The physiologic role of such innervation pattern is not fully understood, and its alteration is connected with impaired cardiac function, activity, and arrhythmias, leading to different pathologies. Indeed, many diseases present unconventional innervation, such as diabetes mellitus, heart failure, and several dystrophies, including Duchenne muscular dystrophy (DMD).

In individuals affected by DMD, despite muscle wasting, cardiomyocytes (CMs) degeneration and necrosis are the main causes of morbidity and death. Heart failure (HF) is generally preceded by disturbances in heart rate variability (HRV), and noninvasive measurement of the autonomic nervous system is an important instrument to envisage adverse cardiovascular events. As major observations in DMD patients, several studies reported a reduced parasympathetic activity and an augmented sympathetic predominance: indeed, regional differences in sympathetic discharge are linked to arrhythmias in both ischemic and structurally normal hearts of arrhythmic patients. This hypothesis is also supported by a reduced presence of neurons at superior cervical ganglia level and by an imbalance of many components linked to the NGF signal, in the same patients. The mechanism, by which regional heterogeneity of

sympathetic discharge triggers arrhythmia, is related to the action potential (AP) dispersion, an electrophysiological state favoring ventricular arrhythmias. The increment in sympathetic tone may be the primary cause or may be a compensatory response (secondary cause) to cardiac dystrophy that further directs DMD patients toward HF. Moreover, there is a robust correlation between reduced HRV and myocardial fibrosis within the DMD population. These patterns manifest in DMD patients at early stage and become more evident as the disease severity and age increment. Because a primary role for autonomic imbalance in DMD is not well sustained, deeper studies are necessary to completely define this possibility.

In this chapter, the relationship between the heart and brain in DMD scenario will be analyzed both morphologically and physiologically, deconstructing the state of the art and focusing on interactions that could promote alternative hypotheses for the treatment of the disease.

Duchenne Muscular Dystrophy

Duchenne muscular dystrophy (DMD) is triggered by mutations of the gene encoding for the dystrophin enzyme, found on the short arm of the X chromosome in the Xp21 region [18], and manifests mostly in males. Although most boys with DMD inherit the abnormal gene from their mothers, some may develop the diseases as the result of a spontaneous mutation of the dystrophin gene that occurs randomly for unknown reasons (de novo or sporadic cases). Some females, who inherit a single copy of the DMD gene, may display some of the symptoms related to the disease, such as weakness of certain muscles, especially those of the arms, legs, and back. Carrier females, who acquire DMD symptoms, are at risk for developing heart abnormalities, which may present as exercise intolerance or shortness of breath, and, if left untreated, heart abnormalities can cause life-threatening complications.

DMD represents the most common lethal genetic disorder and cause progressive muscle degeneration. This pathology is provoked by a mutation of the *DMD* gene, which regulates the assembly of a protein, called dystrophin (Dp427), that is found in association with the inner side of the membrane of skeletal and cardiac muscle cells.

DMD is the most common childhood onset form of muscular dystrophy and affects males almost exclusively. The prevalence is estimated to be 1 in every 3500 live male births. Age of onset is usually 3–5 years old [18], and it is usually recognized between 3 and 6 years of age.

Duchenne disease is characterized by the progressive loss of voluntary movement of the lower limbs and subsequently of the upper ones, caused by the increase of the fibrotic tissue and, in the late stages, by significant intensification of adipose tissue in the muscle compartment. The disease is progressive, and most affected individuals require a wheelchair by the teenage years. The long-term effects imply cardiac or respiratory malfunction, analogically to the skeletal muscle, which fails to accumulate the cytoskeletal protein dystrophin and subsequently lead to death [68].

DMD is an incurable disease, but the life can be made more comfortable by physiotherapy, surgery, and a positive supportive environment. Cares are focused to specific symptoms present in each individual. Boys affected by DMD require multidisciplinary care, including clinical and functional assessment, pharmacological agents, physical exercises, prevention of anticipated complications, and genetic counselling. Surgery may be suggested in some patients to handle contractures or scoliosis. Supports could be utilized to prevent the development of contractures. The use of mechanical aids, such as braces and wheelchairs, may become required to aid walking (ambulation).

End-stage heart failure (HF) is increasingly becoming the main cause of death in DMD patients; consequently, current therapy options include inhibitors of the renin-angiotensin system, which are used as first-line therapy, along with corticosteroid treatment, COX-inhibiting nitric oxide donors, and beta-blockers. Mechanical cardiac support with left ventricular assist devices (LVAD) is a possible treatment, as these patients usually are not recommended for cardiac

transplants, due to progressive myopathy and limited functional capacity. However, the insufficient availability of LVAD devices and the lack of prospective studies with large follow-up periods, for evaluating their use in DMD, are a concern.

Finally, several therapeutic approaches to cure DMD are being investigated, which can be divided into two groups: therapies focused to restore dystrophin expression and those that point to compensate for the lack of dystrophin. Therapies that restore dystrophin expression include read-through therapy, exon skipping, vector-mediated gene therapy, and cell therapy. Among these approaches, the most advanced are the read-through and exon skipping therapies [64].

Dystrophin and the Heart

The dystrophin protein is associated with a large complex of proteins and glycoproteins, known as the dystrophin-glycoprotein complex (DGC). Dystrophin is thought to play an important role in maintaining the membrane (sarcolemma) of skeletal and cardiac muscle cells, and its main function is to connect the cytoskeleton of myocytes with the extracellular matrix (ECM).

The clinical features of DMD include skeletal myopathy and respiratory and cardiac dysfunctions, which are the most common cause of death.

In DMD patients, a high resting heart rate (HR) is present at early stages [31, 58]. Surprisingly, this dysfunction occurs before the onset of changes in the ejection fraction (EF), and this high resting frequency can be considered an abnormal form of heart rate variability (HRV), which could correlate with autonomic dysfunction. HRV is a parameter of autonomic cardiac activity and is connected with various morbidity and mortality, resulting in acute myocardial infarction, congenital heart disease, diabetic neuropathy, and congestive HF, while in DMD, only recently, has been demonstrated the necessity to consider it for the patients' stratification [4, 38, 53, 67].

Currently, two theories have been promoted to explain the mechanisms underlying DMD cardiomyopathy: (i) the loss of myocyte structural integrity, following the absence of dystrophin, leads to a deterioration under hemodynamic stress together with an impairment of ventricular function; and (ii) the cause could be the interruption in the regulatory function and, consequently, in the secondary signaling pathways, triggered by the absence of dystrophin [31].

The lack of dystrophin in cardiomyocytes (CMs) sensitizes the cells to stressful stimuli, such as chemical, mechanical, neurohormonal, or inflammatory insults, inducing apoptosis and a severe cardiac remodeling. Thus, many researchers have hypothesized that autonomic dysfunction in DMD can be traced back to excessive remodeling and to abnormal conduction, given by the extent of the fibrotic cardiac areas, characteristic of the disease.

Duchenne Muscular Dystrophy and Myocardium

Patients affected by DMD, initially, have structurally normal hearts. Successively, CMs death initiates an inflammatory cascade, during which macrophages (MP) migrate to clear the damaged cells and debris. After MP recruitment, fibroblasts invade the damaged area developing scar tissue or fibrosis in the heart, considered as the earliest sign of myocardial involvement. Fibrotic tissue is very inflexible compared to the normal cardiac tissue and thus restricts the efficiency of myocardial contraction. The fibrosis starts in the left ventricular wall, from the epicardium, and advances into the endocardium and progressively extends throughout most of the outer half of the ventricular wall. This pattern of fibrosis is unique to dystrophinopathy. Gradually, the fibrotic region stretches, becomes thinner, loses contractility, and results in dilated cardiomyopathy leading to end-stage HF (Fig. 1). The dilation of the heart increases left ventricular volume, decreases systolic function, and often leads to mitral valve regurgitation, resulting in reduced cardiac output and hemodynamic decompensation. The cardiac phenotype in each DMD patient depends from the patient's particular type of dystrophin gene

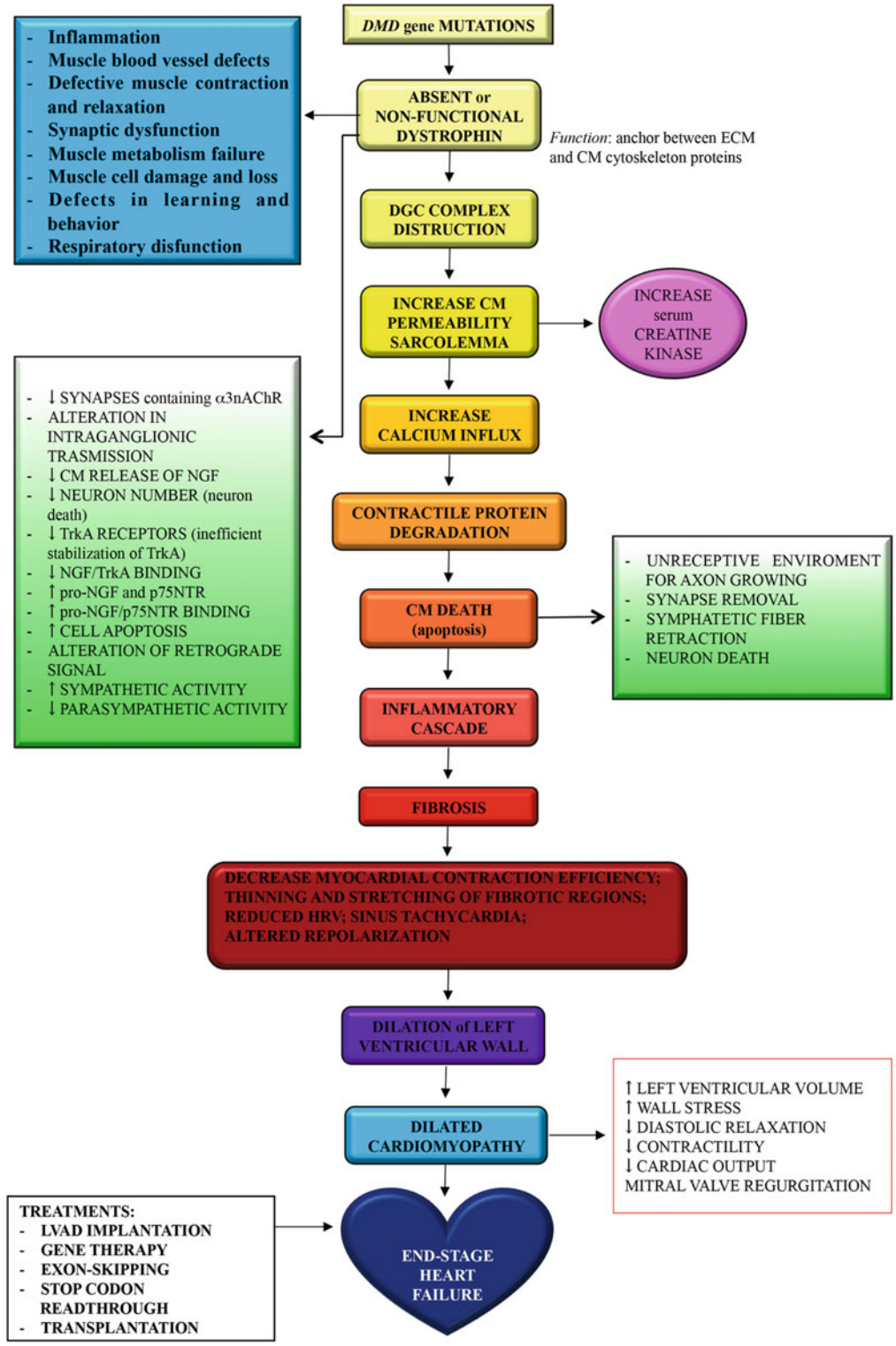

Fig. 1 Flow diagram describing the natural progression of cardiovascular dysfunction in patients affected by DMD and lacking dystrophin. The process begins with cardiomyocyte (CMs) death, develops in dilated cardiomyopathy, and leads to cardiac end-stage failure. ECM, extracellular matrix; NGF, nerve growth factor; HRV, heart rate variability; LVAD, left ventricular assist device

mutation; however, the relationship between genotype and phenotype remains elusive. Recognition of HF symptoms in DMD patients can be difficult due to physical inactivity and other respiratory complaints that can hide the diagnosis. Currently, clinical guidelines recommend the initial cardiac screening at the time of diagnosis of DMD, every 2 years until 10 years of age and yearly thereafter [35].

Many DMD patients develop sinus tachycardia by the age of 5, and conduction changes by 10 years of age. Irregular conduction patterns, named fragmented QRS (fQRS), are characterized by the presence of an additional R-wave (R′) or notching in R-wave or S-wave or the occurrence of more than one R′ without a typical bundle branch block. These outlines indicate wall motion abnormalities and could be one of the first signs of myocardial change in the patients. Depolarization and repolarization abnormalities are gradually prominent in patients over 10 years of age. Shortened PR intervals are appreciated in about 50% of patients, and QT prolongation is rare but can also be present. Resting sinus tachycardia, loss of circadian rhythm, and reduced HRV, caused by increased sympathetic activity, can be detected by electrocardiogram (ECG). More important, arrhythmias could develop with an advanced fibrosis, including atrial fibrillation, atrioventricular block, ventricular tachycardia, and ventricular fibrillation [33, 73]. The presence and progress of fQRS may be a useful marker of cardiac involvement for detection and follow-up. Electrocardiographic evidence of repolarization abnormalities implicating the risks of cardiac dysrhythmias and sudden cardiac death is gradually prominent in patients with DMD over 10 years old.

HF, with multisystem organ involvement and inability to rehabilitate after cardiac transplantation, is a relative contraindication for heart transplantation, limiting the broad use of this therapy in the DMD population. Given the scarcity of organs for heart transplantation, the use of LVADs is demonstrated to be effective in treating patients with end-stage or advanced HF.

Changes in cardiac function, induced by DMD, determine a physiopathological scenario almost unique, whose effects are still to be properly clarified. Normally, cardiac remodeling and fibrosis are compensatory mechanisms consequent to cardiovascular events. Both processes are interrelated and critical, strictly determining the clinical outcome. However, they are also balanced under physiological conditions as they represent the attempt of the cardiac muscle to repair the tissue [56]. The DMD exacerbates this scenario, and fibrosis progressively substitutes all dead CMs, thus leading to cardiac failure and subsequently to death. In addition, patients affected by DMD have a very characteristic electrocardiographic pattern. Some subjects present a reduction in variability in response to sympathetic activation, correlated with a distinct tachycardia [75].

Scientists, from all over the world, have tried to give different explanations of the phenomenon. The cardiac remodeling correlates with reduced contractility, autonomic nervous system, and posture dysfunction that are the main outputs and could affect cardiac performance, but the solution of the problem, faced with a multifactorial approach, has not yet been revealed.

As mentioned, patients affected by DMD have characteristic ECG, showing tachycardia and substantial decreasing in HRV [50, 75]: common and characteristic features, such as sinus tachycardia (40%), mild alteration of repolarization, and reduced HRV (75%), are detected, while no abnormalities are found in arrhythmias. Tachycardia, altered states of repolarization, and HRV presuppose a reduced tone of the parasympathetic system and the predominance of sympathetic tone, already reported in the literature relative to DMD patients.

Electrocardiographic abnormalities have been ascribed to various mechanisms, including postural syndromes that intensify cardiac responses, iperactivation of endogenous compensating mechanisms, and a possible autonomic dysfunction. However, the pathogenesis of electrical and autonomic disorders in patients affected by DMD remains completely unveiled [16]. In most patients, the ECG shows an abnormal cardiac profile. In particular, shortening of atrioventricular conduction time seems to be a feature always present in the pathology. Indeed, some

pathological features, such as persistent sinus tachycardia, appear in the subject before muscular degeneration [11, 54].

The heartbeat of DMD patients presents a higher baseline than the healthy subjects, approximately 20%, regardless of the registration condition or the rash manifestations of the disease [50, 75].

Although there is no clear evidence that the mechanism of autonomous regulation is responsible, many theories are promoting the hypothesis that in the pathological scenario of DMD, there is a decrease of the parasympathetic nervous system in favor of the sympathetic nervous system. Furthermore, the same researchers claim that this condition would be aggravated during the disease progression [12, 50, 74, 75]. The mechanisms of these changes in the ECG are not known, although there is a growing consensus that an abnormal autonomous regulation is responsible.

For this reason, the combination of chronic tachycardia, prolonged sympathetic activation, and impairment of baroreceptor reflex control is thought could be the triggering cause of HF in patients with DMD [65].

Dystrophin and the Brain

In 2005, a theory based on a possible autonomic dysfunction has been proposed as the cause of frequent cognitive impairment in DMD patients [13].

The smooth and cardiac muscles and the nervous system express truncated isoforms of dystrophin, unlike skeletal muscle. These isoforms, encoded by the same gene, are generated by alternative splicing or by a different action of the promoter [3, 47].

Data generated on *mdx* mouse, a DMD animal model, demonstrated that, in the superior cervical ganglia (SCG), dystrophin is localized at the postsynaptic apparatus of a number of intraganglionic synapses where, together with the transmembrane glycoprotein β-dystroglycan (β-DG), it stabilizes the nicotinic acetylcholine receptors, containing the α3 subunit (α3nAChR). In this mouse model, the number of synapses containing α3nAChR is significantly decreased [14], suggesting alterations in the fast intraganglionic synaptic transmission that it could cause the autonomic dysfunction described in patients affected by DMD.

One of the most fascinating theories claims that the damage produced in the heart could affect retrogradely the ganglion neurons [24]. Some characteristics and responses of neurons are regulated by the dynamics of the target organs, such as cell body size, dendritic arborization, synapse formation and plasticity, neurotransmitter secretion, and neuron apoptosis [1, 60]. Recently, dystrophin has been shown to be able to modulate the neuronal size, the dendritic arborization, the stabilization of the neurotransmitter receptor groups, the synaptogenesis, the synaptic plasticity, and the neuronal survival [7].

The analysis carried out at SCG level of adult *mdx* mice showed a 36% neuron reduction compared to the wild-type condition. The degeneration occurred between day 5 and 10, while, at earlier stages, the number of neurons was the same as the wild type. These findings highlight the possibility that degeneration and neuronal loss occur after birth due to the retrograde pathological modulation exerted by the target organ. However, immunofluorescence experiments, labelling tyrosine hydroxylase (T-OH), displayed a reduction of axonal defasciculation and/or terminal germination throughout the SCG target already at day 5, following changes in the dynamic link between the cortical actin cytoskeleton and ECM.

Signals that are conveyed from nerve terminals to remote cell bodies are crucial for neuronal survival. Tropomyosin-related tyrosine kinase receptors (Trks) are internalized from axon membranes and transported by dynein motors to cell bodies, in response to neurotrophin stimulation. Survival maintained by target-derived neurotrophins is abolished when internalization and dynein-based transport of Trks are disrupted [26].

Dystrophin is responsible for the cytoskeleton-ECM connection through the dystrophin-glycoprotein complex [48] and, in the absence/dysfunction condition, dramatically alters this linking. This could also trigger an aberrant

axonal growth, caused by the impairment of ganglionic transmission, following the reduction of intraganglion α3nAChR [14]. Indeed, ganglionic neurons may also be retrogradely affected by the injuries induced in the heart, one of the SCG target organs, by the lack of dystrophin, which develops into the dilated cardiomyopathy, described in DMD patients and *mdx* mice. Neuron survival and differentiation, density of innervation, and collateral sprouting firmly depend on target-derived neurotrophic factors, such as NGF. Therefore, excessive neuron death in *mdx* mouse SCG may be triggered by an insufficient provision of these factors, attributable to their reduced synthesis by cardiac muscle cells damaged by the lack of dystrophin. This condition may also be linked to an impairment of Trks-activated retrograde signals due to degeneration of the actin cortical cytoskeleton degeneration, which can diminish axonal retrograde transmission. Dynein-dependent transport is necessary for retrograde survival signals triggered by Trks in sensory neurons, and the integrity of the cortical actin cytoskeleton is needed for the neurofilament transport based on dynein and myosin [32]. Neurotrophins, secreted by target tissues, bind and activate specific receptors, such as Trks, located on axon terminals of the innervating neurons and thereby initiate retrograde signals that culminate in neuronal survival. If this process requires transport of long-range signals, then defects in dynein function might cause cell death by interfering with neurotrophin-dependent survival.

The dystrophin-glycoprotein complex protects the cell membrane from the mechanical stress developed during contraction. The complex deficiency in DMD causes plasma membrane rupture, and the injured muscle cells show greater permeability to the macromolecules, affecting muscle physiology, contractile properties, and survival [3, 30]. Possible CMs functional alterations, resulting from plasma membrane impairment, may render them unreceptive for axon growing and provoke synapse removal and retraction of the sympathetic fiber. Furthermore, the same deficiency of dystrophin would influence the innervation by neurons that would not be capable to drive the axon in that hostile system [13]. Therefore, the altered physiology of SNs and corresponding muscle target cells, in the DMD scenario, may perform a combined action and trigger the autonomic impairment described in patients affected by DMD.

Sympathetic Innervation System

The autonomic nervous system (ANS) is the component of the peripheral nervous system that controls cardiac muscle contraction, visceral activities, and glandular functions of the body. Specifically, the ANS can regulate heart rate, blood pressure, rate of respiration, body temperature, sweating, gastrointestinal motility and secretion, and other visceral activities that maintain homeostasis. The ANS has two interacting systems: the sympathetic and parasympathetic systems. Sympathetic and parasympathetic neurons exert opposed effects on the heart. The sympathetic system prepares the body for energy spending, emergency, or stressful situations, such as "fight-or-flight" response, while the parasympathetic system is most active under restful conditions. The parasympathetic responds to the sympathetic system, after a stressful event, and reestablishes the body to a restful state. The SNS releases norepinephrine (NE), while the parasympathetic nervous system (PNS) releases acetylcholine (ACh). Sympathetic stimulation increases heart rate and myocardial contractility; therefore during exercise, emotional excitement, or under various pathological conditions, such as HF, the SNS is activated. During rest, sleep, or emotional tranquility, the PNS prevails and regulates the heart rate. Consequently, the ANS effect on the heart is the balance between the opposing actions of the SNS and PNS [23].

Thus, cardiac sympathetic innervation, releasing neurotransmitters, mostly NE, is the principal cardiac rhythm, force, and relaxation/conduction speed modulator, initiating at the late embryonic stage and prosecuting throughout the whole life [61]. On the other hand, the cardiac sympathetic system development, the networking between neurons and their myocardial targets, and the neuronal survival preservation are controlled by the

paracrine effect of cardiac signaling molecules. Indeed, during postnatal development, the equilibrium between the action of chemoattracting neurotrophins, principally NGF, and neurochemorepellent factors allows the verve endings permeation into the cardiac walls [29]. The selective allocation of the neurons to different heart regions and the physiologic function of the innervation outline are not completely understood, and its variation is correlated to a reduced cardiac function/activity and arrhythmias [29]. Though cardiac sympathetic nerve density mirrors the NGF expression levels produced by the heart [34], some myocardial structures, such as sinoatrial node, are more densely innervated, coherently with the SNS function in the control of cardiac rhythm.

NGF and Sympathetic Cardiac Innervation

SN differentiation and viability are supported by NGF secretion from the target organs, as demonstrated by the complete loss of postganglionic neurons in mice ablated for NGF or its receptor, TrkA. Like other neurotrophins, NGF is expressed as a pre-pro protein of the alternative splicing isoforms A and B. NGF maturation occurs through cleavage of the pre-domain in the endoplasmic reticulum and the pro-domain in the Golgi apparatus, and N-linked glycosylation and sulfation gain the expression of mature NGF.

The major NGF source, used by mature SNs, originates in its target organs. In the murine cardiac system, the neurotrophin became detectable around the time of initial innervation by SNs (embryonic day l2) and augmented 14-fold in the following 2 days, to reach adult levels already at embryonic day l4. Successively, there is a reduction of NGF levels, and a second expression peak appears about a week after birth (postnatal day 8); afterward NGF expression decreases to that of the adult heart. The initial growth of postganglionic SNs during development reflects NGF expression, but the penetration of neurons into the myocardial walls occurs postnatally and the adult neuronal pattern appears only 3 weeks after birth (postnatal d21) [37].

Thus, NGF synthesis, in target organs, begins alongside with the onset of sympathetic innervation, and NGF responsiveness, in SNs of the SCG, also progresses parallel to or shortly after the target contact, since the earliest stage, at which a small population of NGF-responsive neurons could be identified, is day l4. Therefore, both, sufficient NGF synthesis and NGF responsiveness, seem not to occur before the establishment of the initial target contact by innervating neurons, indicating that NGF is not implicated in the initial direction of outgrowing sympathetic axons to their target organs and that SNs during development are provided with NGF via retrograde axonal transport from the target organs.

Different cardiac cell types express NGF both in physiological and in pathological conditions: in CMs and smooth muscle cells, NGF modulates the cardiac wall innervation and is regulated by extracellular factors, such as endothelin-1 [28]. Cardiac fibroblasts (CFs) possess a fundamental function in pathological circumstances, such as myocardial infarction, inducing NGF production and consequently higher innervation of the peri-infarcted tissues. MPs, which, in response to ischemic damage, penetrate the myocardium, express NGF [25].

NGF, once released by any of cellular sources, operates on the neurons by binding to specific membrane receptors. Two are the neurotrophin receptors expressed on SNs: TrkA, which is specific for the mature form of NGF and binds it with *intermediate affinity*, and p75NTR, which binds to different neurotrophins and pro-neurotrophins, such as pro-NGF, with *low affinity*. Co-expression of both receptors on neuronal membrane increases NGF affinity for the TrkA.

NGF variants (mature NGF and pro-NGF) possess opposed effects on neuronal viability that depend on their interaction with the receptors (TrkA and p75NTR) co-expressed on the same cell [51]. Mature NGF is released as a homodimer and binds to the *high-affinity* TrkA receptor, triggering its autophosphorylation, endocytosis, and retrograde transport to neuronal soma. These interactions sustain neuronal viability and differentiation by regulation of gene transcription for proteins involved in signaling, in intracellular

trafficking, and in function of synapsis and cell survival [27]. Instead, removal of TrkA activation, following NGF deprivation, or p75NTR activation, by either other neurotrophins or pro-NGF, causes neuronal apoptosis [51].

The function of NGF, in the postnatal days, regards cardiac sympathetic innervation network, through the selection of neurons that will innervate the target organ, meaning that only neurons that successfully innervate the heart would receive sufficient neurotrophin and survive and the quantity of sympathetic nerves that the organ receives becomes proportional to the produced neurotrophin [52].

Co-expression of two neurotrophin receptors with opposite effects on cell viability permits selection by neuronal competition. Indeed, in vitro experiments, using neurons, revealed that NGF treatment increases the expression levels of TrkA and neurotrophins with the following effects: (i) the upregulation of TrkA receptors amplifies the duration of survival signaling in those neurons receiving high amounts of NGF; (ii) the NGF-stimulated neurons release the neurotrophin, which activates p75NTR, and oppose TrkA effects provoking apoptosis of the nearby neurons that receive lower NGF quantity [15]. Beside the effect that NGF exerts on SNs supporting cell survival, the NGF has also a pivotal role in guidance during development [20].

Neuronal survival and differentiation, axonal growth, and terminal branching have been studied mainly on mouse models, and it has been shown that NGF plays a fundamental role in all these processes through its link with the TrkA receptor [21]. As mentioned before, the pro-NGF/p75NTR promotes neuronal apoptosis, especially in limiting NGF-TrkA signaling conditions [21]. Therefore, an imbalance in the relationship between immature form and mature form of NGF could be the cause of the loss of the neurons of the ganglia of the cervical roots, which project toward the heart, altering the peripheral system.

In fact, some data generated in the DMD animal model have indicated a significant increase in the 32 kDa pro-NGF form in both day 5 and day 10. Considering the apoptotic effect of pro-NGF in some conditions [21], the contribution of the pro-NGF in the induction of apoptosis in neurons would emerge [13].

Furthermore, the decrease in TrkA and phospho-TrkA (pTrkA, the tyrosine phosphorylated residues of TrkA that interacts with proteins which have potential roles in signal transduction) in the same animal models also suggests an alteration in the receptor-mediated NGF signaling, which may influence the expression of molecules important for the correct axonal growth and defasciculation [22].

Sympathetic Innervation in Duchenne Muscular Dystrophy

Both, patients affected by DMD and *mdx* mice, display impairment of the autonomic nervous system confirmed by electrocardiographic analysis, but it is not clear yet if the dysfunction induces the sympathetic activity to increase or to decrease: indeed, the greater basal heart rate in DMD patients and *mdx* mice indicates that the sympathetic complex is favored respect to the parasympathetic nervous system. Instead, ECG recording upon inhibition of the PSN system by atropine treatment exhibited augmented heart rate in the wild type and not in the *mdx* mice, suggesting that impairment of cardiac sympathetic innervation occurs in dystrophic mice. This evidence is further reinforced by alterations of the components, implicated in NGF-mediated signaling and by the decreased number of SNs in SCG from *mdx* mice, when compared to controls [13, 42].

NGF Role in Duchenne Muscular Dystrophy

DMD subjects suffer several neural syndromes since selected neuronal populations express dystrophin. In contrast to the muscle scenario, where dystrophin expression reaches a plateau already in fetal life, in the brain it appears to be developmentally regulated, probably because of the need to modulate neurogenesis, neuronal migration and differentiation, neuronal size, and dendritic arborization [47]. Consequently, DMD patients and

mdx mice show, during development, different degrees of cognitive and behavioral anomalies [55, 69]. *Mdx* mice display several structural and functional alterations in SCG, which innervates different muscular, such as the heart, and non-muscular targets; further they present reduced muscular noradrenergic innervation and diminished axon defasciculation and terminal branching [13, 42]. The expression of NGF receptors (TrkA and p75NTR) is also altered, indicating a discrepancy in the NGF signaling cascade [42] and a diverse modulation expression of genes implicated in neuron survival and differentiation [40].

It has been, therefore, hypothesized that dystrophin could have a role in NGF-dependent axonal growth during development and adulthood [42, 43]. After axotomy, axon regeneration potential of SCG neurons was analyzed in *mdx* and wild-type mice: while noradrenergic innervation of *mdx* mouse submandibular gland, main source of NGF, was recovered similarly to wild type, iris innervation (muscular target) didn't restore. Therefore, it was evaluated whether dystrophic SCG neurons were weakly responsive to NGF, particularly at low concentration. Following in vitro axotomy, the number of regenerated axons in *mdx* mouse neuron cultures was indeed diminished, compared to wild type, at the lower concentration of NGF. These results imply that neuronal damages in *mdx* mice are sufficient for dropping regeneration capabilities and that NGF concentration is a limiting factor in vitro and could be in vivo as well: when higher NGF concentration was used, the neuron regenerative performance in *mdx* mouse improved.

Further, it was noticed that neurite growth parameters and NGF/TrkA receptor signaling in differentiating neurons (not injured) were significantly reduced when cultured with low concentration of NGF, as well as with higher NGF concentrations. These data indicate a role for dystrophin in NGF-dependent cytoskeletal dynamics connected to growth cone advancement, possibly through indirect stabilization of TrkA receptors. Decreasing of TrkA/NGF signaling prevents growth cone regeneration and reduces cytoskeleton dynamics at the axon terminal. It has been theorized that, since in *mdx* mice, lower concentrations of NGF recall less TrkA receptors on the neuron membrane, there is a consequent decrease in intracellular signaling pathways, which could be due to the inefficient stabilization of the receptor on the cell surface, indirectly induced by lack of dystrophin. Interestingly, when NGF concentration increases, no differences were observed in terms of TrkA phosphorylation, supporting the hypothesis that the more NGF is present, the more efficiently TrkA receptors in dystrophic neurons are able to bind it. Although the dynamical characteristics to be considered are multiple and intermingled, the main idea is that dystrophic neurons are less sensitive to NGF compared to wild type.

This is very important to address the DMD pathology: muscle-innervating autonomic neuron impairment could convey to weakening axon recovery, neuron survival, and consequently augment dysfunctions. Finally, these data could provide the incentive for new research aimed at developing therapeutic strategies to reduce neural dysfunctions and autonomic failures in DMD patients.

Neuro-Cardiac Junction

The whole mammalian heart is innervated by SNs, which enter the heart from the epicardium and extend their processes throughout the myocardial interstitium, running parallel to capillary vessels. On the other hand, NGF, released by the myocardium, modulates the cardiac innervation by SNs after binding to its receptor (TrkA) and is required for neuronal survival. Therefore, it presents a bidirectional coupling between SNS and the heart. Sympathetic neurons are joined to the heart for neurotrophic stimulation necessary for neuronal viability. On the other hand, the heart requires to be connected to sympathetic neurons to receive NE stimulation for an efficient heart contraction, thus modulating the frequency of heart contraction (positive chronotropic effect), the conduction velocity (positive dromotropic effect), the contractility (positive inotropic effect), the relaxation (positive lusitropic effect), and the

CM size [78]. To achieve such sophisticated functions, sympathetic ganglia incorporate both peripheral and central inputs and transmit information to the heart via motor neurons, directly interacting with target CMs. So far, the dynamics and mode of communication between these two cell types, which determine how neuronal information is adequately translated into the wide spectrum of cardiac responses, are still blurry.

Merging the anatomical and structural information, recently highlighted using imaging technologies, and the functional evidence in cellular systems, it can be promoted the existence of a specific "neuro-cardiac junction" (NCJ), where sympathetic neurotransmission occurs in a "quasi-synaptic" way. The properties of such junctional-type communication meet with those of the physiological responses, generated by the cardiac SNS, and elucidate its capability to coordinate heart function with precision, specificity, and elevated temporal resolution.

Lately several investigators focus on the interactions in the mammalian heart between cardiac SNs and CMs. Similarly, to the specific neuromuscular contact sites of the neuromuscular junction (NMJ), many morphological and ultrastructural analyses revealed that sympathetic varicosities and CM membranes are in close contact [8].

In rodent hearts it was demonstrated by two-photon microscopy that not only all CMs are in contact with several varicosities from the same neuronal process but also that each CM establishes parallel contacts, possibly with processes from different neurons. The heart consists of a complex multicellular network, composed mostly of CMs, CFs, and endothelial cells and is held together by ECM and encapsulated in a dense mesh of neurons. All these cells express receptors for sympathetic neurotransmitters, and, because of the capillary innervation of the heart, each cell type is close to a neuronal process, indicating that cardiac SNs may control myocardial function in a cell-specific fashion [77].

The dense innervation of the myocardium and the direct interaction between SN and myocardial target cells suggest that neuro-cardiac coupling may occur at specific junctional sites.

The existence of a neuro-cardiac communication can be assumed considering the following concepts: (i) sympathetic neurotransmission has to take place powerfully upon maximal neuronal activation ("fight-or-flight" reaction); (ii) neuronal activation requires to initiate cardiac activation almost instantaneously, to quickly increment blood pressure, through frequency of heart contractions; (iii) the system has to guarantee that under stress the entire heart muscle undergoes changes in inotropy at the same time; and (iv) the system must be precise enough to operate almost on a beat-to-beat basis in the regulation of electrophysiology and trophic signaling. To coordinate all these tasks, it is necessary a signaling dynamics of intercellular communication that permit the system to work with wide effect range, precision, and specificity of responses to the diverse stimuli.

However, the NCJ hypothesis is not completely accepted, since specific molecular factors are not determined, and the obtained results are not conclusive [41, 79]. An effort was done to find molecular determinants focusing on proteins that normally participate in intercellular junctions, such as VCAM1 and α4p1 integrins [71]. Larsen and coworkers determined protein complexes present in neurons and CMs at cell-cell interface [39], as β-ARs, SAP97, AKAP79, cadherin, and β-catenins are confirmed in ex vivo studies as well [62]. Still the molecular machinery that links the two membranes together (synapses/junction structure) is not fully reassembled. Remarkably, based on in vitro experiments, even CFs could interact with sympathetic neurons, but the interactions are labile and transient in time, in contrast with stable connection endorsed with CMs [77].

Even if recent studies indicate that the contact site is enriched in presynaptic markers (synapsin I, synaptotagmin), in cell-to-cell adhesion molecules (cadherins, β-catenin), and in postsynaptic specializations of the CM membrane [62], this model has not been explained at the functional level. Moreover, the neurotransmitters, the intercellular signaling dynamics, and how the target cells respond to the intercellular communication have not been clarified.

Animal Models

Several mouse models have been developed to better understand the DMD basic biology. However, there has been a lack of animal models that recapitulate the severe phenotype of DMD disease and facilitate a test of therapeutic strategies.

The *mdx* mouse is the most employed model for studying DMD. This strain originated from a spontaneous mutation in the premature stop codon that terminated exon 23 of the dystrophin gene in the C57BL/10ScSnJ mouse [5]. Although this mutation leads to dystrophin function loss, there is a compensatory upregulation of another protein, named utrophin, which exhibits 80% homology and shares structural and functional motifs with dystrophin [2]. In *mdx* mice the upregulation of utrophin repairs plasma membrane integrity and muscle degeneration [19], while in human DMD muscle, the levels are not sufficient to prevent disease progression [44]. Consequently, the lack of dystrophin and compensatory upregulation of utrophin in the *mdx* mouse indicate that dysfunction of skeletal muscle characteristic of DMD is less severe. In contrast to the degeneration of skeletal muscle, which is rescued to some extent, this strain exhibits myocardial damage, even if it develops cardiomyopathy very late in its life. Starting from 3 months of age, *mdx* mice display altered metabolic processing associated with increased oxygen consumption, decreased cardiac efficiency, and increased cell membrane fragility [36]. At 6 months, *mdx* heart is hypertrophied compared to wild-type controls, suggesting cardiac dysfunction, and, from 9 months of age, fibrosis is evident histologically. 10-month-old mdx mice have poor contraction and slower rate beating than normal [57], and at 15 months, interstitial fibrosis is detectable in the endocardium, myocardium, and epicardium of the ventricular wall and septum [45]. Considering these characteristics, the *mdx* mouse model can provide helpful information on the pathophysiology of the DMD cardiomyopathy.

Many of the knowledge, we have gained over the last few years on DMD, stems from the in-depth study of *mdx* mouse model, although the recapitulation of the disease sometimes appears to be less aggressive. Some scientists have developed echocardiographic profiles of *mdx* mice to confirm the fact that many DMD patients die from HF. Mice also have significant tachycardia and reduced HRV, as already observed in DMD patients. In particular, the recorded heart rate is faster in *mdx* mice than the control mice approximately of 15%, while, the correct QT interval based on speed, the duration, and the PR interval are reduced.

Using atropine, a muscarinic receptor antagonist, it was observed that, in C57 mice, it significantly increases heart rate and reduces the PR interval, while in *mdx* it has a totally inverse effect [9]. Deepening the study with other pharmacological approaches to the blockade of the autonomous system, it was demonstrated an imbalance in the modulation of the autonomic nervous system of heart rate, with a decrease in parasympathetic activity and an increase in sympathetic activity in *mdx* mice. Furthermore, it has also been proven, by the same researchers, that autonomic dysfunction in *mdx* mice may be independent of decreased myocardial nitric neuron oxide synthase (nNOS), which is a component of the dystrophin complex [59]. It was demonstrated that the absence of dystrophin protein, in DMD and in *mdx* mouse, triggers a redistribution of nNOS from the plasma membrane to the cytosol in muscle cells. Aberrant nNOS activity in the cytosol can stimulate free radical oxidation, which is toxic to myofibers. These data are very important and can provide new bases for diagnosing, understanding, and treating DMD patients. Unfortunately, the *mdx* mouse is a mild model of DMD due to a minimal cardiac dysfunction, as they do not develop early-dilated cardiomyopathy as seen in DMD patients.

The most severe cardiomyopathy was found in mice also lacking utrophin, indicating that the homologous protein effectively compensated for the lack of dystrophin in *mdx* mice [24].

Currently, the mdx4cv/mTRG2 model with shortened telomeres seems to most faithfully recapitulate both cardiovascular and skeletal muscle features of the disease. It was shown that species-specific differences in telomere length account for diversities in the regenerative capacity of satellite

cells from *mdx* animals compared to humans and revealed premature telomere shortening in CMs, which was an unknown characteristic of DMD [76].

HDAC Inhibitor Therapy for Duchenne Muscular Dystrophy

Recently, among the biological and molecular mechanisms involved in the adaptive response to a cardiac insult, the histone deacetylases (HDAC)-mediated epigenetic processes are receiving a special attention. HDACs are common enzymes regulating the histone deacetylation in the core histones (preferentially at the amino groups of lysine residues). From a physiological standpoint, HDACs are strictly correlated to the regulation of homeostatic gene expression of vascular and cardiac populations including stem cell commitment [17]. More importantly, abnormal acetylation of core histones, likely linked to environmental factors, is associated with major cardiovascular diseases [70]. After a cardiac insult, HDAC activity is enhanced, resulting in increased proliferation, migration, and apoptosis of adventitial fibroblasts, endothelial and smooth muscle cells, as well as MP activation and phenotype switching [72], suggesting the involvement of HDAC in driving the response to vascular injury and remodeling even through the early inflammatory phase. Hence, targeting HDACs would represent a powerful tool to design novel pharmacological approaches for cardiac disorders. Accordingly, a wide range of molecules, such as trichostatin A, suberoylanilide hydroxamic acid, or valproic acid, has been described to inhibit the activity of HDACs. Pan or selective HDAC inhibitors (HDACis) have been shown to have protective effects and, consequently, to preserve the cardiac function by exerting anti-inflammatory properties, reducing cardiac hypertrophy and remodeling, and modulating the fibrosis and even its potential reversion through definite molecular signaling pathways, mainly targeting oxidase states and/or specific kinases [6, 46].

Despite this, epigenetic therapeutic options available in the cardiovascular field are still limited, and the clinical implications of the use of the HDACis have still to be clearly elucidated, including issues related to their safety and long-term effects. Among these compounds, givinostat (GIV, ITF2357), a powerful pan HDACi, has recently gained considerable attention due to its varied applicability, safety, and efficacy in humans. Described in 2005 [66], GIV is currently employed in ongoing clinical trials for myeloproliferative diseases, as well as for several inflammation-based disorders, such as acute central nervous system injuries, rheumatoid and juvenile idiopathic arthritis, bowel diseases, and DMD [10, 63]. Recent studies suggest that GIV treatment implies a decrease of the TNF-α, IL-6, and IL-1, followed by a striking reduction of the inflammatory response in combination with pro-angiogenic effects [49].

To date, the effects of GIV in cardiac diseases have still to be verified, because the lacking of studies on this specific effect. DMD dispatches, reporting that cardiac dysfunction may parallel the skeletal muscle degeneration [10], suggest that GIV might indirectly and beneficially act on the cardiac muscle, defining this HDACi as a novel potential cardiac therapeutic target and tool.

Milan and coworkers highlighted a cardiac functional recovery concurrently to a reduced fibrosis in the cardiac tissue. It has been postulating that GIV may protect the heart tissue from an excessive remodeling by reverting the endothelial-to-mesenchymal transition (EndMT) process. Based on this, it can be speculated that GIV might represent an excellent candidate both to attenuate the cardiac failure in DMD patients and to treat heart diseases.

From a physiological standpoint, HDACs are strictly correlated with the regulation of homeostatic gene expression of vascular and cardiac cell populations. Targeting HDACs is a potentially powerful strategic target for the treatment of cardiac disorders.

Conclusion

Current care options and constant surveillance have permitted a significant amelioration in the life quality of DMD patients. However, the increased lifespan of DMD patients has revealed the developing cardiomyopathy as an essential

health problem that has to be addressed. Because it could be too late for improving heart performance, the belief that heart medicines should begin when symptoms appear is now reconsidered. Indeed, currently treatments start before the evident symptoms with the idea to protect the heart from damage. It would be advantageous to have matched study protocols intended to achieve the reliability of the results in *mdx* mice and use other models as an additional source of information, as it was done for skeletal muscle studies. Despite the important understandings into the disease progression covered by these many mouse models, there are still few acceptable therapies. The longer life in DMD patients has been mostly due to improvements in cardiac and respiratory support, which only treat symptoms of the disease. Finally, strong and clear protocols can drive a direct comparison between various studies, and any outcomes can be more easily translated into changes in care regimens for patients affected by DMD.

References

1. Bennet MR, Gibson WG, Lemon G. Neuronal cell death, nerve growth factor and neurotrophic models: 50 years on. Auton Neurosci. 2002;95(1–2):1–23.
2. Blake DJ, Tinsley JM, Davies KE. Utrophin: a structural and functional comparison to dystrophin. Brain Pathol. 1996;6(1):37–47.
3. Blake DJ, Weir A, Newey SE, Davies KE. Function and genetics of dystrophin and dystrophin-related proteins in muscle. Physiol Rev. 2002;82(2):291–329. https://doi.org/10.1152/physrev.00028.2001.
4. Boveda S, Galinier M, Pathak A, Fourcade J, Dongay B, Benchendikh D, et al. Prognostic value of heart rate variability in time domain analysis in congestive heart failure. J Interv Card Electrophysiol. 2001;5(2):181–7.
5. Bulfield G, Siller WG, Wight PA, Moore KJ. X chromosome-linked muscular dystrophy (mdx) in the mouse. Proc Natl Acad Sci U S A. 1984;81(4):1189–92.
6. Cao DJ, Wang ZV, Battiprolu PK, Jiang N, Morales CR, Kong Y, et al. Histone deacetylase (HDAC) inhibitors attenuate cardiac hypertrophy by suppressing autophagy. Proc Natl Acad Sci U S A. 2011;108(10):4123–8. https://doi.org/10.1073/pnas.1015081108.
7. Carretta D, Santarelli M, Vanni D, Carrai R, Sbriccoli A, Pinto F, et al. The organisation of spinal projecting brainstem neurons in an animal model of muscular dystrophy. A retrograde tracing study on mdx mutant mice. Brain Res. 2001;895(1–2):213–22.
8. Choate JK, Klemm M, Hirst GD. Sympathetic and parasympathetic neuromuscular junctions in the guinea-pig sino-atrial node. J Auton Nerv Syst. 1993;44(1):1–15.
9. Chu V, Otero JM, Lopez O, Sullivan MF, Morgan JP, Amende I, et al. Electrocardiographic findings in mdx mice: a cardiac phenotype of Duchenne muscular dystrophy. Muscle Nerve. 2002;26(4):513–9. https://doi.org/10.1002/mus.10223.
10. Consalvi S, Saccone V, Mozzetta C. Histone deacetylase inhibitors: a potential epigenetic treatment for Duchenne muscular dystrophy. Epigenomics. 2014;6(5):547–60. https://doi.org/10.2217/epi.14.36.
11. Cox GF, Kunkel LM. Dystrophies and heart disease. Curr Opin Cardiol. 1997;12(3):329–43.
12. D'Orsogna L, O'Shea JP, Miller G. Cardiomyopathy of Duchenne muscular dystrophy. Pediatr Cardiol. 1988;9(4):205–13. https://doi.org/10.1007/BF02078410.
13. De Stefano ME, Leone L, Lombardi L, Paggi P. Lack of dystrophin leads to the selective loss of superior cervical ganglion neurons projecting to muscular targets in genetically dystrophic mdx mice. Neurobiol Dis. 2005;20(3):929–42. https://doi.org/10.1016/j.nbd.2005.06.006.
14. Del Signore A, Gotti C, De Stefano ME, Moretti M, Paggi P. Dystrophin stabilizes alpha 3- but not alpha 7-containing nicotinic acetylcholine receptor subtypes at the postsynaptic apparatus in the mouse superior cervical ganglion. Neurobiol Dis. 2002;10(1):54–66.
15. Deppmann CD, Mihalas S, Sharma N, Lonze BE, Niebur E, Ginty DD. A model for neuronal competition during development. Science. 2008;320(5874):369–73. https://doi.org/10.1126/science.1152677.
16. Dittrich S, Tuerk M, Haaker G, Greim V, Buchholz A, Burkhardt B, et al. Cardiomyopathy in Duchenne muscular dystrophy: current value of clinical, electrophysiological and imaging findings in children and teenagers. Klin Padiatr. 2015;227(4):225–31. https://doi.org/10.1055/s-0034-1398689.
17. Dovey OM, Foster CT, Conte N, Edwards SA, Edwards JM, Singh R, et al. Histone deacetylase 1 and 2 are essential for normal T-cell development and genomic stability in mice. Blood. 2013;121(8):1335–44. https://doi.org/10.1182/blood-2012-07-441949.
18. Duchenne and Becker muscular dystrophy. Genetics Home Reference (GHAR). 2016.
19. Gilbert R, Nalbantoglu J, Petrof BJ, Ebihara S, Guibinga GH, Tinsley JM, et al. Adenovirus-mediated utrophin gene transfer mitigates the dystrophic phenotype of mdx mouse muscles. Hum Gene Ther. 1999;10(8):1299–310. https://doi.org/10.1089/10430349950017987.
20. Glebova NO, Ginty DD. Heterogeneous requirement of NGF for sympathetic target innervation in vivo. J Neurosci. 2004;24(3):743–51. https://doi.org/10.1523/JNEUROSCI.4523-03.2004.
21. Glebova NO, Ginty DD. Growth and survival signals controlling sympathetic nervous system development.

Annu Rev Neurosci. 2005;28:191–222. https://doi.org/10.1146/annurev.neuro.28.061604.135659.
22. Gold BG, Spencer P. Neurotrophic function in normal nerve and in peripheral neuropathies. New York: Raven Press; 1993.
23. Gordan R, Gwathmey JK, Xie LH. Autonomic and endocrine control of cardiovascular function. World J Cardiol. 2015;7(4):204–14. https://doi.org/10.4330/wjc.v7.i4.204.
24. Grady RM, Teng H, Nichol MC, Cunningham JC, Wilkinson RS, Sanes JR. Skeletal and cardiac myopathies in mice lacking utrophin and dystrophin: a model for Duchenne muscular dystrophy. Cell. 1997;90(4):729–38.
25. Hasan W, Jama A, Donohue T, Wernli G, Onyszchuk G, Al-Hafez B, et al. Sympathetic hyperinnervation and inflammatory cell NGF synthesis following myocardial infarction in rats. Brain Res. 2006;1124(1):142–54. https://doi.org/10.1016/j.brainres.2006.09.054.
26. Heerssen HM, Pazyra MF, Segal RA. Dynein motors transport activated Trks to promote survival of target-dependent neurons. Nat Neurosci. 2004;7(6):596–604. https://doi.org/10.1038/nn1242.
27. Huang EJ, Reichardt LF. Trk receptors: roles in neuronal signal transduction. Annu Rev Biochem. 2003;72:609–42. https://doi.org/10.1146/annurev.biochem.72.121801.161629.
28. Ieda M, Fukuda K, Hisaka Y, Kimura K, Kawaguchi H, Fujita J, et al. Endothelin-1 regulates cardiac sympathetic innervation in the rodent heart by controlling nerve growth factor expression. J Clin Invest. 2004;113(6):876–84. https://doi.org/10.1172/JCI19480.
29. Ieda M, Kanazawa H, Kimura K, Hattori F, Ieda Y, Taniguchi M, et al. Sema3a maintains normal heart rhythm through sympathetic innervation patterning. Nat Med. 2007;13(5):604–12. https://doi.org/10.1038/nm1570.
30. Iwata Y, Katanosaka Y, Arai Y, Komamura K, Miyatake K, Shigekawa M. A novel mechanism of myocyte degeneration involving the Ca2+-permeable growth factor-regulated channel. J Cell Biol. 2003;161(5):957–67. https://doi.org/10.1083/jcb.200301101.
31. Judge DP, Kass DA, Thompson WR, Wagner KR. Pathophysiology and therapy of cardiac dysfunction in Duchenne muscular dystrophy. Am J Cardiovasc Drugs. 2011;11(5):287–94. https://doi.org/10.2165/11594070-000000000-00000.
32. Jung C, Chylinski TM, Pimenta A, Ortiz D, Shea TB. Neurofilament transport is dependent on actin and myosin. J Neurosci. 2004;24(43):9486–96. https://doi.org/10.1523/JNEUROSCI.1665-04.2004.
33. Kamdar F, Garry DJ. Dystrophin-deficient cardiomyopathy. J Am Coll Cardiol. 2016;67(21):2533–46. https://doi.org/10.1016/j.jacc.2016.02.081.
34. Kanazawa H, Fukuda K. Cardiac sympathetic nerve plasticity and heart failure. J Pain Relief. 2016;5:1. https://doi.org/10.4172/2187-0846.1000223.
35. Kaspar RW, Allen HD, Montanaro F. Current understanding and management of dilated cardiomyopathy in Duchenne and Becker muscular dystrophy. J Am Acad Nurse Pract. 2009;21(5):241–9. https://doi.org/10.1111/j.1745-7599.2009.00404.x.
36. Khairallah M, Khairallah R, Young ME, Dyck JR, Petrof BJ, Des Rosiers C. Metabolic and signaling alterations in dystrophin-deficient hearts precede overt cardiomyopathy. J Mol Cell Cardiol. 2007;43(2):119–29. https://doi.org/10.1016/j.yjmcc.2007.05.015.
37. Korsching S, Thoenen H. Developmental changes of nerve growth factor levels in sympathetic ganglia and their target organs. Dev Biol. 1988;126(1):40–6.
38. Lanza GA, Guido V, Galeazzi MM, Mustilli M, Natali R, Ierardi C, et al. Prognostic role of heart rate variability in patients with a recent acute myocardial infarction. Am J Cardiol. 1998;82(11):1323–8.
39. Larsen HE, Lefkimmiatis K, Paterson DJ. Sympathetic neurons are a powerful driver of myocyte function in cardiovascular disease. Sci Rep. 2016;6:38898. https://doi.org/10.1038/srep38898.
40. Licursi V, Caiello I, Lombardi L, De Stefano ME, Negri R, Paggi P. Lack of dystrophin in mdx mice modulates the expression of genes involved in neuron survival and differentiation. Eur J Neurosci. 2012;35(5):691–701. https://doi.org/10.1111/j.1460-9568.2011.07984.x.
41. Lockhart ST, Turrigiano GG, Birren SJ. Nerve growth factor modulates synaptic transmission between sympathetic neurons and cardiac myocytes. J Neurosci. 1997;17(24):9573–82.
42. Lombardi L, De Stefano ME, Paggi P. Components of the NGF signaling complex are altered in mdx mouse superior cervical ganglion and its target organs. Neurobiol Dis. 2008;32(3):402–11. https://doi.org/10.1016/j.nbd.2008.07.021.
43. Lombardi L, Persiconi I, Gallo A, Hoogenraad CC, De Stefano ME. NGF-dependent axon growth and regeneration are altered in sympathetic neurons of dystrophic mdx mice. Mol Cell Neurosci. 2017;80:1–17. https://doi.org/10.1016/j.mcn.2017.01.006.
44. Love DR, Hill DF, Dickson G, Spurr NK, Byth BC, Marsden RF, et al. An autosomal transcript in skeletal muscle with homology to dystrophin. Nature. 1989;339(6219):55–8. https://doi.org/10.1038/339055a0.
45. Marques MJ, Oggiam DS, Barbin IC, Ferretti R, Santo Neto H. Long-term therapy with deflazacort decreases myocardial fibrosis in mdx mice. Muscle Nerve. 2009;40(3):466–8. https://doi.org/10.1002/mus.21341.
46. McKinsey TA. Therapeutic potential for HDAC inhibitors in the heart. Annu Rev Pharmacol Toxicol.

2012;52:303–19. https://doi.org/10.1146/annurev-pharmtox-010611-134712.
47. Mehler MF. Brain dystrophin, neurogenetics and mental retardation. Brain Res Brain Res Rev. 2000;32(1):277–307.
48. Michele DE, Campbell KP. Dystrophin-glycoprotein complex: post-translational processing and dystroglycan function. J Biol Chem. 2003;278(18): 15457–60. https://doi.org/10.1074/jbc.R200031200.
49. Milan M, Pace V, Maiullari F, Chirivi M, Baci D, Maiullari S, et al. Givinostat reduces adverse cardiac remodeling through regulating fibroblasts activation. Cell Death Dis. 2018;9(2):108. https://doi.org/10.1038/s41419-017-0174-5.
50. Miller G, D'Orsogna L, O'Shea JP. Autonomic function and the sinus tachycardia of Duchenne muscular dystrophy. Brain and Development. 1989;11(4): 247–50.
51. Mok SA, Lund K, Campenot RB. A retrograde apoptotic signal originating in NGF-deprived distal axons of rat sympathetic neurons in compartmented cultures. Cell Res. 2009;19(5):546–60. https://doi.org/10.1038/cr.2009.11.
52. Oppenheim RW. The neurotrophic theory and naturally occurring motoneuron death. Trends Neurosci. 1989;12(7):252–5.
53. Pagani M, Malfatto G, Pierini S, Casati R, Masu AM, Poli M, et al. Spectral analysis of heart rate variability in the assessment of autonomic diabetic neuropathy. J Auton Nerv Syst. 1988;23(2):143–53.
54. Perloff JK. Cardiac rhythm and conduction in Duchenne's muscular dystrophy: a prospective study of 20 patients. J Am Coll Cardiol. 1984;3 (5):1263–8.
55. Pilgram GS, Potikanond S, Baines RA, Fradkin LG, Noordermeer JN. The roles of the dystrophin-associated glycoprotein complex at the synapse. Mol Neurobiol. 2010;41(1):1–21. https://doi.org/10.1007/s12035-009-8089-5.
56. Prabhu SD, Frangogiannis NG. The biological basis for cardiac repair after myocardial infarction: from inflammation to fibrosis. Circ Res. 2016;119(1): 91–112. https://doi.org/10.1161/CIRCRESAHA.116.303577.
57. Quinlan JG, Hahn HS, Wong BL, Lorenz JN, Wenisch AS, Levin LS. Evolution of the mdx mouse cardiomyopathy: physiological and morphological findings. Neuromuscul Disord. 2004;14(8–9):491–6. https://doi.org/10.1016/j.nmd.2004.04.007.
58. Ryan TD, Taylor MD, Mazur W, Cripe LH, Pratt J, King EC, et al. Abnormal circumferential strain is present in young Duchenne muscular dystrophy patients. Pediatr Cardiol. 2013;34(5):1159–65. https://doi.org/10.1007/s00246-012-0622-z.
59. Sapp JL, Bobet J, Howlett SE. Contractile properties of myocardium are altered in dystrophin-deficient mdx mice. J Neurol Sci. 1996;142(1–2):17–24.
60. Schinder AF, Poo M. The neurotrophin hypothesis for synaptic plasticity. Trends Neurosci. 2000;23(12): 639–45.
61. Shan J, Kushnir A, Betzenhauser MJ, Reiken S, Li J, Lehnart SE, et al. Phosphorylation of the ryanodine receptor mediates the cardiac fight or flight response in mice. J Clin Invest. 2010;120(12):4388–98. https://doi.org/10.1172/JCI32726.
62. Shcherbakova OG, Hurt CM, Xiang Y, Dell'Acqua ML, Zhang Q, Tsien RW, et al. Organization of beta-adrenoceptor signaling compartments by sympathetic innervation of cardiac myocytes. J Cell Biol. 2007;176(4):521–33. https://doi.org/10.1083/jcb.200604167.
63. Shein NA, Shohami E. Histone deacetylase inhibitors as therapeutic agents for acute central nervous system injuries. Mol Med. 2011;17(5–6):448–56. https://doi.org/10.2119/molmed.2011.00038.
64. Shimizu-Motohashi Y, Komaki H, Motohashi N, Takeda S, Yokota T, Aoki Y. Restoring dystrophin expression in Duchenne muscular dystrophy: current status of therapeutic approaches. J Pers Med. 2019;9 (1). https://doi.org/10.3390/jpm9010001.
65. Stewart JM. Autonomic nervous system dysfunction in adolescents with postural orthostatic tachycardia syndrome and chronic fatigue syndrome is characterized by attenuated vagal baroreflex and potentiated sympathetic vasomotion. Pediatr Res. 2000;48(2):218–26. https://doi.org/10.1203/00006450-200008000-00016.
66. Tan J, Cang S, Ma Y, Petrillo RL, Liu D. Novel histone deacetylase inhibitors in clinical trials as anti-cancer agents. J Hematol Oncol. 2010;3:5. https://doi.org/10.1186/1756-8722-3-5.
67. Thomas TO, Morgan TM, Burnette WB, Markham LW. Correlation of heart rate and cardiac dysfunction in Duchenne muscular dystrophy. Pediatr Cardiol. 2012;33(7):1175–9. https://doi.org/10.1007/s00246-012-0281-0.
68. Tyler KL. Origins and early descriptions of "Duchenne muscular dystrophy". Muscle Nerve. 2003;28 (4):402–22. https://doi.org/10.1002/mus.10435.
69. Vaillend C, Billard JM, Laroche S. Impaired long-term spatial and recognition memory and enhanced CA1 hippocampal LTP in the dystrophin-deficient Dmd (mdx) mouse. Neurobiol Dis. 2004;17(1):10–20. https://doi.org/10.1016/j.nbd.2004.05.004.
70. Wang X, Liu J, Zhen J, Zhang C, Wan Q, Liu G, et al. Histone deacetylase 4 selectively contributes to podocyte injury in diabetic nephropathy. Kidney Int. 2014;86(4):712–25. https://doi.org/10.1038/ki.2014.111.
71. Wingerd KL, Goodman NL, Tresser JW, Smail MM, Leu ST, Rohan SJ, et al. Alpha 4 integrins and vascular cell adhesion molecule-1 play a role in sympathetic innervation of the heart. J Neurosci. 2002;22(24):10772–80.

72. Yang JY, Wang Q, Wang W, Zeng LF. Histone deacetylases and cardiovascular cell lineage commitment. World J Stem Cells. 2015;7(5):852–8. https://doi.org/10.4252/wjsc.v7.i5.852.
73. Yoo WH, Cho MJ, Chun P, Kim KH, Lee JS, Shin YB. The evolution of electrocardiographic changes in patients with Duchenne muscular dystrophies. Korean J Pediatr. 2017;60(6):196–201. https://doi.org/10.3345/kjp.2017.60.6.196.
74. Yotsukura M, Sasaki K, Kachi E, Sasaki A, Ishihara T, Ishikawa K. Circadian rhythm and variability of heart rate in Duchenne-type progressive muscular dystrophy. Am J Cardiol. 1995;76(12):947–51.
75. Yotsukura M, Fujii K, Katayama A, Tomono Y, Ando H, Sakata K, et al. Nine-year followup study of heart rate variability in patients with Duchenne-type progressive muscular dystrophy. Am Heart J. 1998;136(2):289–96. https://doi.org/10.1053/hj.1998.v136.89737.
76. Yucel N, Chang AC, Day JW, Rosenthal N, Blau HM. Humanizing the mdx mouse model of DMD: the long and the short of it. NPJ Regen Med. 2018;3:4. https://doi.org/10.1038/s41536-018-0045-4.
77. Zaglia T, Mongillo M. Cardiac sympathetic innervation, from a different point of (re)view. J Physiol. 2017;595(12):3919–30. https://doi.org/10.1113/JP273120.
78. Zaglia T, Milan G, Franzoso M, Bertaggia E, Pianca N, Piasentini E, et al. Cardiac sympathetic neurons provide trophic signal to the heart via beta2-adrenoceptor-dependent regulation of proteolysis. Cardiovasc Res. 2013;97(2):240–50. https://doi.org/10.1093/cvr/cvs320.
79. Zaika O, Zhang J, Shapiro MS. Functional role of M-type (KCNQ) K(+) channels in adrenergic control of cardiomyocyte contraction rate by sympathetic neurons. J Physiol. 2011;589(Pt 10):2559–68. https://doi.org/10.1113/jphysiol.2010.204768.

Part VI

Sleep and Heart

Physiological Sleep and Cardiovascular Disease

34

When the Physiological Rhythms Are Mismatch

Edgar Toschi-Dias, Eleonora Tobaldini, Nicola Montano, and Luigi Ferini-Strambi

Contents

Abstract

It is a consensus in literature that sleep is an important modulator of several physiological functions (e.g., cardiovascular, respiratory, and neurobiological function). In fact, a complex and dynamic rhythmic process involving the activation of several cortical, subcortical, and medullar neural circuits mutually interact in order to synchronize the physiological functions with sleep cycles. During physiological sleep regulation, heart rate and blood pressure lower during NREM sleep cycle, with marked increase during REM sleep cycle. In this process, autonomic nervous system has a pivotal role in the hemodynamic regulation sleep-mediated. In fact, several evidences show that the vagal modulation is predominant during NREM sleep cycle while that during REM sleep cycle occur a prevalence of sympathetic modulation. Thus, due to interaction between

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*, https://doi.org/10.1007/978-3-030-28008-6_36

sympathetic and parasympathetic oscillations, the hemodynamic fluctuations express the effect of the autonomic cardiovascular modulation in each sleep cycle. On the other hand, a growing body of evidences has revealed that chronic sleep deficiency promoted mainly by sleep-disordered breathing (i.e., obstructive sleep apnea) is highly prevalent in patients with cardiovascular diseases. Through a variety of factors including nocturnal hypoxemia and increased oxidative stress, production of pro-inflammatory cytokines, and autonomic and endothelial dysfunctions, a significant overlap among pathophysiology mechanisms of these two conditions has been reported. Therefore, in this chapter we will address the impact of chronic sleep deficiency promoted by obstructive sleep apnea on the cardiovascular system with focus on the autonomic nervous system.

Keywords

Autonomic nervous system · Chronic sleep deficiency · Obstructive sleep apnea · Cardiovascular diseases

Introduction

In the past, sleep was defined as an easily reversible state of reduced responsiveness and interaction with the external environment, where there is a relative motor and sensory quiescence that occurs in periodic episodes to maintenance of health and homeostasis [1]. Currently, National Institute of Mental Health defines sleep as an endogenous, recurring, behavioral state that reflects coordinated changes in the dynamic functional organization of the brain and that optimizes physiology, behavior, and health [2].

The change of this paradigm occurred only with the advent of polysomnography, which is essential for a better understanding of aspects physiology and pathology sleep-related [3, 4]. Based on polysomnographic records, it was possible to determine different sleep stages. In fact, polysomnography (PSG) allows the definition of different sleep stages, by means of continuous recordings of the electroencephalogram (EEG), submental electromyogram (EMG), and electrooculogram (EOG). PSG provides the analysis among synchronization of brain waves together with other physiological signals [e.g., heart rate (HR), pulse oximetry, airflow, and abdominal and thorax excursions] [3, 4].

Classically, normal sleep can be divided into non-rapid eye movement (NREM) and rapid eye movement (REM) stages in a cyclical manner (~4 to 5 NREM-REM cycles) during every night [3–7]. The sleep cycle begins when the fast and low-amplitude brain waves characteristic of wakefulness (alpha rhythm, 8–13 Hz) are replaced by slower waves of greater amplitude as sleep deepens [3–7]. Thus, sleep onset epoch is determined when occurs a decrease of alpha-wave duration of less than 50% of an epoch or a vertex wave, K complex, sleep spindle, or delta activity occurs.

Currently, the NREM sleep cycle is divided into three different stages. In Stage 1, a transitional stage which corresponds to 5% of sleep occurs the missing of alfa rhythm (Stage 0 or W) and is scored when low-voltage mixed-frequency EEG (theta rhythm, 4–7 Hz) is present but there are no K complexes, spindles, or REMs [3–7]. Stage 2 is characterized by the presence of spindles (sigma rhythm, 12–14 Hz bursts) and/or K complexes and high amplitude delta EEG activity (delta rhythm, <4 Hz with ≥ 75 μV amplitude) which occupies less than 20% of the epoch [3–7]. Finally, Stage 3 of the NREM sleep is classified when slow-wave activity occurs in more than 20% of the epoch [3–7].

In REM sleep, muscle atony and eye movements are accompanied by fast and low-amplitude brain waves (rhythm theta, 4–7 Hz). The morphology sawtooth of the EEG tracing may also accompany REM sleep [3–7]. In addition, other physiologic activities accompanying REM sleep includes periorbital integrated potentials, middle ear muscle activity, and sleep-related erections during REM sleep cycle [3–7].

Sleep represents more than 30% of our lives, and it is an important modulator of several physiological functions (i.e., cardiovascular, digestive,

endocrine, and respiratory systems) being that some of your effects are related to circadian rhythms and others to specific sleep stages [8]. Most of the physiological parameters of the body alter during sleep when compared to wake [i.e., HR, blood pressure (BP), and temperature]. For this, a complex and dynamic rhythmic process involving the activation of several cortical, subcortical, and medullar neural circuits mutually interacts in order to control normal sleep according to hormonal changes (e.g., melatonin and orexin), local factors (e.g., adenosine accumulation), circadian variations (e.g., dark-light cycles), and other unknown factors [9].

During physiological sleep regulation, HR and BP lower during NREM sleep cycle, with marked increases during REM sleep cycle [10, 11]. For these physiological responses, autonomic nervous system (ANS) has a pivotal role in the hemodynamic regulation sleep-mediated. In fact, several evidences show that the vagal modulation is predominant during NREM sleep cycle, while that during REM sleep cycle occurs a prevalence of sympathetic modulation [10–12]. Thus, due to sympathetic and parasympathetic oscillations of the sympatho-vagal balance, the hemodynamic fluctuations are expression of the autonomic cardiovascular modulation of HR and BP in each sleep cycle.

As far as we know, the analysis of the heart rate variability (HRV) is one of the most reliable methods capable of evaluating the dynamic and simultaneous interaction of these autonomic branches on the effector organ (i.e., heart). By means of spectral approaches, HRV analysis identifies three main oscillatory components: (1) very low frequency (VLF), marker of hormonal and circadian oscillations; (2) low frequency component (LF), marker of sympathetic modulation; and (3) high frequency component (HF), marker of vagal modulation and synchronous with respiration [12]. HRV has been widely used for the assessment of ANS during sleep, showing a progressive decrease of sympathetic modulation and a predominant vagal modulation, as sleep becomes deeper (i.e., from wakefulness to NREM sleep cycle). On the other hand, during REM sleep cycle occurs a predominant sympathetic modulation on cardiovascular system with surges of sympathetic outflow at levels even upper than in wakefulness [10, 13–15].

Curiously, several scientific evidences document that the simple restriction of the number of hours of sleep can be deleterious to the cardiovascular system. For example, cohort studies suggest sleeping less than 5 h per night may increase the risk of developing hypertension, acute myocardial infarction (MI), and stroke [16–18]. In addition, due to the high prevalence, another growing focus of scientific interest is the impact of sleep-disordered breathing (SDB) in patients with cardiovascular disease [16–18]. Thus, in this chapter we will address the impact of sleep deficiency promoted by SDB on the cardiovascular system with focus on the ANS.

Sleep Deficiency and Cardiovascular Disease

Considering that the average hours of sleep fell approximately 27% in the last century, sleep deficiency has becoming one of the most relevant health problem in modern societies [19]. This phenomenon is supposed to impact upon global health in a significantly way and can culminate in several sleep disorders.

Based in the 2011 National Institutes of Health (NIH) Sleep Disorders Research Plan, the sleep deficiency is defined a "deficit in the quantity or quality of sleep obtained versus the amount needed for optimal health, performance, and well-being; sleep deficiency may result from prolonged wakefulness leading to sleep deprivation, insufficient sleep duration, sleep fragmentation, or a sleep disorder, such as in obstructive sleep apnea (OSA), that disrupts sleep and thereby renders sleep non-restorative" [20, 21].

According to NIH, it is recommended that an individual in adulthood sleeps 7–8 h per night. However, an alarming fact is that it is estimated that in 2020 approximately 30% of the adults will sleep less than 6 h per night [22]. It is worth highlighting that approximately 30% of men and women and 60% of adolescents fail to obtain sufficient amounts of sleep [23, 24], 20% of adults

experience excessive daytime sleepiness [25], 5–25% of adults meet objective criteria for SDB [26], 20–30% report insomnia symptoms [27], and nearly 1/3 of the American workforce is engaged in shift work [28]. Therefore, sleep deficiency has become a huge health-care problem in modern societies.

In view of the foregoing, why are we sleep deprived? To answer this question, several aspects must be taken into account. Firstly, sleep deficiency can be for reasons related to our lifestyle, such as the use of electronic devices before going to sleep, which alter the physiological secretion of hormones that are fundamental for normal sleep (i.e., melatonin and cortisol) [29], hard work schedule, shift work, etc. A second reason to be sleep deprived can be because of aging process, once aging is associated with a reduction of total sleep time and a disruption of physiological sleep [30]. Finally, an individual may suffer from sleep disorders (i.e., SDB, insomnia, periodic limb movements, and restless leg syndrome) [21].

Although with pathophysiological differences, one of the most important common elements of these sleep disorders is the condition of chronic sleep deprivation, which has a complex series of biological consequences. Thus, sleep deprivation can be related to the activation of several biological pathways, for instance, neural regulation of cardiovascular function [31], inflammatory responses and deregulation of immune system [32–34], metabolic dysfunctions [35–37], cognitive functions, and mood's alterations [38].

Several experimental studies have been conducted on the effects of acute sleep deprivation on ANS and cardiovascular system [39–46]. After 24 h of continuous wakefulness, the acute sleep deprivation is able to induce significant increase in HR and systolic BP (SBP) [39–41], as well as a blunted HR and SBP responses to orthostatic stimulus [42, 43]. Yet, other studies report no significant differences in terms of hemodynamic variables before and after acute sleep deprivation [44], thus suggesting a possible confounding factor related to the different experimental criteria used to obtain sleep deprivation among studies.

Curiously, the analysis of HRV also provides crucial information of the consequences of acute sleep deprivation on the ANS. After acute sleep deprivation, showing a significant reduction of HRV [39] represents a drop in capability of the cardiovascular system to react and adapt to stressor stimuli. Besides, this phenomenon is accompanied by a significant alteration of the sympatho-vagal balance with predominance in the sympathetic modulation and a reduction of vagal modulation after acute sleep deprivation. In fact, several evidences revealed an increase of the LF component (marker of sympathetic modulation) and a reduction of HF component (marker of vagal modulation), which impairs in sympatho-vagal balance [39, 47]. Thus, these results suggested that sleep deprivation may importantly affect the ANS in healthy subjects.

Curiously, study assessing direct muscle sympathetic nerve activity showed a significant reduction of the bursts frequency [44]; this result, associated with an increase of the BP values, suggests a global resetting of the baroreflex control and a loss of rhythmical properties of the sympathetic outflow after sleep deprivation. In addition, when evaluating the dynamic response to orthostatic stress, it has been demonstrated that the response of HR, BP, and cardiac sympathetic modulation is significantly blunted when compared to clinostatic position [43]. These findings thus supporting the hypothesis that ANS is less capable of dealing with stressor stimuli after acute sleep deprivation.

The majority of the studies showed important alterations of hemodynamic and autonomic cardiac control after a period of acute sleep deprivation, with a sympatho-vagal balance shifted toward a sympathetic predominance of HR and BP control. Similar results have been observed after partial chronic sleep deprivation. Considering the difficulty in performing this short of experiments, as well as the diversity of experimental protocols (in terms of hours of sleep deprivation per day, number of days, population characteristics, etc.), it is mandatory to consider these results as preliminary. However, interesting but contrasting data have been reported. Five days of partial sleep deprivation were able to induce significant

changes of HRV and blood pressure variability (BPV), with decrease of total HRV, increase of LF, and decrease of HF components [48, 49].

On the other hand, it has been documented that SDB is associated with coronary artery disease (CAD), myocardial infarction, chronic heart failure (CHF), stroke, diabetes mellitus (DM), and obesity [50]. Therefore, these data clearly suggest that sleep deficiency, especially those promoted by SDB, plays a key role in the pathogenesis of cardiovascular diseases.

Obstructive Sleep Apnea and Cardiovascular Disease

OSA, a SDB characterized by recurrent episodes of cessation of respiratory airflow during sleep due to upper airway collapse on inspiration, is primary sleep disorder associated with cardiovascular disease [51–54].

According to epidemiological study, the prevalence of OSA in the general adult population is approximately 25% in men and 10% in women, and this prevalence doubled from the last decade [55], when obesity and metabolic syndrome have been identified as important risk factor [56]. In addition, patients with cardiovascular diseases do have a higher prevalence of OSA, which is present in 30–80% of patients with hypertension, 30–60% of patients with chronic CAD, and 50–80% of patients with CHF [57]. A recent systematic review on the risk of adverse cardiovascular outcomes in patients with OSA showed a relation between the presence of OSA and all causes mortality and composite cardiovascular outcomes (i.e., stroke, CHF, MI) in men, while in women this relation was attenuated [58].

In addition, the apnea/hypopnea index (AHI), an index that sums the amount of apneic and hypopneic events during the sleep period, was the only independent predictor of adverse events [58]. However, the association between OSA and DM did not reach a statistical significance after the adjustment for confounding factors such as age, sex, and BMI [59]. The pathophysiological cascade leading from OSA to cardiovascular events has been extensively described [60–62].

The immediate consequences of respiratory events are exaggerated respiratory effort in an attempt to maintain ventilation which in turn leads to reduced intrathoracic pressure and intermittent hypoxemia. Furthermore, cessation of airflow results in hypercapnia and hypoxemia and, consequently, leads to activation of the central and peripheral chemoreflex control, respectively [63]. This in turn causes an increase in vascular sympathetic outflow as well as in circulating catecholamine, with an accompanying increase in peripheral vascular resistance [64, 65]. Furthermore, due to changes in intrathoracic pressures upon final of apneic event, vasoconstriction in the peripheral vasculature and increased cardiac output lead to dramatic surges in BP [64, 65]. Thus, sleep fragmentation due to frequent arousals of each OSA episode promotes expressive hemodynamic and neuroendocrine disturbances, as well as profound decreases in level of the oxygen saturation with consequent systemic hypoxemia [63–65].

Therefore, intermittent hypoxemia is the most important and major mechanism that connects OSA to cardiovascular disease. Based on data from several experimental studies, animals exposed to chronically intermittent hypoxemia develop multiple cardiovascular complications, such as hypertension, myocardial hypertrophy, endothelial dysfunction, and atherosclerosis [66–69].

Obstructive Sleep Apnea and Arterial Hypertension

The best studied relationship between SDB and cardiovascular disease is between OSA and hypertension. The prevalence of moderate-to-severe OSA in patients with primary hypertension is approximately 30% while 80% in patients with resistant hypertension [70, 71]; therefore the link is clinically relevant. According to international guidelines, the OSA screening for all patients with resistant hypertension is strongly recommended.

Interestingly, patients with OSA have cyclical increases in BP associated with the end of OSA episodes. In addition, it is common that these

patients often do not present the nocturnal descensus of the BP and are considered like non-dippers [72]. This pattern is considered a risk for the development of cardiovascular diseases [73]. Most of the pathophysiological mechanisms of OSA, in particular autonomic dysfunction, have central implications in the genesis of arterial hypertension. In fact, autonomic control is altered not only during nighttime, with a continuous waxing and waning of sympathetic outflow during apneic events, but also during daytime, with a constant predominance of sympathetic modulation to the sinus node and the vessels [74–76].

Yet, from a pathophysiological and an epidemiological point of view, although the relation between OSA and hypertension has been well established, the causality between OSA in hypertension is a still debated issue. In fact, it has been documented that untreated OSA increased the risk of developing hypertension [77]. However, other studies did not confirm this finding after adjusting them for confounding variables (e.g., age, sex, body mass index, neck circumference, and smoking) [78]. This contrasting data can be related mainly to the overlap of the common risk factors between OSA and arterial hypertension (i.e., obesity and metabolic syndrome).

In 2006, a systematic review highlights that continuous positive airway pressure (CPAP) is effective on sleepiness symptoms and quality of life measures in subjects with moderate and severe OSA, being more effective than oral appliances in reducing respiratory disturbances [79]. In addition, data on short-term trials showed that CPAP lowers BP but long-term data are required for all outcomes [79].

Interestingly, a recent meta-analysis showed that the pooled effects after CPAP treatment for 24-h ambulatory systolic and diastolic BP were in average 5 mmHg and 3 mmHg, respectively [80]. However, while CPAP is able to reduce cardiovascular outcomes, it is unclear whether this effect is related to the reduction of arterial hypertension or, more likely, to a synergistic effect among several intermediate mechanisms.

Obstructive Sleep Apnea and Coronary Artery Disease

According to epidemiological studies, approximately 50% of patients with CAD have moderate to severe OSA [81], and one half of the patients admitted to hospitals for a ST-elevation MI have an undiagnosed severe OSA [82]. In addition, prevalence of OSA is higher in CAD patients with reduced ventricular function when compared to CAD patients with preserved ventricular function [83].

Another interesting fact is related to the difference between genders, since OSA is a risk factor for CAD in men, but this result has not been confirmed in women [83].

From a pathophysiological perspective, beyond to sleep fragmentation and autonomic dysfunction promoted by intermittent hypoxemia, the repetitive episodes of upper airways collapse lead also to the uncoupling of coronary blood flow and myocardial workload [84]. Thus, due to this uncoupling, the sudden increase in coronary blood flow after each apneic event could be a pathophysiological mechanism responsible for the strong link between OSA and ischemic events in patients with CAD.

The comorbidity of OSA also impacts on the clinical progression of MI patients. In the early phases of acute MI, the heart is more sensitive to the increased intrathoracic negative pressure induced by apneas in patients with OSA, thus leading to a worse recovery from acute events [83]. Interestingly, patients with OSA tend to have prolonged MI, altered ventricular remodeling, and lower ventricular function [83, 85].

The effects on long-term cardiovascular outcomes have been widely reported. In a prospective study, Gottlieb et al. demonstrated that OSA is a significant risk factor for the incidence of an acute CAD, such as acute MI, revascularization, and death for cardiovascular causes [86]. Additionally, it has been also showed that the event-free survival rate was worse in patients with severe OSA when compared to nonsevere OSA [82].

Thus, besides being highly prevalent, these evidences demonstrate that OSA is an independent risk factor for the development of ischemic cardiomyopathy in patients with CAD. In addition, patients with CAD and OSA have worse short- and long-term outcomes. Therefore, the prompt diagnostic of CAD patients with OSA comorbidity is essential to stratify high-risk patients and thus to tailor the best therapeutic strategy for these patients.

Obstructive Sleep Apnea and Cardiac Arrhythmias

Several factors described in the pathophysiology that connect OSA with cardiovascular diseases may contribute to cardiac arrhythmias, such as ANS activation, cardiac remodeling, and increased inflammatory markers [87, 88]. Among all cardiac arrhythmias, the most common during sleep in patients with OSA are atrial fibrillation (AF), ventricular extra systoles, second-degree atrioventricular block, and non-sustained ventricular tachycardia [54].

According to the American College of Cardiology, it is estimated that the prevalence of secondary bradycardia to SDB (e.g., OSA) is approximately 10% [51]. The occurrence of bradycardia associated with apnea and hypopnea events reflects a parasympathetic hyperactivation in the sense of reducing the consumption of oxygen by the myocardium in a context of hypoxemia.

Although OSA is demonstrated to be related to cardiac and peripheral sympathetic hyperactivation, the cardiac autonomic system undergoes different influences during and shortly after the occurrence of apnea [63, 89]. When hypoxemia occurs in the absence of ventilation, the stimulation of peripheral chemoreceptors has a vagotonic effect causing bradycardia. When ventilation is resumed, even in the presence of hypoxia, stretching of the pulmonary receptors inhibits vagal stimulation, which results in cardiac sympathetic discharge-mediated tachycardia [51, 90, 91].

Yet, ventricular arrhythmias are more prevalent in subjects with OSA when compared to individuals without OSA. Since patients with OSA have a large number of comorbidities (e.g., hypertension, obesity, and CAD), there is a certain difficulty in discriminating the role of OSA as an independent risk factor for the development of ventricular arrhythmias [92].

On the other hand, recent evidence suggests that OSA may be present in approximately 50% of patients with AF [93]. Another important finding is that, by analyzing only those patients with AF who were referred for elective electric cardioversion, the frequency of OSA reached levels close to 80% [94].

In addition to the detrimental effects induced by the hypoxia-reoxigenation episodes during apneas, a major role might be played by the coactivation of the ANS during hypoxemic episodes. Vagal activation would induce an impaired refractoriness of the cardiac conducting system, creating an electrogenic background for triggering AF. Moreover, apneic events induce changes in intrathoracic pressures causing atria enlargement and tissue stretch and remodeling at the pulmonary vein ostia, leading to a "mechanical" trigger for AF onset [95].

Interesting data have been published on the effects of OSA treatment on AF. A recent meta-analysis showed that OSA patients treated with CPAP had a 42% decreased risk of AF, with benefits of CPAP more evident for younger, obese, and male patients. On the contrary, an inverse relation has been established between CPAP therapy and AF recurrence [96]. Two recent papers showed that patients under CPAP therapy had a higher AF-free survival rate and AF-free survival of antiarrhythmic drugs compared to OSA patients without CPAP treatments. Patients with OSA had a greater risk of AF recurrence after catheter ablation compared to patients without OSA and a higher risk to repeat ablation following pulmonary vein isolation. On the contrary, OSA patients under CPAP had a risk of AF recurrence analogous to that of patients without OSA, and the efficacy of catheter ablation for AF was similar

between patients with and without OSA undergoing CPAP treatment [97, 98].

Based in these data, the relationship between OSA and AF is bidirectional, where patients with OSA at higher risk to develop AF and patients with AF have a greater prevalence of OSA. For this reason, the efficacy of AF treatment is affected by the presence of OSA, and an effective OSA treatment with CPAP improves AF outcomes [99]. Thus, a prompt identification of OSA in patients with AF and adequate therapeutic options should be considered in order to improve the long-term outcomes in these patients.

Finally, several studies suggest that patients with OSA have a significant alteration in an established day/night pattern of sudden cardiac death. Specifically, OSA increases risk of sudden cardiac death in more than twofold during the sleeping hours, which is in marked contrast to the low occurrence of sudden cardiac death during this time in individuals without OSA and in the general population [100]. In fact, the severity of OSA correlated directly with the risk of nocturnal sudden cardiac death [100]. However, while these findings suggest that OSA changes the timing of sudden cardiac death and that the acute effects of OSA on cardiac ischemia and arrhythmias may in fact have significant clinical consequences, whether OSA actually increases the overall risk of sudden cardiac death is not yet known.

Obstructive Sleep Apnea and Congestive Heart Failure

CHF is a pathological condition characterized by the inability of the heart to fulfil the oxygen demand of the periphery. CHF can be due to an impairment of the ability of the ventricles to contract properly (i.e., systolic dysfunction) or to an increased stiffness of the ventricular walls during diastolic phase (i.e., diastolic dysfunction) [101].

Although SDB may also occur in the course of CHF, this factor must be considered a very important comorbidity in patients with CHF. In fact, SDB has a high prevalence, affecting more than 50% of the CHF patients with reduced ejection fraction [102] and also in patients with CHF with preserved ejection fraction [53].

Gottlieb and colleagues showed that the presence of OSA increases the risk of new onset CHF in men (hazard ratio, 1.13; 95% CI, 1.02–1.26) per 10-unit increase in apnea-hypopnea index (AHI, the number of episodes of apneas and hypopneas per hour of sleep). Men with a severe OSA (AHI >30) are 58% more likely to develop CHF compared to non-OSA subjects [86]. Patients with CHF are at higher risk of developing central sleep apnea (CSA) and Cheyne-Stoke breathing (CSB), a particular condition characterized by breathing that becomes progressively deeper and faster followed by a gradual slowing of the breathing followed by an apnea [103–105]. Interestingly, CSA is an independent risk of adverse outcome in patients with CHF [103, 106], and also the more severe the CSA, the higher the probability to develop clinical symptoms and signs of heart failure and to develop decompensated CHF in older men [107]. It has been also shown that CSA is an independent risk factor that predicts hospital 6-month readmission [108]. Thus, OSA and CSA are often coexisting in CHF patients.

It is known that OSA and CHF shown a strong link, and the relation between diseases has important consequences on long-term outcomes in these patients. In fact, CHF patients with a comorbid untreated OSA (i.e., AHI >15) double the all-cause mortality compared to CHF patients without OSA [109], and besides this OSA is an independent risk factor of mortality in these patients [110]. We know that progressive loss of oscillatory pattern associated with an increased efferent sympathetic discharge is a hallmark of CHF. Thus, due to saturation of sympathetic nervous system, the progressive loss of rhythmical properties of adrenergic outflow is accompanied by an expressive reduction in HRV [111]. In addition to this autonomic dysfunction, patients with CHF and OSA not only have repetitive bursts of sympathetic efferent during apneas due to the chemoreflex hypersensitivity [74, 75] but due to hypoxia and upper airway obstruction also shown increased vagal activity. This pathophysiological phenomenon triggers a reflex bradycardia, which

is then followed by a sympathoexcitation after apneic event [112]. During the coactivation of autonomic branches, simultaneously to hypoxic pulmonary vasoconstriction, both right ventricular hypertension and acute stretch of the atria wall and pulmonary vein could promote the onset of arrhythmias in patients with CHF, especially AF [112, 113]. Thus, in considering the deleterious effects of this combined sympathetic and vagal activation, a growing interest has been focused on the possible beneficial effects of OSA treatment in patients with CHF, mainly in terms of mortality. Until now, it has been recommended the use of CPAP as optimal therapy for OSA, once that it is able to reduce symptoms, to improve quality of life, and to significantly reduce the incidence of cardiovascular outcomes [114].

Curiously, the effectiveness of CPAP treatment in patients with CHF is still discussed. It has been reported that 1–3 months of CPAP in patients with CHF and OSA were able to reduce HR and BP and to improve left ventricular ejection fraction and NHYA functional class [115]. In line with these findings, the Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure trial (CANPAP study) reported that CPAP treatment was able to reduce the number of obstructive apneas, to improve nocturnal oxygenation, and to increase the left ventricular ejection fraction, but without altering survival rate [116]. A recent randomized clinical trial focused on the use of a specific ventilation (adaptive servo-ventilation) in CHF patients with reduced ejection fraction and central apneas, failed to reach its primary endpoints (i.e., cardiovascular intervention, worsening heart failure, and reduction of death for any cause) [117]. And contrary to initial expectations, results showed that cardiovascular mortality and all-cause mortality were higher in the adaptive servo-ventilation group compared to the conventional therapy group [117]. Therefore, there is still lack of clinical evidence based to randomized trials that the reduction in obstructive as well as central apneas in patients with CHF is associated with a reduction in morbidity and mortality in these patients.

Conclusion

As chronic sleep deficiency has becoming one of the most relevant health problems in modern societies, this phenomenon has an impact upon global health in the whole world. This condition is related to changes in lifestyle habits and an increased prevalence of OSA. Independently of its primary cause, chronic sleep deficiency promoted by OSA can impinge upon several physiological pathways, such as cardiovascular autonomic control, oxidative stress, inflammatory responses, and endothelial function. Therefore, all these pathophysiological mechanisms are responsible by mismatch among the physiological rhythms that link between sleep deficiency with increased risk of cardiovascular diseases, such as arterial hypertension, cardiac arrhythmias, coronary artery disease, and chronic heart failure. Thus, an early diagnosis and treatment of subjects with OSA is essential in order to reduce the risk of cardiovascular diseases in general population, since chronic sleep deficiency promoted by OSA might be trigger to the development of cardiovascular disease.

References

1. Campbell SS, Tobler I. Animal sleep: a review of sleep duration across phylogeny. Neurosci Biobehav Rev. 1984;8(3):269–300.
2. National Institute of Mental Health. Arousal and regulatory systems: workshop proceedings. 2013.
3. Practice parameters for the indications for polysomnography and related procedures. Polysomnography Task Force, American Sleep Disorders Association Standards of Practice Committee. Sleep. 1997;20(6):406–22.
4. Kushida CA, Littner MR, Morgenthaler T, Alessi CA, Bailey D, Coleman J Jr, et al. Practice parameters for the indications for polysomnography and related procedures: an update for 2005. Sleep. 2005;28(4):499–521.
5. Loomis AL, Harvey EN, Hobart G. Potential rhythms of the cerebral cortex during sleep. Science. 1935;81(2111):597–8.
6. Siegel JM. The neurobiology of sleep. Semin Neurol. 2009;29(4):277–96.
7. Watson NF, Badr MS, Belenky G, Bliwise DL, Buxton OM, Buysse D, et al. Recommended amount of sleep for a healthy adult: a joint consensus

statement of the American Academy of Sleep Medicine and Sleep Research Society. Sleep. 2015;38(6):843–4.
8. Murali NS, Svatikova A, Somers VK. Cardiovascular physiology and sleep. Front Biosci. 2003;8:s636–52.
9. Saper CB, Scammell TE, Lu J. Hypothalamic regulation of sleep and circadian rhythms. Nature. 2005;437(7063):1257–63.
10. Trinder J, Kleiman J, Carrington M, Smith S, Breen S, Tan N, et al. Autonomic activity during human sleep as a function of time and sleep stage. J Sleep Res. 2001;10(4):253–64.
11. Somers VK, Dyken ME, Mark AL, Abboud FM. Sympathetic-nerve activity during sleep in normal subjects. N Engl J Med. 1993;328(5):303–7.
12. Montano N, Porta A, Cogliati C, Costantino G, Tobaldini E, Casali KR, et al. Heart rate variability explored in the frequency domain: a tool to investigate the link between heart and behavior. Neurosci Biobehav Rev. 2009;33(2):71–80.
13. Brandenberger G, Viola AU, Ehrhart J, Charloux A, Geny B, Piquard F, et al. Age-related changes in cardiac autonomic control during sleep. J Sleep Res. 2003;12(3):173–80.
14. Legramante JM, Marciani MG, Placidi F, Aquilani S, Romigi A, Tombini M, et al. Sleep-related changes in baroreflex sensitivity and cardiovascular autonomic modulation. J Hypertens. 2003;21(8):1555–61.
15. Tobaldini E, Costantino G, Solbiati M, Cogliati C, Kara T, Nobili L, et al. Sleep, sleep deprivation, autonomic nervous system and cardiovascular diseases. Neurosci Biobehav Rev. 2017;74:321–9.
16. Sabanayagam C, Shankar A. Sleep duration and cardiovascular disease: results from the National Health Interview Survey. Sleep. 2010;33(8):1037–42.
17. Pan A, De Silva DA, Yuan JM, Koh WP. Sleep duration and risk of stroke mortality among Chinese adults: Singapore Chinese health study. Stroke. 2014;45(6):1620–5.
18. Gangwisch JE. A review of evidence for the link between sleep duration and hypertension. Am J Hypertens. 2014;27(10):1235–42.
19. National Sleep Foundation. 2006 Sleep in America poll: summary of findings. Washington, DC: National Sleep Foundation; 2006.
20. National Institutes of Health. National Institutes of Health sleep disorders research plan. Bethesda: National Institutes of Health; 2011.
21. Buysse DJ. Sleep health: can we define it? Does it matter? Sleep. 2014;37(1):9–17.
22. Schoenborn CA, Adams PF, Peregoy JA. Health behaviors of adults: United States, 2008–2010. Vital Health Stat. 2013;10(257):1–184.
23. McKnight-Eily LR, Eaton DK, Lowry R, Croft JB, Presley-Cantrell L, Perry GS. Relationships between hours of sleep and health-risk behaviors in US adolescent students. Prev Med. 2011;53(4–5):271–3.
24. Liu Y, Wheaton AG, Chapman DP, Croft JB. Sleep duration and chronic diseases among U.S. adults age 45 years and older: evidence from the 2010 Behavioral Risk Factor Surveillance System. Sleep. 2013;36(10):1421–7.
25. Ram S, Seirawan H, Kumar SK, Clark GT. Prevalence and impact of sleep disorders and sleep habits in the United States. Sleep Breath. 2010;14(1):63–70.
26. Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. Am J Epidemiol. 2013;177(9):1006–14.
27. Roth T. Insomnia: definition, prevalence, etiology, and consequences. J Clin Sleep Med. 2007;3(5 Suppl):S7–10.
28. Alterman T, Luckhaupt SE, Dahlhamer JM, Ward BW, Calvert GM. Prevalence rates of work organization characteristics among workers in the U. S.: data from the 2010 National Health Interview Survey. Am J Ind Med. 2013;56(6):647–59.
29. Ackermann K, Plomp R, Lao O, Middleton B, Revell VL, Skene DJ, et al. Effect of sleep deprivation on rhythms of clock gene expression and melatonin in humans. Chronobiol Int. 2013;30(7):901–9.
30. Li J, Vitiello MV, Gooneratne NS. Sleep in normal aging. Sleep Med Clin. 2018;13(1):1–11.
31. Tobaldini E, Nobili L, Strada S, Casali KR, Braghiroli A, Montano N. Heart rate variability in normal and pathological sleep. Front Physiol. 2013;4:294.
32. Meier-Ewert HK, Ridker PM, Rifai N, Regan MM, Price NJ, Dinges DF, et al. Effect of sleep loss on C-reactive protein, an inflammatory marker of cardiovascular risk. J Am Coll Cardiol. 2004;43(4):678–83.
33. Irwin MR, Wang M, Ribeiro D, Cho HJ, Olmstead R, Breen EC, et al. Sleep loss activates cellular inflammatory signaling. Biol Psychiatry. 2008;64(6):538–40.
34. Imeri L, Opp MR. How (and why) the immune system makes us sleep. Nat Rev Neurosci. 2009;10(3):199–210.
35. Rafalson L, Donahue RP, Stranges S, Lamonte MJ, Dmochowski J, Dorn J, et al. Short sleep duration is associated with the development of impaired fasting glucose: the Western New York Health Study. Ann Epidemiol. 2010;20(12):883–9.
36. Tasali E, Mokhlesi B, Van Cauter E. Obstructive sleep apnea and type 2 diabetes: interacting epidemics. Chest. 2008;133(2):496–506.
37. Taheri S, Lin L, Austin D, Young T, Mignot E. Short sleep duration is associated with reduced leptin, elevated ghrelin, and increased body mass index. PLoS Med. 2004;1(3):e62.
38. Alkadhi K, Zagaar M, Alhaider I, Salim S, Aleisa A. Neurobiological consequences of sleep deprivation. Curr Neuropharmacol. 2013;11(3):231–49.
39. Zhong X, Hilton HJ, Gates GJ, Jelic S, Stern Y, Bartels MN, et al. Increased sympathetic and decreased parasympathetic cardiovascular modulation in normal humans with acute sleep deprivation. J Appl Physiol. 2005;98(6):2024–32.

40. Sunbul M, Kanar BG, Durmus E, Kivrak T, Sari I. Acute sleep deprivation is associated with increased arterial stiffness in healthy young adults. Sleep Breath. 2014;18(1):215–20.
41. Sauvet F, Drogou C, Bougard C, Arnal PJ, Dispersyn G, Bourrilhon C, et al. Vascular response to 1 week of sleep restriction in healthy subjects. A metabolic response? Int J Cardiol. 2015;190:246–55.
42. Franzen PL, Gianaros PJ, Marsland AL, Hall MH, Siegle GJ, Dahl RE, et al. Cardiovascular reactivity to acute psychological stress following sleep deprivation. Psychosom Med. 2011;73(8):679–82.
43. Tobaldini E, Cogliati C, Fiorelli EM, Nunziata V, Wu MA, Prado M, et al. One night on-call: sleep deprivation affects cardiac autonomic control and inflammation in physicians. Eur J Intern Med. 2013;24(7):664–70.
44. Kato M, Phillips BG, Sigurdsson G, Narkiewicz K, Pesek CA, Somers VK. Effects of sleep deprivation on neural circulatory control. Hypertension. 2000; 35(5):1173–5.
45. Esen Ö, Akçakoyun M, Açar G, Bulut M, Alýzade E, Kargin R, et al. Acute sleep deprivation is associated with increased atrial electromechanical delay in healthy young adults. Pacing Clin Electrophysiol. 2011;34(12):1645–51.
46. Açar G, Akçakoyun M, Sari I, Bulut M, Alizade E, Özkan B, et al. Acute sleep deprivation in healthy adults is associated with a reduction in left atrial early diastolic strain rate. Sleep Breath. 2013;17(3): 975–83.
47. Glos M, Fietze I, Blau A, Baumann G, Penzel T. Cardiac autonomic modulation and sleepiness: physiological consequences of sleep deprivation due to 40 h of prolonged wakefulness. Physiol Behav. 2014;125:45–53.
48. Takase B, Akima T, Satomura K, Ohsuzu F, Mastui T, Ishihara M, et al. Effects of chronic sleep deprivation on autonomic activity by examining heart rate variability, plasma catecholamine, and intracellular magnesium levels. Biomed Pharmacother. 2004;58(Suppl 1):S35–9.
49. Dettoni JL, Consolim-Colombo FM, Drager LF, Rubira MC, Souza SB, Irigoyen MC, et al. Cardiovascular effects of partial sleep deprivation in healthy volunteers. J Appl Physiol. 2012;113(2): 232–6.
50. Grandner MA, Jackson NJ, Pak VM, Gehrman PR. Sleep disturbance is associated with cardiovascular and metabolic disorders. J Sleep Res. 2012;21(4): 427–33.
51. Somers VK, White DP, Amin R, Abraham WT, Costa F, Culebras A, et al. Sleep apnea and cardiovascular disease: an American Heart Association/American College of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing. J Am Coll Cardiol. 2008;52(8):686–717.
52. Mooe T, Franklin KA, Wiklund U, Rabben T, Holmström K. Sleep-disordered breathing and myocardial ischemia in patients with coronary artery disease. Chest. 2000;117(6):1597–602.
53. Herrscher TE, Akre H, Øverland B, Sandvik L, Westheim AS. High prevalence of sleep apnea in heart failure outpatients: even in patients with preserved systolic function. J Card Fail. 2011;17(5): 420–5.
54. Guilleminault C, Connolly SJ, Winkle RA. Cardiac arrhythmia and conduction disturbances during sleep in 400 patients with sleep apnea syndrome. Am J Cardiol. 1983;52(5):490–4.
55. Tufik S, Santos-Silva R, Taddei JA, Bittencourt LR. Obstructive sleep apnea syndrome in the Sao Paulo Epidemiologic Sleep Study. Sleep Med. 2010; 11(5):441–6.
56. Drager LF, Lopes HF, Maki-Nunes C, Trombetta IC, Toschi-Dias E, Alves MJ, et al. The impact of obstructive sleep apnea on metabolic and inflammatory markers in consecutive patients with metabolic syndrome. PLoS One. 2010;5(8):e12065.
57. Stopford E, Ravi K, Nayar V. The association of sleep disordered breathing with heart failure and other cardiovascular conditions. Cardiol Res Pract. 2013;2013:Article ID 356280, 9 pages.
58. Kendzerska T, Gershon AS, Hawker G, Leung RS, Tomlinson G. Obstructive sleep apnea and risk of cardiovascular events and all-cause mortality: a decade-long historical cohort study. PLoS Med. 2014;11(2):e1001599.
59. Reichmuth KJ, Austin D, Skatrud JB, Young T. Association of sleep apnea and type II diabetes: a population-based study. Am J Respir Crit Care Med. 2005;172(12):1590–5.
60. Narkiewicz K, Somers VK. The sympathetic nervous system and obstructive sleep apnea: implications for hypertension. J Hypertens. 1997;15(12 Pt 2): 1613–9.
61. Kasai T, Floras JS, Bradley TD. Sleep apnea and cardiovascular disease: a bidirectional relationship. Circulation. 2012;126(12):1495–510.
62. Shamsuzzaman AS, Winnicki M, Lanfranchi P, Wolk R, Kara T, Accurso V, et al. Elevated C-reactive protein in patients with obstructive sleep apnea. Circulation. 2002;105(21):2462–4.
63. Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. J Clin Invest. 1995;96(4):1897–904.
64. Bradley TD, Floras JS. Obstructive sleep apnoea and its cardiovascular consequences. Lancet. 2009; 373(9657):82–93.
65. Leung RS, Bradley TD. Sleep apnea and cardiovascular disease. Am J Respir Crit Care Med. 2001; 164(12):2147–65.
66. Drager LF, Togeiro SM, Polotsky VY, Lorenzi-Filho G. Obstructive sleep apnea: a cardiometabolic risk in obesity and the metabolic syndrome. J Am Coll Cardiol. 2013;62(7):569–76.

67. Sunderram J, Androulakis IP. Molecular mechanisms of chronic intermittent hypoxia and hypertension. Crit Rev Biomed Eng. 2012;40(4):265–78.
68. Drager LF, Bortolotto LA, Figueiredo AC, Silva BC, Krieger EM, Lorenzi-Filho G. Obstructive sleep apnea, hypertension, and their interaction on arterial stiffness and heart remodeling. Chest. 2007; 131(5):1379–86.
69. Drager LF, Yao Q, Hernandez KL, Shin MK, Bevans-Fonti S, Gay J, et al. Chronic intermittent hypoxia induces atherosclerosis via activation of adipose angiopoietin-like 4. Am J Respir Crit Care Med. 2013;188(2):240–8.
70. Pedrosa RP, Drager LF, Gonzaga CC, Sousa MG, de Paula LK, Amaro AC, Amodeo C, et al. Obstructive sleep apnea: the most common secondary cause of hypertension associated with resistant hypertension. Hypertension. 2011;58(5):811–7.
71. Floras JS. Hypertension and sleep apnea. Can J Cardiol. 2015;31(7):889–97.
72. Wolf J, Hering D, Narkiewicz K. Non-dipping pattern of hypertension and obstructive sleep apnea syndrome. Hypertens Res. 2010;33(9):867–71.
73. Birkenhäger AM, van den Meiracker AH. Causes and consequences of a non-dipping blood pressure profile. Neth J Med. 2007;65(4):127–31.
74. Narkiewicz K, Montano N, Cogliati C, van de Borne PJ, Dyken ME, Somers VK. Altered cardiovascular variability in obstructive sleep apnea. Circulation. 1998;98(11):1071–7.
75. Narkiewicz K, van de Borne PJ, Montano N, Dyken ME, Phillips BG, Somers VK. Contribution of tonic chemoreflex activation to sympathetic activity and blood pressure in patients with obstructive sleep apnea. Circulation. 1998;97(10):943–5.
76. Konecny T, Kara T, Somers VK. Obstructive sleep apnea and hypertension: an update. Hypertension. 2014;63(2):203–9.
77. Marin JM, Agusti A, Villar I, Forner M, Nieto D, Carrizo SJ, et al. Association between treated and untreated obstructive sleep apnea and risk of hypertension. JAMA. 2012;307(20):2169–76.
78. Cano-Pumarega I, Durán-Cantolla J, Aizpuru F, Miranda-Serrano E, Rubio R, Martínez-Null C, et al. Obstructive sleep apnea and systemic hypertension: longitudinal study in the general population: the Vitoria Sleep Cohort. Am J Respir Crit Care Med. 2011;184(11):1299–304.
79. Giles TL, Lasserson TJ, Smith BH, White J, Wright J, Cates CJ. Continuous positive airways pressure for obstructive sleep apnoea in adults. Cochrane Database Syst Rev. 2006;(3):CD001106.
80. Liu L, Cao Q, Guo Z, Dai Q. Continuous positive airway pressure in patients with obstructive sleep apnea and resistant hypertension: a meta-analysis of randomized controlled trials. J Clin Hypertens. 2016;18(2):153–8.
81. Peker Y, Kraiczi H, Hedner J, Löth S, Johansson A, Bende M. An independent association between obstructive sleep apnoea and coronary artery disease. Eur Respir J. 1999;14(1):179–84.
82. Lee CH, Khoo SM, Chan MY, Wong HB, Low AF, Phua QH, et al. Severe obstructive sleep apnea and outcomes following myocardial infarction. J Clin Sleep Med. 2011;7(6):616–21.
83. Arzt M, Hetzenecker A, Steiner S, Buchner S. Sleep-disordered breathing and coronary artery disease. Can J Cardiol. 2015;31(7):909–17.
84. Hamilton GS, Meredith IT, Walker AM, Solin P. Obstructive sleep apnea leads to transient uncoupling of coronary blood flow and myocardial work in humans. Sleep. 2009;32(2):263–70.
85. Nakashima H, Katayama T, Takagi C, Amenomori K, Ishizaki M, Honda Y, et al. Obstructive sleep apnoea inhibits the recovery of left ventricular function in patients with acute myocardial infarction. Eur Heart J. 2006;27(19):2317–22.
86. Gottlieb DJ, Yenokyan G, Newman AB, O'Connor GT, Punjabi NM, Quan SF, et al. Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the sleep heart health study. Circulation. 2010;122(4): 352–60.
87. Digby GC, Baranchuk A. Sleep apnea and atrial fibrillation; 2012 update. Curr Cardiol Rev. 2012; 8(4):265–72.
88. Goudis CA, Ketikoglou DG. Obstructive sleep and atrial fibrillation: pathophysiological mechanisms and therapeutic implications. Int J Cardiol. 2017;230: 293–300.
89. Arias MA, Sánchez AM. Obstructive sleep apnea and its relationship to cardiac arrhythmias. J Cardiovasc Electrophysiol. 2007;18(9):1006–14.
90. Somers VK, Dyken ME, Mark AL, Abboud FM. Parasympathetic hyperresponsiveness and bradyarrhythmias during apnoea in hypertension. Clin Auton Res. 1992;2(3):171–6.
91. Grimm W, Hoffmann J, Menz V, Köhler U, Heitmann J, Peter JH, et al. Electrophysiologic evaluation of sinus node function and atrioventricular conduction in patients with prolonged ventricular asystole during obstructive sleep apnea. Am J Cardiol. 1996;77 (15):1310–4.
92. Mehra R, Benjamin EJ, Shahar E, Gottlieb DJ, Nawabit R, Kirchner HL, et al. Association of nocturnal arrhythmias with sleep-disordered breathing: the Sleep Heart Health Study. Am J Respir Crit Care Med. 2006;173(8):910–6.
93. Gami AS, Pressman G, Caples SM, Kanagala R, Gard JJ, Davison DE, et al. Association of atrial fibrillation and obstructive sleep apnea. Circulation. 2004;110(4):364–7.
94. Albuquerque FN, Calvin AD, Sert Kuniyoshi FH, Konecny T, Lopez-Jimenez F, Pressman GS, et al.

Sleep-disordered breathing and excessive daytime sleepiness in patients with atrial fibrillation. Chest. 2012;141(4):967–73.
95. Caples SM, Somers VK. Sleep-disordered breathing and atrial fibrillation. Prog Cardiovasc Dis. 2009; 51(5):411–5.
96. Qureshi WT, Nasir UB, Alqalyoobi S, O'Neal WT, Mawri S, Sabbagh S, et al. Meta-analysis of continuous positive airway pressure as a therapy of atrial fibrillation in obstructive sleep apnea. Am J Cardiol. 2015;116(11):1767–73.
97. Li L, Wang ZW, Li J, Ge X, Guo LZ, Wang Y, et al. Efficacy of catheter ablation of atrial fibrillation in patients with obstructive sleep apnoea with and without continuous positive airway pressure treatment: a meta-analysis of observational studies. Europace. 2014;16(9):1309–14.
98. Fein AS, Shvilkin A, Shah D, Haffajee CI, Das S, Kumar K, et al. Treatment of obstructive sleep apnea reduces the risk of atrial fibrillation recurrence after catheter ablation. J Am Coll Cardiol. 2013;62(4): 300–5.
99. Ng CY, Liu T, Shehata M, Stevens S, Chugh SS, Wang X. Meta-analysis of obstructive sleep apnea as predictor of atrial fibrillation recurrence after catheter ablation. Am J Cardiol. 2011;108(1):47–51.
100. Gami AS, Howard DE, Olson EJ, Somers VK. Day-night pattern of sudden death in obstructive sleep apnea. N Engl J Med. 2005;352(12):1206–14.
101. Toschi-Dias E, Rondon MUPB, Cogliati C, Paolocci N, Tobaldini E, Montano N. Contribution of autonomic reflexes to the hyperadrenergic state in heart failure. Front Neurosci. 2017;11:162.
102. Schulz R, Blau A, Börgel J, Duchna HW, Fietze I, Koper I, et al. Sleep apnoea in heart failure. Eur Respir J. 2007;29(6):1201–5.
103. Lanfranchi PA, Braghiroli A, Bosimini E, Mazzuero G, Colombo R, Donner CF, et al. Prognostic value of nocturnal Cheyne-Stokes respiration in chronic heart failure. Circulation. 1999;99(11):1435–40.
104. Bradley TD, Floras JS. Sleep apnea and heart failure: part I: obstructive sleep apnea. Circulation. 2003; 107(12):1671–8.
105. Bradley TD, Floras JS. Sleep apnea and heart failure: part II: central sleep apnea. Circulation. 2003; 107(13):1822–6.
106. La Rovere MT, Pinna GD, Maestri R, Robbi E, Mortara A, Fanfulla F, et al. Clinical relevance of short-term day-time breathing disorders in chronic heart failure patients. Eur J Heart Fail. 2007;9(9): 949–54.
107. Javaheri S, Blackwell T, Ancoli-Israel S, Ensrud KE, Stone KL, Redline S, et al. Sleep-disordered breathing and incident heart failure in older men. Am J Respir Crit Care Med. 2016;193(5):561–8.
108. Khayat R, Abraham W, Patt B, Brinkman V, Wannemacher J, Porter K, et al. Central sleep apnea is a predictor of cardiac readmission in hospitalized patients with systolic heart failure. J Card Fail. 2012;18(7):534–40.
109. Levy D, Kenchaiah S, Larson MG, Benjamin EJ, Kupka MJ, Ho KK, et al. Long-term trends in the incidence of and survival with heart failure. N Engl J Med. 2002;347(18):1397–402.
110. Wang H, Parker JD, Newton GE, Floras JS, Mak S, Chiu KL, et al. Influence of obstructive sleep apnea on mortality in patients with heart failure. J Am Coll Cardiol. 2007;49(15):1625–31.
111. Guzzetti S, Magatelli R, Borroni E, Mezzetti S. Heart rate variability in chronic heart failure. Auton Neurosci. 2001;90(1–2):102–5.
112. Mehra R, Redline S. Arrhythmia risk associated with sleep disordered breathing in chronic heart failure. Curr Heart Fail Rep. 2014;11(1):88–97.
113. Romero-Corral A, Somers VK, Pellikka PA, Olson EJ, Bailey KR, Korinek J, et al. Decreased right and left ventricular myocardial performance in obstructive sleep apnea. Chest. 2007;132(6): 1863–70.
114. Marin JM, Carrizo SJ, Vicente E, Agusti AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. Lancet. 2005;365(9464): 1046–53.
115. Mansfield DR, Gollogly NC, Kaye DM, Richardson M, Bergin P, Naughton MT. Controlled trial of continuous positive airway pressure in obstructive sleep apnea and heart failure. Am J Respir Crit Care Med. 2004;169(3):361–6.
116. Bradley TD, Logan AG, Kimoff RJ, Sériès F, Morrison D, Ferguson K, et al. Continuous positive airway pressure for central sleep apnea and heart failure. N Engl J Med. 2005;353(19):2025–33.
117. Cowie MR, Woehrle H, Wegscheider K, Angermann C, d'Ortho MP, Erdmann E, et al. Adaptive servo-ventilation for central sleep apnea in systolic heart failure. N Engl J Med. 2015;373(12):1095–105.

Sleep Disorders and Cardiovascular Disease

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Contents

Abstract

Sleep and heart show a bidirectional relationship, in which sleep disorders influence cardiac function and cardiac pathology may conversely disrupt sleep architecture. Sleep is considered a dynamic process with strong effects on cardiovascular homeostasis. Normally, sympathovagal balance ensures a sympathetic predominance during the day and a prevailing parasympathetic activity during the night; during REM sleep, sympathetic burst occur,

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*,
https://doi.org/10.1007/978-3-030-28008-6_37

leading to blood pressure and heart rate instability. Moreover, many sleep disorders may induce sleep fragmentation, leading to increased sympathetic activity and hypothalamic-pituitary axis hyperactivity; these factors may induce vasoconstriction, increased arterial stiffness, and vascular remodeling. Sleep-disordered breathing is associated with hypertension, congestive heart failure, and cardiac rhythm disturbances. Insomnia and short sleeping time are associated with increased risk of coronary heart disease, hypertension, and heart failure. Sleep-related movement disorders, namely, periodic limb movements and restless leg syndrome, show a strong relationship with cardiovascular disease, but further studies are needed. Autonomic dysregulation has been described in Idiopathic REM sleep behavior disorder, with possible consequences on cardiovascular function. Narcolepsy type 1 patients show a nocturnal non-dipping profile, resulting from impaired sympathovagal balance.

Keywords

Sleep · Cardiovascular disease · Sleep disorders · Non-dipping · Hypertension · Sympathovagal homeostasis · OSA · Insomnia · RLS · RBD

Introduction

Sleep is a complex, finely organized dynamic process, which is considered essential for human health. Despite its exact biological function remains to be fully understood, sleep is thought to have restorative, conservative, adaptive, thermoregulatory, and memory consolidative functions. Moreover, it is indisputable that sleep deprivation can be harmful (quoad vitam and quoad valetudinem). Indeed, loss of attention and concentration are considered low-term consequences of sleep deprivation, but increased mortalities due to coronary heart disease, heart failure, and high blood pressure, together with obesity, diabetes mellitus, and mood disorders (other than car accidents), are included among the long-term consequences of sleep deprivation [1].

Due to the effects on cardiovascular dysfunction of sleep deprivation, the relationship between sleep and cardiovascular function has largely been studied. However, many aspects of this relationship still remain unknown. The link between sleep and cardiovascular function is considered bidirectional: on the one hand, sleep modulates and influences the cardiovascular function, and on the other side, cardiovascular function influences sleep (e.g., cardiac pathology as chronic heart failure can disrupt sleep architecture).

Sleep influence on cardiovascular function is strong in both physiological and pathological conditions. From a physiological point of view, sleep exerts numerous effects on the autonomic nervous system, systemic hemodynamics, cardiac function, endothelial function, and coagulations, through direct effect of sleep architecture or indirect effects resulting from circadian rhythms [2].

In relationship with pathological conditions, frequently diagnosed sleep disorders, such as sleep apnea or periodic limb movements (PLMs), have been shown to negatively influence cardiac function, while sleep deprivation is strongly associated with blood vessel and metabolic disorders [3].

In the following chapter, sleep physiology will be discussed with special regard to sleep and sympathovagal homeostasis and receptor-mediated cardiovascular control. Cardiovascular implications of sleep disorders will be analyzed and discussed.

Sleep and Sympathovagal Homeostasis

During wakefulness and sleep, rhythmic patterns of homeostatic regulatory mechanisms, including the autonomic nervous system, influence cardiovascular function [2]. Sympathovagal tone is modulated through circadian patterns of sleep-wake activity, with general prevalence of sympathetic activity during the day and parasympathetic activity during the night [4].

Two main sleep phases are recognized according to physiological and behavioral criteria,

the nonrapid eye movement (NREM) and rapid eye movement (REM) sleep, cyclically alternating for a total of 4–5 NREM/REM cycles in a night; NREM sleep is further divided into stages 1, 2, and 3 (N1, N2, and N3). During NREM sleep, an increase in parasympathetic tone and a decrease in sympathetic tone are observed, which leads to progressive blood pressure and heart rate decrease, increasing from stages 1 to 3 of NREM [5]. During REM sleep, a further increase of parasympathetic tone with sympathetic depression occurs, but sympathetic activity increases intermittently.

The central autonomic network (CAN), through its upward and downward connections between the hypothalamic-limbic region and the medullary nucleus tractus solitarius (NTS), controls the sympathetic and parasympathetic divisions of the autonomic nervous system. NREM-REM sleep cycles are controlled by sleep-promoting neurons, scattered nearby the CAN and its connections, along with cholinergic REM-on and catecholaminergic REM-off cells in the ponto-mesencephalic junction and pons [6].

During NREM sleep, the previously mentioned changes in autonomic activity lead to heart rate slowing and consequently to a reduction in cardiac output and blood pressure. REM sleep is considered a vagotonic stage in which superimposed bursts of sympathetic nerve activity occur; the hemodynamic changes in this phase result in blood pressure, heart rate, and eventually oxygen saturation instability [1, 2]. This may explain the increasing mortality observed during the early morning hours, in which REM activity prevails. Cardiovascular diseases, such as myocardial ischemia, acute myocardial infarct, and supraventricular and ventricular arrhythmias, actually show a higher incidence in the morning and during daytime [7].

The increased parasympathetic activity during sleep may also have negative consequences on the cardiac function: marked sinus arrhythmia, conduction disturbances (first- and second-degree atrioventricular block), and sinus pauses have been reported to occur in healthy people during sleep, especially REM sleep [8].

The interconnection between sleep and cardiovascular function is even more noteworthy in case of many sleep disorders, in which sleep architecture disruption results in sleep fragmentation and increased sympathetic activity, leading to blood pressure surge, systolic and/or diastolic non-dipping tendency, and cardiovascular consequences.

Role of Peripheral Receptors in Cardiovascular Autonomic Control

Along with the CAN, medullary reflexes, triggered by activations of baroreceptors, chemoreceptors, and cardiac receptors, control sympathetic and parasympathetic activity [9].

Baroreceptors are mechanoreceptors located in the carotid sinuses and aortic arch, responding to stretches determined by modifications in arterial blood pressure; through IX and X cranial nerves (glossopharyngeal and vagus nerves), they provide inputs directed to the nucleus of solitary tract (NTS) of the medulla oblongata. A blood pressure increase provides an excitatory input to the NTS, which inhibits the sympathetic response of the rostro-ventrolateral medulla and activates vagal neurons in nucleus ambiguus, resulting in peripheral resistance decrease and heart rate decrease.

Chemoreceptors in the carotid bodies and aortic arch respond to hypoxia with a vasoconstriction resulting in blood pressure increase, mediated by sympathetic system, and with heart rate decrease, mediated by vagal system.

Cardiac receptors are mechanically and chemically sensitive receptors located in atria ad ventricles, responsible for heart rate and intravascular volume regulation [10].

Baroreceptors and chemoreceptors are implicated in the cardiovascular consequences in sleep-related breathing disorders.

Sleep-Related Breathing Disorders

Sleep-related breathing disorders are grouped into obstructive sleep apnea disorders, central sleep apnea disorders, sleep-related hypoventilation disorders, and sleep-related hypoxemia disorders. Many subjects can be diagnosed with more than

one of these disorders. Cardiovascular alterations are strictly linked to sleep-related breathing disorders, particularly in the case of obstructive sleep apnea disorders and central sleep apnea disorders.

Obstructive Sleep Apnea (OSA)

OSA is characterized by increased pharyngeal collapsibility and upper airway obstructions during sleep [11], leading to complete cessation (apnea) or partial reduction of airflow (hypopnea). OSA syndrome (OSAS) results from an RDI (Respiratory Disturbance Index) >=5 plus daytime or nighttime symptoms or RDI >=15 during a polysomnography or monitoring. Excessive daytime sleepiness, fatigue, nycturia, and morning headache are the most reported symptoms; bed partners often report breathing cessations and loud and irregular snoring during sleep [12]. OSAS is considered a major public health issue, affecting 5–15% of general population with an increasing prevalence with aging [13, 14].

Pathophysiology of OSA and cardiovascular disease. Obstructive apneic events activate multiple mechanisms involved in initiation and progression of cardiac, vascular, and metabolic diseases: apnea or hypopnea, due to obstruction of the upper airways, cause hypoxemia and hypercapnia; intermittent hypoxia/reoxygenation amplifies the hypoxemic stress, leading to generation of reactive oxygen species (ROS) and inflammation [15]; sleep arousals due to apnea or hypopnea lead to sleep fragmentation and deprivation, which is associated with a broad of cardiovascular and metabolic diseases [16]; negative intrathoracic pressure induced by obstructed breathing stretches intrathoracic structures, including atria and large blood vessels [17]; and OSA patients have high levels of sympathetic activity, during both night and daytime.

Intermittent hypoxia causes an activation of chemoreceptors located in the carotid bodies, leading to sympathetic activation and consequent renin-angiotensin-aldosterone system activation which enhances vasoconstriction; reactive oxygen species increase causes reduction in nitric oxide (NO), leading to increased peripheral resistances [17]; and impaired baroreflex and increased endothelin may also promote an increase in blood pressure [18]. Vascular endothelial growth factor (VEGF), fibrinogen, C-reactive protein, and adhesion molecule expression are also triggered by intermittent hypoxia, leading to increased risk for atherosclerosis [17]. Increased sympathetic tone is responsible for impairment in plasma glucose and insulin homeostasis on OSAS [19], probably due to beta-cell death caused by oxidative stress [20]. Increased serum cholesterol and phospholipid levels [21] facilitate the progression of atherosclerosis. Figure 1 resumes the events caused by intermittent hypoxia and increased sympathetic tone in OSA patients.

OSA and cardiovascular rhythm. OSA and CSA with Cheyne-Stokes respiration (see below) are both associated with increased risk of cardiac arrhythmia, which may lead to sudden cardiac death and premature mortality. In the initial part of the apneic period, patients with OSA demonstrate either a normal or slowing heart rate, while blood pressure slowly rises from baseline; profound vagal activation can occur at the beginning of the apneic event (diving reflex), resulting in potentially serious bradyarrhythmias: sinus bradycardia, AV (atrioventricular) block and asystole have been observed in OSA patients [17]. C-PAP therapy has been reported to reduce arrhythmias [22].

OSA and cardiovascular disease. OSA is a clearly demonstrated independent risk factor for the development of arterial hypertension, heart failure, and stroke.

Sympathetic activation is thought to be the major responsible, as previously described, of increased hypertension risk. Both sleep apnea and hypertension are common conditions; about 60% of sleep apnea patients are hypertensive [23], and about 30% of hypertensive patients have sleep apnea [24]. Increased sympathetic activation, arterial hypertension, and intermittent hypoxia may promote diastolic heart failure [25 26, and 27]. It has been shown that C-PAP therapy could reverse the remodeling of the myocardial structure [26, 27].

Major cardiac events, restenosis of coronary vessels, and mortality are also associated with

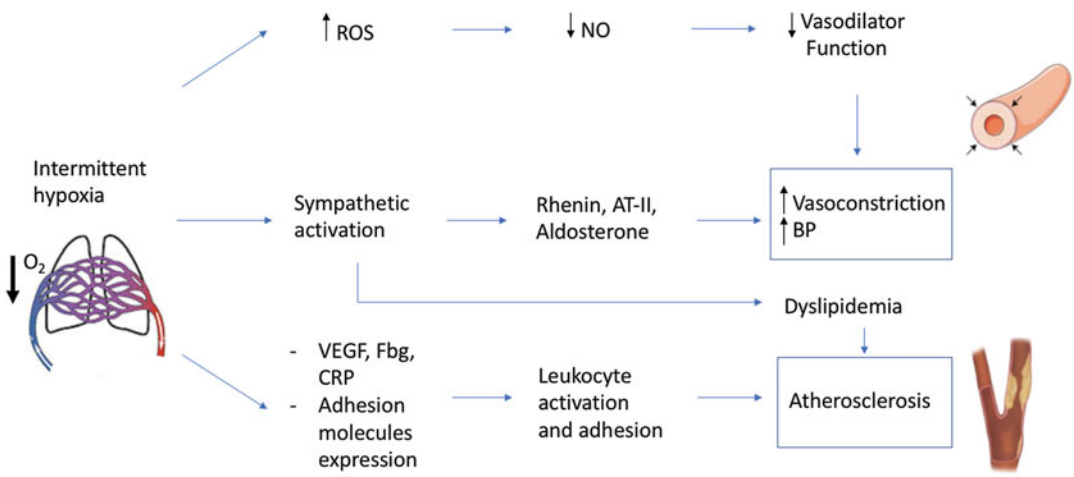

Fig. 1 Cascade induced by respiratory events in OSA. Figure modified from Refs. [17] and [18]. *ROS* reactive oxygen species, *NO* nitric oxide, *BP* blood pressure, *AT* angiotensin, *VEGF* vascular endothelial growth factor, *Fbg* fibrinogen, *CRP* C-reactive protein

sleep breathing disturbance. Mortality linked to OSA is primarily due to cardiovascular disease. Mortality rate in OSA patients has been proved to increase proportionally to AHI (apnea/hypopnea index) [12], while survival rates improve with C-PAP therapy [28].

Central Sleep Apnea (CSA)

CSA is characterized by recurrent cessations or reduction of airflow due to lack of drive to breathe during sleep [29]. Albeit it is a rare disorder in general population, CSA occurs frequently in many cardiovascular disorders, including heart failure, atrial fibrillation, and pulmonary hypertension [12].

CSA and congestive heart failure. A high prevalence of CSA has been described in patients with systolic heart failure, diastolic dysfunction, and asymptomatic systolic dysfunction. In congestive heart failure, CSA is frequently observed in a crescendo-decrescendo pattern known as Cheyne-Stokes breathing (CSB). In the pathogenesis of CSB, it should be kept in mind that chemoreceptor inputs in the medulla respond to changes in acid-base status, while peripheral chemoreceptors in the carotid bodies are sensitive to changes in PaO_2 and $PaCO_2$; central and peripheral chemoreceptor inputs integrated in the medulla modulate breath amplitude. Pulmonary stretch receptors, irritant receptors, and juxtacapillary (J) receptors act as other sensors in the lungs and circulation.

When a hyperventilation (disturbance) causes a reduction in $PaCO_2$, chemoreceptors will respond to this disturbance with a ventilatory drive reduction (response) with an interval that depends from the circulation delay. This response (hypoventilation) can be greater than the disturbance (hyperventilation) if the system is instable: the concept of loop of gain has been used to predict the occurrence of CSB and its resistance to treatment [30, 31]. Loop of gain is the magnitude of ventilatory response to a sinusoidal respiratory disturbance; if response>disturbance, loop gain is >1; thus feedback loop is unstable, and periodic oscillations in breathing occur.

If response<disturbance and then loop gain is <1, transient oscillations are attenuated.

Loop gain results from the following formula:

$$\text{Loop gain} = \text{G}\frac{\text{PaCO}_2}{\text{LungVolume}}\text{T}$$

where G is the chemosensitivity (change in ventilation in response to change in $PaCO_2$), Lung

Volume is the functional residual capacity, and T is the lung-chemoreceptor circulatory delay.

Congestive heart failure affects control of breathing by increasing chemosensitivity and the circulatory delay. An increased left atrial pressure is thought to modify chemosensitivity via stretch receptors in left atrium or pulmonary vein (direct pathway) and via juxtapulmonary J receptors activated by pulmonary edema (indirect pathway). Lower left ventricular ejection fraction causes a decreased cardiac output and thus an increased lung-to-chemoreceptor circulatory delay. Both factors enhance loop gain, i.e., the response to respiratory disturbance, leading to CSB development [32].

CSB treatment includes the following:

- Positive airway pressure (C-PAP), which could not resolve CSB especially in patients with highest loop gain.
- Bi-level PAP (Bi-PAP), which can improve CSB severity over C-PAP [33], and adaptive servo ventilation (ASV).
- Oxygen, which could reduce chemosensitivity and loop gain, resulting in resolution of CRB.
- Ventilatory stimulants (acetazolamide and theophylline) and lung volume manipulation through lateral positioning and bed elevation [32].
- Therapies for the chronic heart failure, including diuretics, beta blockers, cardiac resynchronization therapy, and heart transplantation: CSB could persist despite the most aggressive therapies, so further more specific treatments are needed.

CSA and atrial fibrillation. Atrial fibrillation patients with congestive heart failure show an increased prevalence of CSA [34]; conversely, the increased prevalence of atrial fibrillation among patients with CSA has been observed in the absence of other cardiac disease [35]. No clear etiopathogenetic mechanisms associating cause and effect between CSA and atrial fibrillation have been found. It has been hypothesized that severe CSA is associated with impaired cardiac autonomic control and consequently with generally increased arrhythmias risk [36].

Insomnia

Chronic insomnia is defined as (1) difficulty in falling asleep or in maintaining sleep or waking up earlier than desired; (2) impairment in sleep is associated with daytime impairment or distress; (3) the difficulty is present despite adequate opportunity and circumstance to sleep; and (4) sleep difficulty occurs at least three times per week and has been a problem for at least 3 months [37].

The prevalence of insomnia is about 33% in the general population according to insomnia symptoms, without application of restrictive criteria [38]; applying more stringent criteria, as the DSM-IV diagnostic criteria, current prevalence switches to approximately 6% [39].

Existing data show that insomnia, especially when accompanied by short sleep duration, is associated with increased risk of hypertension, coronary heart disease, recurrent acute coronary syndrome, and heart failure [40]. Insomnia has been estimated to be as high as 44% among cardiac patients [41, 42].

Pathophysiology of insomnia and cardiovascular disease. Insomnia is associated with increase in adrenocorticotropic hormone and cortisol secretion, suggesting a hypothalamic-pituitary axis (HPA) hyperactivity. This is thought to be due a conditioned hyperarousal state with increased sympathetic activity and increased hormones implicated in arousal and sleeplessness. Dysregulation of HPA axis has been associated with increased risk of cardiovascular disease, insulin resistance, diabetes, anxiety, and depression [40]. Furthermore, in short sleepers and insomnia patients, an autonomic dysregulation with sympathetic nervous system (SNS) hyperactivity [43] has been observed; this leads to increased heart rate and altered or blunted heart rate variability and, indirectly, to increased cardiovascular disease.

Insomnia and hypertension. Insomnia is found to be significantly associated with hypertension in short sleepers (<6 h) [44, 45]. Furthermore, while in normal conditions, blood pressure fluctuates and follows a circadian pattern with lower values at nighttime (dipping), patients

suffering from insomnia display a non-dipping tendency. In patients showing clinically significant symptoms of insomnia, sleep improvement may lead to better blood pressure control [46].

Putative mechanisms of the association between insomnia and hypertension include:

- Activation of autonomic nervous system, SNS and HPA hyperactivity, and proinflammatory conditions, which may lead to increased sodium retention and reabsorption (due to increased aldosterone release), volume overload, vasoconstriction, arterial stiffness, and vascular remodeling; SNS and systemic inflammation may also cause endothelial dysfunction. All these factors may cause hypertension.
- Circadian rhythm desynchronization, which is linked to pathological vascular remodeling, vascular stiffness, and endothelial dysfunction.
- Hyperarousal, enhancing autonomic nervous system dysregulation.

Insomnia and heart disease. Insomnia is associated with increased risk of coronary heart disease, recurrent acute coronary syndrome, and mortality [40], probably through mechanisms involving hypertension, diabetes, and obesity [47].

Due to the strong association between insomnia and diabetes, it has been hypothesized that chronic sleep deprivation may increase the risk of type II diabetes [48]. The underlying mechanisms are partially understood, and some data suggest a role of increased sympathetic tone, raised cortisol concentration, and decrease in cerebral glucose utilization, which may lead to insulin resistance [48]. A number of studies have found an association between insufficient sleep (but even longer sleep), obesity, and related dietary behaviors [49], but levels of evidence are insufficient to draw conclusive findings [50].

Insomnia is described in 23–73% of patients suffering from congestive heart failure. Despite insomnia could be a consequence of disease-related anxiety, depression, medications, and Cheyne-Stokes breathing [40], some studies reported insomnia to precede heart failure onset [51].

Sleep-Related Movement Disorders

Periodic Limb Movements Disorder (PLMD)

Periodic limb movements during sleep (PLMS) are repetitive and stereotyped limb movements occurring during sleep, determining clinical sleep disturbance or fatigue (PLMD) [37]. A correlation between blood pressure increases and periodic limb movements occurrence was shown independently of arousal. This correlation increases with age and the duration of illness, and repetitive nocturnal blood pressure fluctuations related to PLMs occurrence has been reported to be a prognostic factor for incident cardiovascular disease [52, 53]. It has been hypothesized that recurrent surges in blood pressure every night for many years may determine repeated mechanical stress inducing vascular remodeling; sheer stress, platelet activation, atherosclerosis, and potentially hypercoagulability may be induced by repetitive blood pressure oscillations. Other mechanisms, including inflammation, oxidative stress, sympathetic activation, metabolic dysregulation, HPA activation, sleep disturbance, and deprivation, are considered responsible for the association between PLMD and cardiovascular disease [53].

Restless Leg Syndrome (RLS)

RLS is defined as an urge to move legs due to unpleasant sensations in the legs, which worsens during periods of rest, occurs predominantly in the evening or in the night, and is relieved by movements [37]. It is a common neurological disorder frequently comorbid with pathologies known to have detrimental effect on cardiovascular system such as obesity, hypercholesterolemia, diabetes mellitus, OSA, and insomnia.

Many studies report an association between RLS and cardiovascular disease. The following characteristics of RLS may contribute to increased cardiovascular risk [54]:

- Sleep deprivation, which may induce neural and vascular dysregulation as previously discussed.

- Micro-arousals and sleep fragmentation, which lead to repeated increases of blood pressure and heart rate; this may trigger a non-dipping circadian pattern of blood pressure and could be the cause of increased risk for hypertension.
- Periodic limb movements of sleep (PLMs), which are associated with large increases in heart rate and blood pressure.
- Iron deficiency, which is recognized as a risk factor for cardiovascular disease.

Although RLS and cardiovascular disease show to be correlated, the extent and direction of this relationship have not yet been adequately clarified [55].

Parasomnias

REM Sleep Behavior Disorder (RBD)

REM sleep behavior disorder is defined as abnormal behaviors emerging during REM sleep, sleep-related vocalization, and/or complex motor behaviors, with polysomnographic evidence of REM sleep without atonia [37]. RBD may be idiopathic (iRBD) or associated with alpha-synucleinopathies (including Parkinson disease, Lewy body dementia, multiple system atrophy).

Spectral analysis of RR interval and respiration shows absent REM-related cardiac [56, 57] and respiratory responses in subjects with idiopathic RBD (iRBD) [58], suggesting an underlying autonomic dysfunction [59]. Reduction in heart rate variability has been proposed as a biomarker of autonomic dysfunction in RBD patients, irrespectively of the presence of PD diagnosis [57]. An association between iRBD with ischemic heart disease, not explained by cardiovascular risk factors, has been reported [60]. The autonomic dysfunction may be responsible for impaired cardiac function and heart disease in RBD patients, but further data are needed. Whether this autonomic dysfunction is a prodromal condition of phenoconversion to alfa-synucleinopathy is still controversial [9].

Narcolepsy

Narcolepsy type 1 (NT1) is a disorder characterized by excessive daytime sleepiness and signs of REM sleep dissociation, the most specific of which is cataplexy (i.e., sudden muscle weakness caused by emotions) [37]. In NT1, excessive sleepiness is combined with low or undetectable levels of hypocretin (orexin) in cerebrospinal fluid. Orexin is normally produced by neurons of the lateral and posterior hypothalamus; this neuropeptide plays an important role in arousal, feeding, homeostasis of energy, thermoregulation, and neuroendocrine control, through multiple connections between orexinergic neurons and areas involved in central autonomic control [61].

NT1 patients may show a nocturnal non-dipper blood pressure profile, potentially influencing cardiovascular risk; this may be due to increased sympathovagal balance, resulting from either sympathetic prevalence or parasympathetic withdrawal. Normal and decreased balances during sleep and wakefulness have also been reported in these patients [9].

Summary

Sleep is a complex and dynamic process which influences the cardiovascular function and is, in turn, influenced by it. Strong changes in autonomic nervous system activity occur physiologically during sleep, and sleep disorders may be associated with cardiovascular disease through the deterioration of cardiovascular autonomic control. Indeed, sympathetic burst occurring during REM sleep may explain the increase in mortality due to heart disease that is reported in the early morning hours. Sleep disorders lead from one hand to immediate effects on blood pressure and heart rate and from the other to long-term negative consequences. Sleep-related breathing disorders (OSA, CSA), chronic insomnia, sleep-related movement disorders (PLMSD, RLS), REM sleep behavior disorder, and narcolepsy type 1 have been reported to be associated with cardiovascular disease, although the mechanisms underlying this association are

only partially understood. Further studies exploring the 24-h sympathetic-parasympathetic modulation and its influence on cardiovascular parameters could help to understand these mechanisms.

Cross-References

- ▶ Consequences of Altered Cardiac Activity on Brain Activity
- ▶ Night, Darkness, Sleep, and Cardiovascular Activity
- ▶ Physiological Sleep and Cardiovascular Disease

References

1. Chokroverty S. Overview of sleep & sleep disorders. Indian J Med Res. 2010;131:126–40.
2. Wolk R, Gami A, Garcia-Touchard A, Somers V. Sleep and cardiovascular disease. Curr Probl Cardiol. 2005;30(12):625–62.
3. Michiaki N, Satoshi H, Kazuomi K. Sleep duration as a risk factor for cardiovascular disease – a review of the recent literature. Curr Cardiol Rev. 2010;6(1):54–61.
4. Furlan R, Guzzetti S, Crivellaro W, Dassi S, Tinelli M, Baselli G, Cerutti S, Lombadi F, Pagani M, Mallani A. Continuous 24-hour assessment of the neural regulation of systemic arterial pressure and RR variabilities in ambulant subjects. Circulation. 1990;81(2):537–47.
5. Coccagna G, Mantovani M, Brignani F, Manzini A, Lugaresi E. Laboratory note. Arterial pressure changes during spontaneous sleep in man. Electroencephalogr Clin Neurophysiol. 1971;31(3):277–81.
6. Cortelli P, Lombardi C. Chapter 29 sleep and autonomic nervous system dysfunction. Handb Clin Neurol. 2005;6:243–353.
7. Portaluppi F, Tiseo R, Smolensky M, Hermida R, Ayala D, Fabbian F. Circadian rhythms and cardiovascular health. Sleep Med Rev. 2012;16(2):151–66.
8. Guilleminault C, Pool P, Motta J, Gillis A. Sinus arrest during REM sleep in young adults. N Engl J Med. 1984;11(16):1006–10.
9. Calandra-Buonaura G, Provini F, Guaraldi P, Plazzi G, Cortelli P. Cardiovascular autonomic dysfunctions and sleep disorders. Sleep Med Rev. 2016;26:43–56.
10. Longhurst J. Cardiac receptors: their function in health and disease. Prog Cardiovasc Dis. 1984;27(3):201–22.
11. Malhotra A, White D. Obstructive sleep apnoea. Lancet. 2002;360(9328):237–45.
12. Chokroverty S, Ferini-Strambi L. Sleep and the heart. In: Oxford textbook of sleep disorders. Oxford: Oxford University Press; 2017.
13. Young T, Peppard P, Gottlieb D. Epidemiology of obstructive sleep apnea: a population health perspective. Am J Respir Crit Care Med. 2002; 165(9):1217–39.
14. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med. 1993;328(17):1230–5.
15. Ryan S, Taylor C, McNicholas W. Selective activation of inflammatory pathways by intermittent hypoxia in obstructive sleep apnea syndrome. Circulation. 2005;112(17):2660–7.
16. Levy P, Tamisier R, Arnaud C, Monneret D, Baguet J, Stanke-Labesque F, Dematteis M, Godin-Ribuot D, Ribuot C, Pepin J. Sleep deprivation, sleep apnea and cardiovascular diseases. Frontal Biosci (Elite Ed). 2012;4:2007–21.
17. Lévy P, Kohler M, McNicholas W, Barbé F, McEvoy R, Somers V, Lavie L, Pépin J. Obstructive sleep apnoea syndrome. Nat Rev Dis Primers. 2015;25(1):15015.
18. Foster G, Poulin M, Hanly P. Intermittent hypoxia and vascular function: implications for obstructive sleep apnoea. Exp Physiol. 2007;92(1):51–65.
19. Dewan N, Nieto F, Somers V. Intermittent hypoxemia and OSA: implications for comorbidities. Chest. 2015;147(1):266–74.
20. Xu J, Long Y, Gozal D, Epstein P. Beta-cell death and proliferation after intermittent hypoxia: role of oxidative stress. Free Radic Biol Med. 2009;46(6):783–90.
21. Drager L, Polotsky V. Lipid metabolism: a new frontier in sleep apnea research. Am J Respir Crit Care Med. 2011;184(3):288–90.
22. Koeler U, Reinke C, Sibal E. Autonomic dysfunction and cardiac arrhythmia in patients with obstructive and central sleep apnea. Dtsch Med Wochenschr. 2011;136(50):2622–8.
23. Silverberg D, Oksenberg A, Iaina A. Sleep-related breathing disorders as a major cause of essential hypertension: fact or fiction? Curr Opin Nephrol Hypertens. 1998;7(4):353–7.
24. Kales A, Bixier E, Cadieux R, et al. Sleep apnoea in a hypertensive population. Lancet. 1984;2(8410):1005–8.
25. Somers V, Javaheri S. Cardiovascular effects of sleep-related breathing disorders. In: Principles and practice of sleep medicine. 5th ed. Philadelphia: WB Saunders; 2011. p. 1370–80.
26. Arias M, Garcia-Rio F, Alonso-Fernandez A, et al. Obstructive sleep apnea syndrome affects left ventricular diastolic function: effects of nasal continuous positive airway pressure in men. Circulation. 2005;112(3):375–83.
27. Shivalkar B, Van de Heyning C, Kerremans M, et al. Obstructive sleep apnea syndrome: more insights on structural and functional cardiac alterations, and the effects of treatment with continuous positive airway pressure. J Am Coll Cardiol. 2006;47(7):1433–9.

28. Marin J, Carizzo S, Vincente E, et al. Long-term cardiovascular outcomes in men with obstructive sleep-apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. Lancet. 2005;365(9464):1046–53.
29. Eckert D, Jordan A, Merchia P, et al. Central sleep apnea: pathophysiology and treatment. Chest. 2007;131(2):595–607.
30. Francis D, Willson K, Davies L, et al. Quantitative general theory for periodic breathing in chronic heart failure and its clinical implications. Circulation. 2000;102(18):2214–21.
31. Sands S, Edwards B, Kee K. Loop gain as a means to predict a positive airway pressure suppression of Cheyne-Stokes respiration in patients with heart failure. Am J Respir Crit Care Med. 2011;184(9):1067–75.
32. Sands S, Owens R. Congestive heart failure and central sleep apnea. Crit Care Clin. 2015;31(3):473–95.
33. Köhnlein T, Welte T, Tan L, et al. Assisted ventilation for heart failure patients with Cheyne-Stokes respiration. Eur Respir J. 2002;20(4):934–41.
34. Ferrier K, Campbell A, Yee B, et al. Sleep-disordered breathing occurs frequently in stable outpatients with congestive heart failure. Chest. 2005;128(4):2116–22.
35. Leung R, Huber M, Rogge T. Association between atria fibrillation and central sleep apnea. Sleep. 2005;28(12):1543–6.
36. Lanfranchi P, Somers V, Braghiroli A. Central sleep apnea in left ventricular dysfunction: prevalence and implications for arrhythmic risk. Circulation. 2003;107(5):727–32.
37. American Academy of Sleep Medicine. International classification of sleep disorders. Darien: American Academy of Sleep Medicine; 2014.
38. Roth T. Insomnia: definition, prevalence, etiology and consequences. J Clin Sleep Med. 2007;3(5 Suppl):S7–S10.
39. Ohayon M. Prevalence of DSM-IV diagnostic criteria of insomnia: distinguishing insomnia related to mental disorders from sleep disorders. J Psychiatr Res. 1997;31(3):333–46.
40. Javaheri S, Redline S. Insomnia and risk of cardiovascular disease. Chest. 2017;152(2):435–44.
41. Bankier B, Januzzi J, Littman A. The high prevalence of multiple psychiatric disorders in stable outpatients with coronary heart disease. Psyhcosom Med. 2004;66:645–50.
42. Taylor D, Mallory L, Lichstein K, et al. Comorbidity of chronic insomnia with medical problems. Sleep. 2007;30:213–8.
43. Zhang J, Ma R, Kong A. Relationship of sleep quantity and quality with 24-hour urinary catecholamines and salivary awakening cortisol in healthy middle-aged adults. Sleep. 2011;34(2):225–33.
44. Fernandez-Mendoza J, Vgontzas A, Liao D. Insomnia with objective short sleep duration and incident hypertension: the Penn State cohort. Hypertension. 2012;60(4):929–35.
45. Vgontzas A, Liao D, Bixler E. Insomnia with objective short sleep duration is associated with a high risk for hypertension. Sleep. 2009;32(4):491–7.
46. Jarrin D, Alvaro P, Bouchard M, et al. Insomnia and hypertension: a systematic review. Sleep Med Rev. 2018;41:3–38.
47. Sands-Lincoln M, Loucks E, Lu B, et al. Sleep duration, insomnia, and coronary heart disease among postmenopausal women in the women's health initiative. J Women's Health (Larchmt). 2013;22(6):477–86.
48. Chaput J-P, Després J-P, Bouchard C. Sleep duration as a risk factor for the development of type 2 diabetes or impaired glucose tolerance: analyses of the Quebec Family Study. Sleep Med. 2009;10(8):919–24.
49. Coughlin J, Smith M. Sleep, obesity, and weight loss in adults: is there a rationale for providing sleep interventions in the treatment of obesity? Int Rev Psychiatry. 2014;26(2):177–88.
50. Crönlein T. Insomnia and obesity. Curr Opin Psychiatry. 2016;29(6):409–12.
51. Strand L, Laugsand L, Dalen H. Insomnia and left ventricular function – an echocardiography study. Scand Cardiovasc J. 2016;50(3):187–92.
52. Koo B, Blackwell T, Ancoli-Israel S, et al. Association of incident cardiovascular disease with periodic limb movements during sleep in older men: outcomes of sleep disorders in older men (MrOS) study. Circulation. 2001;124(11):1223–31.
53. Kendzerska T, Kamra M, Murray BJ, Boulos MI. Incident Cardiovascular Events and Death in Individuals With Restless Legs Syndrome or Periodic Limb Movements in Sleep: A Systematic Review. Sleep. 2017 Mar 1;40(3). https://doi.org/10.1093/sleep/zsx013.
54. Gottlieb D, Somers V, Punjabi N, et al. Restless legs syndrome and cardiovascular disease: a research roadmap. Sleep Med. 2017;31:10–7.
55. Cholley-Roulleau M, Chenini S, Béziat S, et al. Restless legs syndrome and cardiovascular diseases: a case-control study. PLoS One. 2017;12(4):e0176552.
56. Barone D, Ebben M, Samie A, et al. Autonomic dysfunction in isolated rapid eye movement sleep without atonia. Clin Neurophysiol. 2015;126(4):731–5.
57. Bugalho P, Mendonça M, Lempreia T, et al. Heart rate variability in Parkinson disease and idiopathic REM sleep behavior disorder. Clin Auton Res. 2018. https://doi.org/10.1007/s10286-018-0557-4.
58. Lanfranchi P, Fradette L, Gagnon J, et al. Cardiac autonomic regulation during sleep in idiopathic REM sleep behavior disorder. Sleep. 2007;30(8):1019–25.
59. Frauscher B, Nomura T, Duerr S, et al. Investigation of autonomic function in idiopathic REM sleep behavior disorder. J Neurol. 2012;259(6):1056–61.
60. Frauscher B, Jennum P, Ju Y, et al. Comorbidity and medication in REM sleep behavior disorder: a multicenter case-control study. Neurology. 2014;82(12):1076–9.
61. Grimaldi D, Silvani A, Benarroch E, Cortelli P. Orexin/hypocretin system and autonomic control: new insights and clinical correlations. Neurology. 2014;82(3):271–8.

Night, Darkness, Sleep, and Cardiovascular Activity

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*,
https://doi.org/10.1007/978-3-030-28008-6_38

Abstract

We humans tend to spend a significant fraction of the night asleep in the dark and to stay awake with daylight. However, the widespread availability of electrical power is progressively imparting 24/7 activity schedules to our modern societies, in which artificial ambient light and illuminated screens of electronic devices allow people to stay awake at night for work or leisure, postponing sleep. Sleep disorders such as insomnia and sleep-disordered breathing may reduce the quantity and quality of nocturnal sleep and entail excessive daytime sleepiness as a consequence. Not only these environmental and behavioral factors but also a range of genetic, epigenetic, and age-dependent factors may cause the body to be regulated out of phase with the environment, mimicking in many respect conditions of jet lag associated with long-range flights. This chapter will discuss the effects of night/day, darkness/light, and sleep/wakefulness on cardiovascular activity considering firstly each factor on its own and secondly the interactions among the different factors. The chapter will focus on the control of arterial blood pressure and heart rate in human subjects. The chapter will also touch upon the hemodynamic consequences of the control of vascular resistance and blood volume, as well as upon the bidirectional translation between research on human subjects and model organisms such as mice, which are arguably the mammals of choice for mechanistic studies of functional genomics.

Keywords

Sleep · Darkness · Circadian rhythms · Arterial blood pressure · Heart rate

Introduction

This chapter aims at providing a self-contained update on the cardiovascular effects of night, darkness, sleep, and their opposites, namely, day, light, and wakefulness. We humans tend to spend a significant fraction of the night asleep in the dark and to stay awake with daylight. However, the widespread availability of electrical power is progressively imparting 24/7 activity schedules to our modern societies, in which artificial ambient light and illuminated screens of electronic devices allow people to stay awake at night for work or leisure, postponing sleep. Sleep disorders such as insomnia and sleep-disordered breathing may reduce the quantity and quality of nocturnal sleep and entail excessive daytime sleepiness as a consequence. Not only these environmental and behavioral factors but also a range of genetic, epigenetic, and age-dependent factors may cause the body to be regulated out of phase with the environment, mimicking in many respect conditions of jet lag associated with long-range flights.

From this perspective, this chapter will discuss the effects of night/day, darkness/light, and sleep/wakefulness on cardiovascular activity, considering firstly each factor on its own and secondly the interactions among the different factors. In addressing the control of cardiovascular activity, this chapter will focus on the control of arterial blood pressure (ABP) and heart rate (HR) in human subjects. Where relevant, however, the discussion will also touch upon the hemodynamic consequences of the control of vascular resistance and blood volume, as well as upon the bidirectional translation between research on human subjects and model organisms such as mice, which are arguably the mammals of choice for mechanistic studies of functional genomics.

Circadian Rhythms

Definition and Essential Terminology

A circadian rhythm may be broadly defined as a biological rhythm that satisfies three criteria [1]: (1) it is endogenous, potentially occurring (i.e., free-running) in the absence of periodic changes in the environment; (2) it is endowed with a temperature-compensated endogenous period (tau, τ) that ranges between 19 and 28 h; and (3) it is entrainable, being capable to acquire the period of suitable environmental changes (Zeitgeber,

"time givers" in German) while maintaining a constant difference between its own phase and the Zeitgeber phase. The individual cells within an organism are sensitive to endogenous Zeitgeber (Eigenzeitgeber) such as energy availability and glucocorticoid hormone levels. However, it is ambient light that represents the most important Zeitgeber for whole organisms such as humans and mice [2].

Entrainment to the light (photic) Zeitgeber converts the free-running period τ of circadian rhythms to the 24 h period of Earth's rotation. Entrainment is mainly obtained by causing a phase shift of the circadian rhythm, namely, a delay or advance of a given fraction of its period [3]. This process is akin to shifting the hands of an analog clock by a given angle either clockwise or counterclockwise. Phase shift is, appropriately, expressed in angular terms (most often in radians, where 2π radians correspond to the perigon, or 360°).

The Molecular Clockwork

The intrinsic ability of cells to keep track of time is achieved by a sophisticated molecular system known as the molecular clock, which is highly conserved among organisms ranging from yeast to mammals [4]. The 2017 Nobel Prize in Physiology or Medicine was awarded jointly to Jeffrey C. Hall, Michael Rosbash, and Michael W. Young for their discoveries of molecular mechanisms controlling the circadian rhythm using fruit flies (*Drosophila melanogaster*) as model organisms [5]. These mechanisms have since been translated to mammals including mice and humans.

At the core of the molecular clock is a delayed negative feedback circuit consisting of gene transcription, mRNA translation, intracellular transfer of protein products, and eventual degradation of these proteins. In mammals, this core circuit involves transcription of the *Period* (*Per1*, *Per2*, and *Per3*) and *Cryptochrome* (*Cry1* and *Cry2*) genes that are regulated by opposing sets of molecular signals: stimulated by heterodimers of the protein products BMAL1 and CLOCK and inhibited by complexes of the protein products PER and CRY themselves. The CRY1 protein stability depends on the cellular energy status through the activity of the 5' AMP-activated protein kinase. This represents a deep link between the circadian and the energy homeostatic machinery [4].

A number of additional molecular circuits interact with the core molecular clock circuit to tailor its period τ at approximately 24 h. In addition to acting as key players of the core molecular clockwork, the core clock genes act as transcription factors for a number of other genes. As a result, a substantial fraction of the ensemble of all cellular transcripts (the transcriptome) undergoes a circadian modulation [6], which affects circadian rhythms of protein abundance (the proteome) depending on factors such as mRNA and protein mean half-lives and rhythms of posttranscriptional regulation [7].

A Hierarchy of Molecular Clocks

The ubiquitous expression of the core molecular clockwork in different cells and tissues makes the body at risk of exposure to controversial time signals. This risk is limited by a hierarchical organization of cellular clocks, whereby a leading (master) ensemble of cellular clocks entrains all other cellular clocks.

This master body clock is a collective property of the neurons of the suprachiasmatic nucleus (SCN) of the hypothalamus [8]. Experimental damage to the SCN causes behavioral arhythmicity in mouse models [9]. A possible exception is represented by the so-called food-entrainable oscillator, which causes food-anticipatory activity in conditions of restricted feeding. However, the anatomical and molecular mechanisms of this oscillator have so far remained elusive [10]. The SCN is strategically located in proximity of the optic chiasm to receive information on the photic Zeitgeber from the retina [11]. When dispersed artificially in culture, each individual SCN neuron expresses the working molecular clockwork described in the previous section, but the rhythms of individual neurons are out of phase with each other [12]. In the intact SCN, the individual molecular rhythms at single neuron level translate into changes in electrical activity, and hence in synaptic activity.

Synaptic connections between SCN neurons, which use different neuropeptides as well as the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), synchronize the different cellular rhythms into a coherent output [8, 13]. The electrical activity of the SCN is higher during the subjective day even in the absence of light and is further increased when light is present [14].

The SCN broadcasts the master circadian signal to the other cells of the body by means of complex neurohumoral pathways, the first step of which consists of short synaptic projection to nearby hypothalamic structures [15]. A direct inhibitory projection from the SCN targets the paraventricular nucleus (PVN) of the hypothalamus, a master regulator of autonomic and endocrine control, and is critical for the circadian and photic control of melatonin release. In particular, the PVN is the starting point of a chain of excitatory synapses that target sequentially the sympathetic preganglionic neurons of the cervical spinal cord and the sympathetic ganglionic neurons of the superior cervical ganglion. The sympathetic postganglionic fibers eventually stimulate melatonin release by the pineal gland by releasing norepinephrine that binds to β_1 adrenergic receptors on pineal cells. Since, as previously discussed, SCN activity is increased by light, this synaptic arrangement causes light to effectively inhibit melatonin release by the pineal gland [16].

Other projections from the SCN reach the PVN indirectly, with synaptic connections in the dorsal and ventral paraventricular zone (SPZ) and in the dorsomedial nucleus of the hypothalamus (DMH). This hypothalamic circuitry is thought to mediate the different phase shifts between circadian rhythms and the photic Zeitgeber in diurnal species, such as human subjects, vs. nocturnal species such as laboratory mice. Projections from the SPZ and the DMH to the PVN are instrumental in mediating the circadian rhythm of glucocorticoid release and may play a role in autonomic control. Projections from the same structures to the medial preoptic area of the hypothalamus (MPO) are key in mediating the circadian rhythms in body temperature, and those to the ventrolateral preoptic nucleus (VLPO) of the hypothalamus and the lateral hypothalamic area (LHA) are important in the control of sleep and wakefulness [15].

The Eigenzeitgeber through which the SCN entrains the different peripheral clocks are still incompletely clarified. While in-vitro evidence points to a key role of norepinephrine and glucocorticoid hormones, in-vivo evidence is less clear and suggests differences among different cells and tissues [2, 17, 18]. Feeding-related cues are particularly relevant to entrain the liver circadian transcriptome [19] and may compete with SCN-driven sympathetic control to entrain oscillators in other cells [20].

Circadian and Non-circadian (Masking) Effects of Light

Light entrains the master SCN clock via a dedicated retino-hypothalamic tract. This tract originates from a subset of retinal ganglion cells which express their own photopigment, called melanopsin, in addition to receiving information from rods and cones. Melanopsin is particularly sensitive to visible light in the blue-cyan range, with period length of about 480 nm [11]. Retinohypothalamic tract terminals synapse on SCN neurons and release glutamate, an excitatory neurotransmitter, and a neuropeptide (pituitary adenylate cyclase-activating polypeptide, PACAP), which raises intracellular levels of the second messenger cyclic adenosine monophosphate (cAMP). In turn, cAMP increases the activity of protein kinase A, which ultimately leads to upregulation of *Per* genes in SCN neurons [13, 16]. These effects are counteracted by melatonin, whose binding to its MT1 and MT2 receptors on SCN neurons decreases cellular cAMP levels [16]. Melatonin is therefore a darkness signal that reinforces the entrainment of the SCN clock to the photic Zeitgeber by antagonizing the effects of light on SCN neurons. Accordingly, melatonin may be used in combination with light therapy to correct pathological phase shifts of the SCN pacemaker that cause the delayed or advanced sleep phase syndrome, and to keep the SCN rhythm entrained to

the photic Zeitgeber in totally blind people, in whom intrinsically photosensitive retinal ganglion cells are dysfunctional [21].

Light sensed by the retina elicits a range of biological effects in addition of entraining the SCN clock, which may alter ("mask") the circadian control of a range of body functions [22]. A clear-cut example of this masking is the suppression of melatonin synthesis by light that involves the SCN in parallel with the clock entrainment. The masking effects of light have been mostly studied on experimental models. In nocturnal rodents, light at night reduces activity levels, whereas dark pulses during the daytime may stimulate activity. Conversely, light can trigger activity in diurnal mammals [23]. The masking effects of light may show complex interactions with the output of the body clock. Thus, light decreases body temperature more at the end of the subjective night than in the middle and at the end of the subjective day in rats [24].

The Wake-Sleep States

Operative Definitions of the Wake-Sleep States and Stages

Sleep is a reversible state of motor disengagement from the external environment. As such, sleep in mammals such as humans and mice may be an evolutionary adaptation of the dormant states that occur in the simplest organisms such as yeast [25]. Sleep in mammals is a heterogeneous behavior, which is usually subdivided in two main states, named non-rapid eye movement (non-REM) sleep and rapid eye movement (REM) sleep. The operative definitions of these sleep states are based on the features of the electroencephalogram (EEG) and of the electromyogram (EMG) of the submentalis (genioglossus, hyoglossus, and digastricus) muscles in addition to patterns of eye movements recorded with the electrooculogram (EOG) [26, 27]. Wakefulness is scored when the EEG has low voltage and mixed frequencies, the EMG is relatively high and variable, and the EOG shows eye movements associated with behavioral activity. Non-REM sleep is scored when the EMG tone is lower than in wakefulness, the EEG shows typical sleep figures such as sleep spindles and K-complexes or high-amplitude low-frequency delta waves (0.5–4 Hz), and the EOG may indicate slow eye movements, particularly when falling asleep. In addition to the characteristic rapid movements, REM sleep physiologically entails muscle atonia, which spares the diaphragm and may be interrupted by short-lasting muscle twitches, and EEG signals of low amplitude and mixed frequency. In humans, non-REM sleep is further subdivided into stages termed 1 to 4 with the traditional scoring rules by Rechtschaffen and Kales (R&K) [27], and N1 to N3 with the new scoring rules issued by the American Academy of Sleep Medicine in 2007, which also refer to REM sleep as stage R sleep [26]. For the sake of consistency, reference to sleep stages in humans will be made employing these new scoring rules in the rest of this chapter.

In laboratory rodents such as mice and rats, recording the EOG is not a standard practice for sleep scoring, and the chin EMG is usually substituted by the EMG of postural neck muscles. While the rodent EEG during non-REM sleep may show sleep spindles, K complexes, and high-amplitude delta waves similar to those in humans, these features are not usually employed as the basis for non-REM sleep subdivision into stages. REM sleep in rats and mice is also accompanied by muscle atonia, but at variance with humans, the EEG shows a prominent synchronous rhythm in the theta (4–8 Hz) frequency range [28].

In humans in physiological conditions, sleep onset typically occurs in stage N1 sleep, which then gives way progressively to stages N2 and N3 sleep. A return to stage N2 sleep typically precedes transition to stage R sleep, which ends with another episode of stage N1–N2 sleep or with a brief awakening. These non-REM-REM sleep cycles follow each other during the night with a period of 90–120 min. The stage N3 sleep is most abundant in the first part of the night, whereas the stage R sleep is most abundant in the second part of the night. Overall, non-REM sleep accounts for approximately 80% and 90% of total sleep time in humans and mice, respectively, the remainder being represented by REM sleep [29].

At a short time scale of a few seconds, sleep entails a rich microstructure consisting of transient EEG, EMG, and respiratory changes such as arousals [30], limb movements [31], and apneas-hypopneas [32]. During non-REM sleep, these short-lived events often cluster constituting the so-called A phases of the cyclic alternating pattern (CAP) [33]. On the other hand, REM sleep may be subdivided in periods rich in EOG and EMG bursts (phasic REM sleep) and periods of relative quiescence (tonic REM sleep), although this distinction is not standard practice [29].

Circadian and Homeostatic Control of Sleep

Human subjects typically consolidate sleep into one single period during the night, with the possible exception of a daytime nap. Laboratory rodents instead show polyphasic sleep periods, with short sleep episodes of few minutes' duration that occur throughout the day and night. Nonetheless, nocturnal rodents also have greater sleep propensity during the daytime (light/rest period) than during the nighttime (dark/activity period) [34]. Both in humans and in rodent models, these day/night changes of sleep propensity reflect a strong circadian control of sleep, which, as previously mentioned, is mediated by the SCN through a hypothalamic circuitry that involves the VLPO and LHA [15]. Accordingly, experimental damage to the SCN in mice abolishes the circadian rhythms of wake-sleep states either under entrained or under free-running conditions [9].

The circadian rhythm affects both the timing and intensity of non-REM sleep depending on the amount of time previously spent in wakefulness or sleep, which is relevant to the so-called homeostatic control of sleep. This interaction has been framed into rigorously quantitative terms in the context of the two-process model, which was originally developed on rats and subsequently translated to other species, including mice and humans [35]. In this model, the drive to non-REM sleep is estimated based on the EEG slow-wave activity (SWA), a measure of spectral EEG power in the delta frequency range. In essence, the two-process model posits that spontaneous awakenings from non-REM sleep tend to occur when the drive to non-REM sleep, as quantified by the EEG SWA, falls below a lower threshold that is modulated by the circadian rhythm. During the course of the wakefulness bouts, the drive to non-REM sleep rises exponentially with time. If not precluded by volitional or environmental arousing factors, non-REM sleep then ensues when its drive crosses an upper threshold, which also varies with a circadian rhythm. The drive to non-REM sleep is progressively dissipated during the course of non-REM sleep episodes, as quantified by an exponential decrease of EEG SWA with time. When the drive to non-REM sleep falls below the lower circadian threshold mentioned previously, another awakening starts the cycle again. The circadian sleep propensity is physiologically lower in the subjective late afternoon, thus effectively counteracting the increasing sleep pressure due to the prolonged waking bout. Compared to that of non-REM sleep, the effectiveness of the homeostatic control of REM sleep time is greater in laboratory rodents [36] than in humans [37]. REM sleep timing is, nonetheless, subjected to a strong circadian control, with increasing propensity to REM sleep at the end of the subjective rest period [38].

Night, Darkness, Sleep, and the Central Autonomic Control of the Cardiovascular System

The control of the cardiovascular system is exerted at three different, hierarchically organized levels. The lowest level involves local, tissue-, and organ-specific mechanisms of regulation. These include the control of blood vessels by autoregulation and flow-metabolism coupling, the direct effects of partial pressures of O_2 and CO_2 on vascular resistance, and the effects on cardiac contractile force of cardiac fiber length (Starling's law of the heart), HR (Bowditch phenomenon), and cardiac afterload. These local mechanisms require neither hormones nor neurotransmitters.

The intermediate level of cardiovascular regulation consists of cardiovascular reflexes, which generally operate as negative feedback control circuits. These reflexes involve receptors, interneurons, and neurohumoral effector mechanisms such as sympathetic and parasympathetic postganglionic fibers, adrenaline, angiotensin II, and arginine vasopressin. The most powerful cardiovascular reflex for the control of ABP is the arterial baroreceptor reflex (baroreflex), which controls cardiac and vascular effectors in response to changes in the stretch of afferent fibers in the walls of the aortic arch and carotid sinuses [39]. The chemoreceptor reflex (chemoreflex) exerts important effects on the heart and blood vessels, although it is primarily involved in driving respiratory responses to changes in arterial pH and in O_2 and CO_2 partial pressures [40]. The exercise pressor reflex increases HR and vascular resistance in response to afferent signals from mechano- and chemoreceptors in skeletal muscles [41]. Overall, these reflexes interact with the local level of control of the heart and blood vessels, modulating it to a variable extent depending on the specific reflex and target tissue.

The top level of cardiovascular regulation consists of central autonomic commands, which are proactive autonomic drives exerted by the central nervous system in anticipation of an expected behavior, without the need for reflex cues. Central autonomic commands may modulate not only the local level of cardiovascular control, as autonomic reflexes also do, but also the cardiovascular reflexes. The study of central autonomic commands is not new, dating back at least to the end of the nineteenth century [42]. The concept has been traditionally applied to describe the cardiovascular changes during physical exercise that could not be explained by either local or reflex mechanisms [43–45] and has been expanded only recently to include mental stress and sleep [39, 46]. A further potential extension of the concept of central autonomic commands to the cardiovascular effects of circadian rhythms will be addressed in the section "Circadian Control of the Cardiovascular System Under Unmasking Conditions" of this chapter.

Day-Night Rhythms of Cardiovascular Variables

Day-Night Rhythm of ABP and HR

Description and Quantification

The occurrence of a measurable ABP decrease from daytime to nighttime has long been known, at least in real-life conditions, in which people mainly spend the night sleeping in the dark and the day waking with ambient light [47]. More recent studies performed on thousands of subjects employing automated ABP measurements have substantiated these early observations [48]. The nocturnal fall in systolic ABP averages more than 15 mm Hg, but the distribution of its values in different subjects is wide. This has led to the concept of classifying subjects based on the fall ("dip") in ABP from daytime to nighttime, normalized as a percentage of the average diurnal value of ABP. In particular, subjects have been classified as "inverse dippers" (ABP dip $<0\%$, with higher values of ABP during the night than during the day), non-dippers (ABP dip 0%–10%), normal dippers (ABP dip 10%–20%), and "extreme dippers" (ABP dip $>20\%$) [49]. The day-night rhythm of ABP has also been quantified by computing the "morning surge" of ABP, taking the difference between the average value of ABP in the 2 h after morning awakening and either the average ABP value in the 2 h before awakening or the lowest ABP values during nocturnal sleep [50, 51].

The day-night rhythm of ABP is associated with a rhythm of HR, which is lower during the night than during the day. The decrease in HR during the night compared to the day has also been quantified in terms of a dipping pattern, in analogy to what has been done for ABP [52]. HR variability (HRV) also shows a distinct day-night rhythm in humans in real-life conditions. Indexes of short-term HRV reflecting parasympathetic modulation are higher during the night than during the day, whereas the contribution of lower-frequency fluctuations to HRV varies in the opposing direction [53]. While these low-frequency fluctuations have long been considered as an index of the sympathetic modulation

of the heart, this is now highly contentious [54]. On the other hand, no clear-cut day-night rhythm in cardiac baroreflex sensitivity has so far been reported [55].

In analogy with results on human subjects, studies on nocturnal laboratory rodents such as mice and rats have also shown robust day-night rhythms of ABP and HR, with higher values during the dark (active) period than during the light (rest) period [56, 57].

Hemodynamic Mechanisms

The hemodynamic mechanisms of the different day-night rhythms ("dipping patterns") of ABP are still unclear. One view, based on indirect measurements made on healthy human subjects, is that the nocturnal decrease in ABP is caused by a decrease in cardiac output, which is incompletely compensated by an increase in peripheral vascular resistance [58]. This view is supported by data on monkeys [59], rats [60], and mice [61]. In monkeys, the nocturnal decrease in cardiac output has been attributed to a decrease in blood volume [62]. A possible explanation is that during sleep, water intake ceases in the face of continued water vapor loss and urine production, leading to negative water balance. It is unclear whether a similar mechanism may be at stake for nocturnal laboratory rodents, whose polyphasic sleep pattern would allow for water intake during the brief wake bouts that often interrupt their sleep. In line with this view, it has been suggested that a non-dipping pattern of ABP may ensue because of insufficient renal clearance of fluids and electrolytes, itself associated with an upregulation of renal sodium resorption [63, 64]. The mechanisms of the reported nocturnal increase in vascular resistance are also unclear, particularly in light of evidence that this increase is unaffected or even enhanced by blockade of α_1 and β_1 adrenergic receptors [59].

Contrasting the view that the nocturnal ABP decline is mainly due to a decrease in cardiac output, recent data on human subjects with untreated mild hypertension have found an overnight decrease in peripheral vascular resistance, whose extent was related to the amount of ABP dipping [65]. Accordingly, ABP non-dipping in hypertensive subjects has been associated to a non-dipping of the urinary catecholamine concentration and to heightened ABP responsiveness to α_1 adrenergic receptor agonists [66]. This would suggest that, at least in hypertensive subjects, the day-night rhythm of ABP is largely due to the sympathetic control of vascular resistance. Further studies, including on normotensive subjects, are needed to clarify the discrepancies between these findings and those that support a major role of changes in blood volume and cardiac output in the ABP dipping pattern.

Sleep-Related Control of the Cardiovascular System

Effects of the Wake-Sleep States on ABP and HR

Wakefulness entails variable cardiovascular changes, which closely depend on the specific ongoing behavior. For example, HR increases with the workload of physical exercise, whereas ABP remains relatively stable. Posture is also relevant to cardiovascular control, with increasing mean values of ABP and HR and increased ABP variability on passing from the lying to the sitting and the active standing positions, at least in healthy subjects [67]. In pathological conditions and particularly in the elderly, standing may instead be accompanied by orthostatic hypotension because of baroreflex dysfunction and of mismatches between cardiac output and vascular resistance [68]. The opposing condition is represented by supine hypertension, which may occur in patients with cardiovascular autonomic insufficiency [69]. Orthostatic hypotension and/or supine hypertension may contribute to inverse ABP dipping at least in a subset of patients [70, 71]. Meals may also entail postprandial hypotension, particularly in the elderly [72].

In human subjects and rodent models, non-REM sleep entails decreases in ABP and HR in terms of absolute values and of short-term variability compared to wakefulness, whereas REM sleep entails cardiovascular changes in the opposing direction. In human subjects, the decreases in ABP and HR

during non-REM sleep do not differ remarkably as a function of the sleep stage [73], start already before sleep onset during relaxed wakefulness with lights out [74, 75], and also occur during daytime naps [75–77].

At the microstructural level, arousals from non-REM sleep entail short-term increases in ABP and HR, whose magnitude is similar to that of the nocturnal average decrease in systolic ABP [30]. As a result, repeated sleep fragmentation by arousals may limit the ABP-lowering effect of non-REM sleep [78]. Milder increases in ABP and HR occur also with K-complexes, which may be considered as elements of an arousal continuum. The association of arousals with increases in ABP and HR may explain why increases in these variables have been found associated with the phase A of CAP [30]. Periodic leg movements during sleep entail substantial increases in ABP and HR, particularly if accompanied by micro-arousals [79, 80]. The changes in ABP and HR associated with these events are characteristically biphasic: ABP and HR start increasing almost simultaneously, but while ABP returns to baseline, HR shows a rebound decrease after the ABP peak [30]. A similar biphasic pattern of changes in ABP and HR has been uncovered in rodent models with analyses of coherent averaging time-locked to spontaneous increases ("surges") in ABP during non-REM sleep and REM sleep [81]. During REM sleep in rats, these spontaneous ABP surges occur together with phasic changes in central neural activity, which manifest with respiratory perturbations and an acceleration of the EEG theta rhythm [82].

The analysis of spontaneous cardiovascular fluctuations indicates that the wake-sleep states entail a distinct pattern of changes in cardiovascular coupling, with common features in species as diverse as human subjects, rats, mice, and sheep [46]. In particular, non-REM sleep entails a pattern of positive correlation between the values of heart period (i.e., the reciprocal of HR) and the previous values of ABP, which is consistent with baroreflex control. This pattern is much weakened or even reversed during quiet wakefulness in the lying position in human subjects, as well as during REM sleep in rats [83] and in mice at thermoneutrality [84]. This reversal has been attributed to central autonomic commands acting on the heart, an interpretation supported by a mathematical model of the cardiovascular system [85]. Interestingly, in humans, the pattern of tight baroreflex control of the heart that is characteristic of non-REM sleep reinstates during sitting and particularly during standing in wakefulness, in the face of a decrease in cardiac baroreflex sensitivity [67].

Apneas during sleep are associated with marked changes in ABP and HR. In particular, obstructive apneas entail a progressive decrease in HR, while ABP remains relatively stable [86]. Once apneas are resolved, an increase in ventilation ensues because of the chemoreflex drive and is often accompanied by an arousal [32]. This entails a sharp rise in HR and ABP, which may reach up to 200 mm Hg, before returning to baseline levels. Altogether, these changes abolish the ABP decrease that occurs physiologically during sleep [86]. The transient cardiovascular changes associated with central sleep apneas are less well studied but may also be significant, at least in children [87].

Autonomic and Hemodynamic Mechanisms of the Effects of Wake-Sleep States on ABP and HR

Non-REM sleep decreases the sympathetic nerve activity (SNA) to skeletal muscle blood vessels, kidneys, and skin compared to wakefulness [46]. The changes in skin SNA may be responsible for the characteristic pattern of peripheral (hands, feet) vasodilation during non-REM sleep, which reverses upon awakening [88]. On the other hand, compared to non-REM sleep, REM sleep was found to increase SNA to skeletal muscle blood vessels, at least when motor twitches do not occur [89], and to decrease the SNA to the splanchnic (intestinal) bed and to the kidneys [73].

Non-REM sleep has also been reported to decrease cardiac output compared to wakefulness, mainly due to the decrease in HR, itself attributed to an increase in cardiac parasympathetic (vagal) activity. Some evidence also indicates that cardiac output may increase during REM sleep compared

with non-REM sleep [73]. These findings ask the question of whether the changes in ABP associated with the wake-sleep states are mainly due to changes in cardiac output or in vascular resistance. A recent study on mice attempted to clarify the picture by performing sleep recordings during the administration of autonomic receptor blockers [90]. The changes in HR associated with the wake-sleep states were due to strikingly balanced contributions of the parasympathetic and sympathetic nervous systems: HR decreased during non-REM sleep compared to wakefulness because of both an increase in parasympathetic activity and a decrease in sympathetic activity, whereas the opposite held true during REM sleep compared with non-REM sleep. However, these changes in cardiac parasympathetic and sympathetic activities had negligible effects on the decrease in ABP during non-REM sleep compared with REM sleep, which was entirely attributed to a decrease in adrenergic activity mediated by vascular α_1 sympathetic receptors. The increase in ABP from non-REM sleep to REM sleep was instead attributed to an increase in sympathetic activity mediated by both α_1 and β_1 receptors. Overall, these results evidenced a critical role of the modulation of vascular resistance in the effects of sleep on ABP [90].

The changes in cardiac and vascular activity during sleep cannot be simply explained based on reflexes such as the arterial baroreflex [73]. Indeed, the concomitant decreases in ABP, HR, and muscle SNA during non-REM sleep in human subjects contrast with the operating logic of the arterial baroreflex, which would be expected to increase HR and muscle SNA in response to a drop in ABP [89]. Another critical piece of evidence is that on passing from non-REM sleep to REM sleep, rats show decreases in renal SNA and HR that precede an increase in ABP, and cannot therefore represent baroreflex responses [91]. On the other hand, studies on human subjects and animal models have revealed a marked resetting of the cardiac and vascular arms of the arterial baroreflex during the different wake-sleep states, whereas the gain or sensitivity of either arm does not change consistently [73].

The increases in ABP associated with arousals have been attributed to increases in vascular resistance in the face of decreases in stroke volume, although recordings of SNA bursts have led to conflicting results [92]. Similar mechanisms may underlie the increases in ABP and HR associated with leg movements during sleep [79]. Once again, the occurrence of concomitant increases in ABP and HR associated with arousals and leg movements cannot be explained only based on the arterial baroreflex, given that the expected baroreflex response to the increase in ABP should be a decrease in HR. As previously discussed, such a decrease in HR ensues only after the ABP peak and is preceded by an increase in HR. These considerations and their quantification with a mathematical model of the cardiovascular system [85] raise the hypothesis that the cardiovascular changes associated with the wake-sleep states, either tonic or phasic, are due to central autonomic commands that transiently modulate the baroreceptor reflex.

The cardiovascular changes associated with sleep apneas are even more complex, resulting from the interplay of physical hemodynamic and autonomic mechanisms [86]. In the course of an obstructive apnea, the chemoreflex causes bradycardia and increases SNA to vascular effectors. Negative intrathoracic pressure due to inspiratory strains against the closed upper airways may decrease the left ventricular stroke volume because of increased left ventricular afterload and decreased left ventricular preload. The end result is that HR slows down, while ABP increases little during the apnea. At the resumption of breathing, HR rises because the chemoreflex inhibition is counteracted by the neural drives associated with hyperventilation, with a possible contribution of the central autonomic command associated with arousal. SNA may also undergo a short-lasting increase associated with arousal but then drops abruptly, partly because of chemoreflex withdrawal. Nevertheless, due to the relatively long delay and time constant of the vascular response to changes in SNA, the increase in cardiac output upon resumption of breathing occurs while the systemic circulation is still constricted. This leads to a marked rise in ABP, which is buffered by the baroreflex, contributing to decrease SNA and to limit the HR rise.

Postulated Central Neural Mechanisms of the Cardiovascular Effects of the Wake-Sleep States

The neural mechanisms that may underlie the sleep-related cardiovascular changes are still largely uncharted. However, a set of testable hypotheses has been proposed based on the available neuroanatomical and neurophysiological evidence [46]. Increases in the activity of non-REM sleep-active neurons in the VLPO may target the median preoptic nucleus of the hypothalamus (MnPO). These projections may modulate the thermoregulatory pathways for heat generation and retention, which include the medullary raphe pallidus, so as to decrease SNA and cause peripheral vasodilation during non-REM sleep. The generalized decrease in SNA to different vascular effectors during non-REM sleep may instead be due to inhibitory projections from the VLPO to the hypothalamic PVN, a master switch of the autonomic and endocrine systems, to the pedunculopontine nucleus between the caudal midbrain and rostral pons, which is associated with the central locomotor region, and to the parabrachial nucleus of the pons, which may disinhibit the baroreflex by projecting to the medullary nucleus of the solitary tract (NTS). Conversely, transient increases in parabrachial nucleus activity may transiently inhibit the baroreflex at the onset of arousals during non-REM sleep. In turn, the NTS controls parasympathetic activity to the heart by projecting to the nucleus ambiguus of the medulla, and sympathetic activity by projecting to the caudal ventrolateral medulla, which then projects to the rostral ventrolateral medulla (RVLM) [93].

The increases in SNA to skeletal muscle and the heart during REM sleep may result from direct excitatory projections from the REM-active pontine sublaterodorsal nucleus to the RVLM, the pedunculopontine nucleus, and the parabrachial and NTS nuclei. The disparate changes in SNA to different vascular beds (i.e., increases in SNA to the skeletal muscle and heart and decreases in SNA to the splanchnic and renal vascular beds) may reflect changes in the activity of the medullary raphe obscurus and the ventrolateral and lateral regions of the midbrain periaqueductal gray, which include neurons that excite and others that inhibit SNA. The enhanced cardiovascular variability typical of REM sleep may result from the activity of the medial and inferior vestibular nuclei of the medulla, which receive sleep-related synaptic input from the hypothalamic VLPO, and may modulate the activity of the pedunculopontine tegmental nucleus, the pontine parabrachial nucleus, and the NTS [93].

Circadian Control of the Cardiovascular System Under Unmasking Conditions

The variety of cardiovascular changes associated with the wake-sleep states at different time scales indicates that the sleep states and the multifarious behaviors of wakefulness may powerfully mask the circadian control of the cardiovascular system. Specific unmasking protocols are thus necessary to evaluate the circadian cardiovascular control properly. One such protocol, called constant routine protocol, typically involves prolonged ($\geq$24 h) recordings in conditions of sleep deprivation, semi-recumbency, and scheduled isocaloric meals under dim light. A point of weakness of this protocol is that the prolonged sleep deprivation is a stressor and entails a progressive homeostatic increase in the sleep drive. To overcome these limitations, a different unmasking protocol has been developed consisting of a few weeks of exposure to an artificial light-dark cycle, with a period so different from the free-running period τ to make circadian entrainment impossible. Under these conditions of "forced desynchrony," the circadian clock is running free, whereas masking factors due to light, sleep, and activity occur at different phases of the circadian rhythm on different days. Final averaging of the results over several days can therefore even out the role of these masking factors [94]. The forced desynchrony protocol is more protected than the constant routine protocol from the stressful effects of prolonged sleep deprivation but is even more demanding in terms of logistics and costs.

The complications just described contribute to explain the paucity of studies of the circadian rhythms of ABP and HR under unmasking conditions. A recent study that employed both forced desynchrony and constant routine protocols in healthy human subjects provided robust evidence for the existence of circadian rhythms of ABP and HR [95]. A key finding was that the circadian rhythm of ABP is unrelated to that of HR in humans. In particular, the rhythm of HR was found to peak at the beginning of the subjective day, with a minimum at the end of the subjective night [95]. A previous study had shown that this circadian HR minimum in humans is approximately synchronized with the minima of metabolic heat production and core body temperature [96]. On the other hand, ABP was found to peak at the end of the subjective day, whereas the phase corresponding to its minimum value was less consistent [95]. A study performed on mice, which spontaneously enter into wakefulness and sleep bouts throughout the light and dark phases, confirmed the occurrence of a circadian rhythm of ABP during each wake-sleep state. This ABP rhythm peaked during the dark period, when the fraction of time that mice spend spontaneously awake is the highest [34]. These data on mice are in broad agreement with those on humans, given that, as discussed in section "Circadian and Homeostatic Control of Sleep," the circadian sleep drive is the least powerful at the end of the subjective activity period [35].

Another key finding on the circadian rhythm of ABP in humans was that the amplitude of this rhythm [95] was only a small fraction of the amplitude recorded in presence of masking by the wake-sleep states in real-life conditions [48]. Accordingly, the amplitude of the ABP circadian rhythm within each wake-sleep state in mice was significantly lower than that computed on all time bins irrespective of the wake-sleep state [34]. A different study on circadian mutant mice also concluded that the behavioral SCN effects on wake-sleep states are more significant than direct outputs in terms of the circadian control of ABP and HR [97]. Taken together, these pieces of evidence thus indicate that the day-night rhythm of ABP in real-life conditions mainly results from the masking effects of the day-night differences in wake-sleep time and the attendant cardiovascular changes, with a minor component for the circadian rhythm of ABP. In agreement with this conclusion, there is evidence that poor sleep quality may be responsible for a pattern of ABP and HR non-dipping, both in human subjects and in animal models [98–100].

The study that showed the existence of a circadian rhythm of ABP in each wake-sleep state was reported on C57Bl/6J mice, which are arguably the most widely studied mouse strain [34]. Intriguingly, these mice carry a spontaneous mutation that dramatically decreases melatonin production [101]. This would suggest that the melatonin rhythm is not key for the circadian rhythm of ABP, at least in mice. Nonetheless, melatonin has been found to exert distinct cardiovascular effects, including a decrease of nocturnal ABP [102–104]. However, the study of the effects of melatonin is complex because this hormone feeds back on the central SCN clock, and its receptors are expressed by a vast array of peripheral cells [16]. On the other hand, projections from the SCN to the hypothalamic PVN control separate populations of pre-sympathetic and pre-parasympathetic neurons [105]. The circadian rhythms of ABP and HR may thus result, in part, from central autonomic command issues directly by the SCN [106]. Another area of high interest for circadian cardiovascular control concerns the potential contribution of peripheral vascular clocks, particularly in the heart [107], blood vessels [108], and kidneys [109], to circadian cardiovascular changes. In particular, evidence is accruing that the cardiomyocyte clock is involved in multiple functions, such as the temporal partition of the metabolic fuel utilization by the heart [110]. The vascular clock may also be involved in altering the responsiveness of the blood vessels to the autonomic nervous system [111]. The kidney clock may cause circadian rhythms of electrolyte and water resorption [109], thus affecting blood volume and the ABP dipping pattern [112]. In summary, the limited direct effects of the circadian clocks on ABP and HR may be due to the effects of peripheral clocks in the heart, vessels, and kidneys entrained by the SCN, to direct autonomic effects of the SCN, and, potentially, to effects of melatonin.

Masking Effects of Light on the Cardiovascular System

As previously discussed, light exerts a masking effect on physical activity, which has been mainly studied on animal models [22, 94]. Evidence that light masks also the effects of the circadian clock on the cardiovascular system is scant and also limited to animals. In mice, light during the dark period was found to decrease HR, whereas bright light during the light period was found to increase HR. [113] These effects may be largely mediated by the SCN in response to information from the retino-hypothalamic tract [114]. Surprisingly, this information seems to originate from retinal rods and cones [113], at variance with the phase-shifting effects of light on the SCN, for which the intrinsically photosensitive retinal ganglion cells are critically involved [11]. Overall, light may thus affect the cardiovascular system by three mechanisms that involve the SCN: by eliciting direct autonomic effects [114], by masking the circadian rhythm of melatonin [16], and by phase-shifting the SCN circadian clock [115], with the ensuing sleep and wake changes. The sum of these effects may be particularly relevant due to the extreme environmental light pollution of industrialized countries and to the exposure to artificial domestic ambient light during the subjective night because of shift work or leisure [116, 117].

Conclusions: Sleep and Wakefulness as the Key Intermediate Mechanisms of Circadian Cardiovascular Control

This chapter has summarized evidence on the effects of the night/day, in terms of the corresponding circadian phases, darkness/light, and sleep/wakefulness pairs, on ABP and HR at descriptive and mechanistic (hemodynamic, autonomic, neurophysiological, molecular) levels. There is a wealth of evidence indicating that day-night rhythms of ABP and HR are ample and robust and occur in human subjects and in other species, such as rats and mice. These rhythms are mostly due to the powerful cardiovascular masking effects of the wake-sleep states. Direct circadian control of ABP and HR has been demonstrated convincingly but is relatively weak. Nevertheless, the circadian clock does exert a powerful control on the timing and intensity of sleep, interacting with sleep homeostasis. Thus, the first key take-home message of this chapter is that the wake-sleep states are a fundamental intermediate mechanism of circadian cardiovascular control. In this picture, light emerges as a powerful factor essentially due to its ability to act as a Zeitgeber and entrain the circadian clock. Direct, masking effects of light on the cardiovascular system cannot be excluded but are probably subtler. Local mechanisms associated with the intrinsic peripheral clocks of the heart, vessels, and kidneys may also be involved in the day-night rhythms of ABP and HR. Reflex mechanisms are at stake essentially because they can be modulated or reset as a function of behavior. This leads to postulate a prominent role for central autonomic commands at different time scales, from seconds (sleep-related changes in cardiovascular fluctuations, cardiovascular correlates of sleep microstructure) to minutes (tonic effects of the sleep states and of exercise, posture, and meals), all the way up to hours (day-night and circadian rhythms). At each of these time scales, the central commands would share the common feature of controlling the cardiovascular system, modulating cardiovascular reflexes, and anticipating changes in behavior. Reflexes such as the arterial baroreflex are often modelled as negative feedback control circuits, whose control action depends on the mismatch between the measured output and a reference signal that serves as a set point. The second key take-home message of this chapter is therefore that central autonomic commands associated with sleep and circadian rhythms may encode the reference signal of the arterial baroreflex at different time scales. Unravelling the complexities of the day-night changes in ABP and HR is of evident scientific interest. However, this endeavor is not without practical implications, as it may lead to better prevention of adverse cardiovascular events [126], which have a strong day-night rhythm [118, 119], and to reduction of the cardiovascular risk associated with high nocturnal values of ABP and

HR [52, 120, 121], circadian misalignment [122, 123], and shift work [124, 125].

Cross-References

- Physiological Sleep and Cardiovascular Disease
- Sleep Disorders and Cardiovascular Disease

References

1. Refinetti R. Circadian physiology. 2nd ed. Hoboken: CRC Press; 2005.
2. Roenneberg T, Merrow M. The circadian clock and human health. Curr Biol. 2016;26:R432–43. https://doi.org/10.1016/j.cub.2016.04.011.
3. Johnson CH, Elliott JA, Foster R. Entrainment of circadian programs. Chronobiol Int. 2003;20:741–74.
4. Eckel-Mahan K, Sassone-Corsi P. Metabolism and the circadian clock converge. Physiol Rev. 2013;93:107–35. https://doi.org/10.1152/physrev.00016.2012.
5. Callaway E, Ledford H. Medicine Nobel awarded for work on circadian clocks. Nature. 2017;550:18. https://doi.org/10.1038/nature.2017.22736.
6. Doherty CJ, Kay SA. Circadian control of global gene expression patterns. Ann Rev Genet. 2010;44:419–44. https://doi.org/10.1146/annurev-genet-102209-163432.
7. Luck S, Thurley K, Thaben PF, et al. Rhythmic degradation explains and unifies circadian transcriptome and proteome data. Cell Rep. 2014;9:741–51. https://doi.org/10.1016/j.celrep.2014.09.021.
8. Patton AP, Hastings MH. The suprachiasmatic nucleus. Curr Biol. 2018;28:R816–22. https://doi.org/10.1016/j.cub.2018.06.052.
9. Easton A, Meerlo P, Bergmann B, et al. The suprachiasmatic nucleus regulates sleep timing and amount in mice. Sleep. 2004;27:1307–18.
10. Pendergast JS, Yamazaki S. The mysterious food-entrainable oscillator: insights from mutant and engineered mouse models. J Biol Rhythm. 2018;33:458. https://doi.org/10.1177/0748730418789043.
11. Benarroch EE. The melanopsin system: Phototransduction, projections, functions, and clinical implications. Neurology. 2011;76:1422–7. https://doi.org/10.1212/WNL.0b013e31821671a5.
12. Welsh DK, Takahashi JS, Kay SA. Suprachiasmatic nucleus: cell autonomy and network properties. Annu Rev Physiol. 2010;72:551–77. https://doi.org/10.1146/annurev-physiol-021909-135919.
13. Hastings MH, Maywood ES, Brancaccio M. Generation of circadian rhythms in the suprachiasmatic nucleus. Nat Rev Neurosci. 2018;19:453–69. https://doi.org/10.1038/s41583-018-0026-z.
14. Deboer T, Vansteensel MJ, Detari L, et al. Sleep states alter activity of suprachiasmatic nucleus neurons. Nat Neurosci. 2003;6:1086–90. https://doi.org/10.1038/nn1122.
15. Saper CB, Scammell TE, Lu J. Hypothalamic regulation of sleep and circadian rhythms. Nature. 2005;437:1257–63. https://doi.org/10.1038/nature04284.
16. Benarroch EE. Suprachiasmatic nucleus and melatonin: reciprocal interactions and clinical correlations. Neurology. 2008;71:594–8. https://doi.org/10.1212/01.wnl.0000324283.57261.37.
17. Reilly DF, Curtis AM, Cheng Y, et al. Peripheral circadian clock rhythmicity is retained in the absence of adrenergic signaling. Arter Thromb Vasc Biol. 2008;28:121–6. https://doi.org/10.1161/atvbaha.107.152538.
18. Oster H, Challet E, Ott V, et al. The functional and clinical significance of the 24-hour rhythm of circulating glucocorticoids. Endocr Rev. 2017;38:3–45. https://doi.org/10.1210/er.2015-1080.
19. Mukherji A, Kobiita A, Chambon P. Shifting the feeding of mice to the rest phase creates metabolic alterations, which, on their own, shift the peripheral circadian clocks by 12 hours. Proc Natl Acad Sci U S A. 2015;112:E6683–90. https://doi.org/10.1073/pnas.1519735112.
20. Vujovic N, Davidson AJ, Menaker M. Sympathetic input modulates, but does not determine, phase of peripheral circadian oscillators. Am J Physiol Regul Integr Comp Physiol. 2008;295:R355–60. https://doi.org/10.1152/ajpregu.00498.2007.
21. Burgess HJ, Sharkey KM, Eastman CI. Bright light, dark and melatonin can promote circadian adaptation in night shift workers. Sleep Med Rev. 2002;6:407–20.
22. Mrosovsky N. Masking: history, definitions, and measurement. Chronobiol Int. 1999;16:415–29.
23. Redlin U. Neural basis and biological function of masking by light in mammals: suppression of melatonin and locomotor activity. Chronobiol Int. 2001;18:737–58.
24. Scheer FA, Pirovano C, Van Someren EJ, et al. Environmental light and suprachiasmatic nucleus interact in the regulation of body temperature. Neuroscience. 2005;132:465–77. https://doi.org/10.1016/j.neuroscience.2004.12.012.
25. Siegel JM. Sleep viewed as a state of adaptive inactivity. Nat Rev Neurosci. 2009;10:747–53. https://doi.org/10.1038/nrn2697.
26. American Academy of Sleep Medicine. The AASM manual for the scoring of sleep and associated events. v2.5.0. 2018.
27. Rechtschaffen A and Kales A. A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. Bethesda, Md: U. S. National Institute of Neurological Diseases and Blindness; 1968.
28. Bastianini S, Berteotti C, Gabrielli A, et al. SCOPRISM: a new algorithm for automatic sleep scoring in mice. J Neurosci Methods. 2014;235:277–84. https://doi.org/10.1016/j.jneumeth.2014.07.018.

29. Carskadon MA, Dement WC. Normal human sleep: an overview. In: Kryger MH, Roth T, Dement WC, editors. Principles and practice of sleep medicine. 5th ed. Amsterdam: Elsevier; 2011.
30. Silvani A, Calandra-Buonaura G, Benarroch EE, et al. Bidirectional interactions between the baroreceptor reflex and arousal: an update. Sleep Med. 2015;16:210–6. https://doi.org/10.1016/j.sleep.2014.10.011.
31. Ferri R, Rundo F, Silvani A, et al. Sequence analysis of leg movements during sleep with different intervals (<10, 10–90 and >90 s) in restless legs syndrome. J Sleep Res. 2017;26:436–43. https://doi.org/10.1111/jsr.12500.
32. White DP, Younes MK. Obstructive sleep apnea. Compr Physiol. 2012;2:2541–94. https://doi.org/10.1002/cphy.c110064.
33. Parrino L, Ferri R, Bruni O, et al. Cyclic alternating pattern (CAP): the marker of sleep instability. Sleep Med Rev. 2012;16:27–45. https://doi.org/10.1016/j.smrv.2011.02.003.
34. Bastianini S, Silvani A, Berteotti C, et al. Mice show circadian rhythms of blood pressure during each wake-sleep state. Chronobiol Int. 2012;29:82–6. https://doi.org/10.3109/07420528.2011.635231.
35. Daan S, Beersma DG, Borbely AA. Timing of human sleep: recovery process gated by a circadian pacemaker. Am J Physiol Regul Integr Comp Physiol. 1984;246:R161–83. https://doi.org/10.1152/ajpregu.1984.246.2.R161.
36. Amici R, Cerri M, Ocampo-Garces A, et al. Cold exposure and sleep in the rat: REM sleep homeostasis and body size. Sleep. 2008;31:708–15.
37. Endo T, Roth C, Landolt HP, et al. Selective REM sleep deprivation in humans: effects on sleep and sleep EEG. Am J Physiol Regul Integr Comp Physiol. 1998;274:R1186–94.
38. Wehr TA, Aeschbach D, Duncan WC Jr. Evidence for a biological dawn and dusk in the human circadian timing system. J Physiol. 2001;535:937–51.
39. Dampney RAL. Resetting of the baroreflex control of sympathetic vasomotor activity during natural behaviors: description and conceptual model of central mechanisms. Front Neurosci. 2017;11:461. https://doi.org/10.3389/fnins.2017.00461.
40. Kara T, Narkiewicz K, Somers VK. Chemoreflexes–physiology and clinical implications. Acta Physiol Scand. 2003;177:377–84. https://doi.org/10.1046/j.1365-201X.2003.01083.x.
41. Murphy MN, Mizuno M, Mitchell JH, et al. Cardiovascular regulation by skeletal muscle reflexes in health and disease. Am J Physiol Heart Circ Physiol. 2011;301:H1191–204. https://doi.org/10.1152/ajpheart.00208.2011.
42. Johansson JE. Ueber die Einwirkung der Muskelthaetigkeit auf die Ahtmung und die Herzthaetigkeit. Skandinavische Archiv fuer Physiologie. 1895;5:20–66.
43. Gandevia SC, Hobbs SF. Cardiovascular responses to static exercise in man: central and reflex contributions. J Physiol. 1990;430:105–17.
44. Goodwin GM, McCloskey DI, Mitchell JH. Cardiovascular and respiratory responses to changes in central command during isometric exercise at constant muscle tension. J Physiol. 1972;226:173–90.
45. Krogh A, Lindhard J. The regulation of respiration and circulation during the initial stages of muscular work. J Physiol. 1913;47:112–36.
46. Silvani A, Dampney RA. Central control of cardiovascular function during sleep. Am J Physiol Heart Circ Physiol. 2013;305:H1683–92. https://doi.org/10.1152/ajpheart.00554.2013.
47. Brush CE, Fayerweather R. Observations on the changes in blood pressure during normal sleep. Am J Phys. 1901;5:199–210.
48. Staessen JA, Bieniaszewski L, O'Brien E, et al. Nocturnal blood pressure fall on ambulatory monitoring in a large international database. The "Ad Hoc" Working Group. Hypertension. 1997;29:30–9.
49. Hermida RC, Smolensky MH, Ayala DE, et al. 2013 ambulatory blood pressure monitoring recommendations for the diagnosis of adult hypertension, assessment of cardiovascular and other hypertension-associated risk, and attainment of therapeutic goals. Chronobiol Int. 2013;30:355–410. https://doi.org/10.3109/07420528.2013.750490.
50. Bilo G, Grillo A, Guida V, et al. Morning blood pressure surge: pathophysiology, clinical relevance and therapeutic aspects. Integr Blood Press Control. 2018;11:47–56. https://doi.org/10.2147/ibpc.s130277.
51. Fujiwara T, Tomitani N, Sato K, et al. The relationship between a blunted morning surge and a reversed nocturnal blood pressure dipping or "riser" pattern. J Clin Hypertens. 2017;19:1108–14. https://doi.org/10.1111/jch.13087.
52. Cuspidi C, Facchetti R, Bombelli M, et al. Night--time heart rate nondipping: clinical and prognostic significance in the general population. J Hypertens. 2018;36:1311–7. https://doi.org/10.1097/hjh.0000000000001703.
53. Van de Borne P, Nguyen H, Biston P, et al. Effects of wake and sleep stages on the 24-h autonomic control of blood pressure and heart rate in recumbent men. Am J Physiol Heart Circ Physiol. 1994;266:H548–54. https://doi.org/10.1152/ajpheart.1994.266.2.H548.
54. Martelli D, Silvani A, McAllen RM, et al. The low frequency power of heart rate variability is neither a measure of cardiac sympathetic tone nor of baroreflex sensitivity. Am J Physiol Heart Circ Physiol. 2014;307:H1005–12. https://doi.org/10.1152/ajpheart.00361.2014.
55. Kasting GA, Eckberg DL, Fritsch JM, et al. Continuous resetting of the human carotid baroreceptor-cardiac reflex. Am J Physiol Regul Integr Comp Physiol. 1987;252:R732–6. https://doi.org/10.1152/ajpregu.1987.252.4.R732.
56. Janssen BJ, Tyssen CM, Duindam H, et al. Suprachiasmatic lesions eliminate 24-h blood pressure variability in rats. Physiol Behav. 1994;55:307–11.
57. Li P, Sur SH, Mistlberger RE, et al. Circadian blood pressure and heart rate rhythms in mice. Am J Physiol Regul Integr Comp Physiol. 1999;276:R500–4.

58. Veerman DP, Imholz BP, Wieling W, et al. Circadian profile of systemic hemodynamics. Hypertension. 1995;26:55–9.
59. Talan MI, Engel BT. Effect of sympathetic blockade on diurnal variation of hemodynamic patterns. Am J Physiol Regul Integr Comp Physiol. 1989;256:R778–85.
60. Smith TL, Coleman TG, Stanek KA, et al. Hemodynamic monitoring for 24 h in unanesthetized rats. Am J Physiol Heart Circ Physiol. 1987;253:H1335–41. https://doi.org/10.1152/ajpheart.1987.253.6.H1335.
61. Kurtz TW, Lujan HL, DiCarlo SE. The 24 h pattern of arterial pressure in mice is determined mainly by heart rate-driven variation in cardiac output. Physiol Rep. 2014;2 https://doi.org/10.14814/phy2.12223.
62. Talan MI, Engel BT, Kawate R. Overnight increases in haematocrit: additional evidence for a nocturnal fall in plasma volume. Acta Physiol Scand. 1992;144:473–6. https://doi.org/10.1111/j.1748-1716.1992.tb09323.x.
63. Fukuda M, Uzu T, Kimura G. Duration until nighttime blood pressure fall indicates excess sodium retention. Chronobiol Int. 2012;29:1412–7. https://doi.org/10.3109/07420528.2012.728663.
64. Ivy JR, Oosthuyzen W, Peltz TS, et al. Glucocorticoids induce nondipping blood pressure by activating the thiazide-sensitive cotransporter. Hypertension. 2016;67:1029–37. https://doi.org/10.1161/hypertensionaha.115.06977.
65. Sherwood A, Hill LK, Blumenthal JA, et al. Circadian hemodynamics in men and women with high blood pressure: dipper vs. nondipper and racial differences. J Hypert. 2018;36:250–8. https://doi.org/10.1097/hjh.0000000000001533.
66. Sherwood A, Steffen PR, Blumenthal JA, et al. Nighttime blood pressure dipping: the role of the sympathetic nervous system. Am J Hypert. 2002;15:111–8.
67. Silvani A, Calandra-Buonaura G, Johnson BD, et al. Physiological mechanisms mediating the coupling between heart period and arterial pressure in response to postural changes in humans. Front Physiol. 2017;8:163. https://doi.org/10.3389/fphys.2017.00163.
68. van Wijnen VK, Finucane C, Harms MPM, et al. Noninvasive beat-to-beat finger arterial pressure monitoring during orthostasis: a comprehensive review of normal and abnormal responses at different ages. J Int Med. 2017;282:468–83. https://doi.org/10.1111/joim.12636.
69. Fanciulli A, Jordan J, Biaggioni I, et al. Consensus statement on the definition of neurogenic supine hypertension in cardiovascular autonomic failure by the American Autonomic Society (AAS) and the European Federation of Autonomic Societies (EFAS): endorsed by the European Academy of Neurology (EAN) and the European Society of Hypertension (ESH). Clin Auton Res. 2018;28:355. https://doi.org/10.1007/s10286-018-0529-8.
70. Milazzo V, Di Stefano C, Vallelonga F, et al. Reverse blood pressure dipping as marker of dysautonomia in Parkinson disease. Parkins Relat Disord. 2018;56:82. https://doi.org/10.1016/j.parkreldis.2018.06.032.
71. Voichanski S, Grossman C, Leibowitz A, et al. Orthostatic hypotension is associated with nocturnal change in systolic blood pressure. Am J Hypert. 2012;25:159–64. https://doi.org/10.1038/ajh.2011.191.
72. Trahair LG, Horowitz M, Jones KL. Postprandial hypotension: a systematic review. J Am Med Dir Assoc. 2014;15:394–409. https://doi.org/10.1016/j.jamda.2014.01.011.
73. Silvani A. Physiological sleep-dependent changes in arterial blood pressure: central autonomic commands and baroreflex control. Clin Exp Pharmacol Physiol. 2008;35:987–94. https://doi.org/10.1111/j.1440-1681.2008.04985.x.
74. Carrington MJ, Barbieri R, Colrain IM, et al. Changes in cardiovascular function during the sleep onset period in young adults. J Appl Physiol. 2005;98:468–76. https://doi.org/10.1152/japplphysiol.00702.2004.
75. Zaregarizi M, Edwards B, George K, et al. Acute changes in cardiovascular function during the onset period of daytime sleep: comparison to lying awake and standing. J Appl Pysiol. 2007;103:1332–8. https://doi.org/10.1152/japplphysiol.00474.2007.
76. Bursztyn M, Mekler J, Wachtel N, et al. Siesta and ambulatory blood pressure monitoring. Comparability of the afternoon nap and night sleep. Am J Hypert. 1994;7:217–21.
77. Cellini N, Whitehurst LN, McDevitt EA, et al. Heart rate variability during daytime naps in healthy adults: autonomic profile and short-term reliability. Psychophysiology. 2016;53:473–81. https://doi.org/10.1111/psyp.12595.
78. Carrington MJ, Trinder J. Blood pressure and heart rate during continuous experimental sleep fragmentation in healthy adults. Sleep. 2008;31:1701–12.
79. Pennestri MH, Montplaisir J, Colombo R, et al. Nocturnal blood pressure changes in patients with restless legs syndrome. Neurology. 2007;68:1213–8. https://doi.org/10.1212/01.wnl.0000259036.89411.52.
80. Ferri R, Rundo F, Silvani A, et al. Short-interval leg movements during sleep entail greater cardiac activation than periodic leg movements during sleep in restless legs syndrome patients. J Sleep Res. 2017;26:602–5. https://doi.org/10.1111/jsr.12529.
81. Silvani A, Bastianini S, Berteotti C, et al. Control of cardiovascular variability during undisturbed wake-sleep behavior in hypocretin-deficient mice. Am J Physiol Regul Integr Comp Physiol. 2012;302:R958–64. https://doi.org/10.1152/ajpregu.00668.2011.
82. Berteotti C, Franzini C, Lenzi P, et al. Surges of arterial pressure during REM sleep in spontaneously hypertensive rats. Sleep. 2008;31:111–7.
83. Berteotti C, Asti V, Ferrari V, et al. Central and baroreflex control of heart period during the wake-sleep cycle in spontaneously hypertensive rats. Am J Physiol Regul Integr Comp Physiol. 2007;293:R293–8. https://doi.org/10.1152/ajpregu.00086.2007.
84. Lo Martire V, Silvani A, Bastianini S, et al. Effects of ambient temperature on sleep and cardiovascular

regulation in mice: the role of hypocretin/orexin neurons. PLoS One. 2012;7:e47032. https://doi.org/10.1371/journal.pone.0047032.
85. Silvani A, Magosso E, Bastianini S, et al. Mathematical modeling of cardiovascular coupling: central autonomic commands and baroreflex control. Auton Neurosci. 2011;162:66–71. https://doi.org/10.1016/j.autneu.2011.04.003.
86. Somers VK, Dyken ME, Clary MP, et al. Sympathetic neural mechanisms in obstructive sleep apnea. J Clin Invest. 1995;96:1897–904. https://doi.org/10.1172/jci118235.
87. O'Driscoll DM, Foster AM, Ng ML, et al. Central apnoeas have significant effects on blood pressure and heart rate in children. J Sleep Res. 2009;18:415–21. https://doi.org/10.1111/j.1365-2869.2009.00766.x.
88. Silvani A. Orexins and the cardiovascular events of awakening. Temperature. 2017;4:128–40. https://doi.org/10.1080/23328940.2017.1295128.
89. Somers VK, Dyken ME, Mark AL, et al. Sympathetic-nerve activity during sleep in normal subjects. New Engl J Med. 1993;328:303–7. https://doi.org/10.1056/nejm199302043280502.
90. Lo Martire V, Silvani A, Alvente S, et al. Modulation of sympathetic vasoconstriction is critical for the effects of sleep on arterial pressure in mice. J Physiol. 2018;596:591–608. https://doi.org/10.1113/jp275353.
91. Miki K, Kato M, Kajii S. Relationship between renal sympathetic nerve activity and arterial pressure during REM sleep in rats. Am J Physiol Regul Integr Comp Physiol. 2003;284:R467–73. https://doi.org/10.1152/ajpregu.00045.2002.
92. Morgan BJ, Crabtree DC, Puleo DS, et al. Neurocirculatory consequences of abrupt change in sleep state in humans. J Appl Physiol. 1996;80:1627–36. https://doi.org/10.1152/jappl.1996.80.5.1627.
93. Silvani A, Calandra-Buonaura G, Dampney RA, et al. Brain-heart interactions: physiology and clinical implications. Philos Trans R Soc A. 2016;374:20150181. https://doi.org/10.1098/rsta.2015.0181.
94. Minors DS, Waterhouse JM. Masking in humans: the problem and some attempts to solve it. Chronobiol Int. 1989;6:29–53.
95. Shea SA, Hilton MF, Hu K, et al. Existence of an endogenous circadian blood pressure rhythm in humans that peaks in the evening. Circ Res. 2011;108:980–4. https://doi.org/10.1161/circresaha.110.233668.
96. Krauchi K, Wirz-Justice A. Circadian rhythm of heat production, heart rate, and skin and core temperature under unmasking conditions in men. Am J Physiol Regul Integr Comp Physiol. 1994;267:R819–29. https://doi.org/10.1152/ajpregu.1994.267.3.R819.
97. Sheward WJ, Naylor E, Knowles-Barley S, et al. Circadian control of mouse heart rate and blood pressure by the suprachiasmatic nuclei: behavioral effects are more significant than direct outputs. PLoS One. 2010;5:e9783. https://doi.org/10.1371/journal.pone.0009783.
98. Chen CW, Kuo TB, Chen CY, et al. Reduced capacity of autonomic and baroreflex control associated with sleep pattern in spontaneously hypertensive rats with a nondipping profile. J Hypertens. 2017;35:558–70. https://doi.org/10.1097/hjh.0000000000001205.
99. Lanfranchi PA, Pennestri MH, Fradette L, et al. Nighttime blood pressure in normotensive subjects with chronic insomnia: implications for cardiovascular risk. Sleep. 2009;32:760–6.
100. Sherwood A, Routledge FS, Wohlgemuth WK, et al. Blood pressure dipping: ethnicity, sleep quality, and sympathetic nervous system activity. Am J Hypertens. 2011;24:982–8. https://doi.org/10.1038/ajh.2011.87.
101. Kasahara T, Abe K, Mekada K, et al. Genetic variation of melatonin productivity in laboratory mice under domestication. Proc Natl Acad Sci U S A. 2010;107:6412–7. https://doi.org/10.1073/pnas.0914399107.
102. Baker J, Kimpinski K. Role of melatonin in blood pressure regulation: an adjunct anti-hypertensive agent. Clin Exp Pharmacol Physiol. 2018;45:755. https://doi.org/10.1111/1440-1681.12942.
103. Cagnacci A, Cannoletta M, Renzi A, et al. Prolonged melatonin administration decreases nocturnal blood pressure in women. Am J Hypertens. 2005;18:1614–8. https://doi.org/10.1016/j.amjhyper.2005.05.008.
104. Grossman E, Laudon M, Zisapel N. Effect of melatonin on nocturnal blood pressure: meta-analysis of randomized controlled trials. Vasc Health Risk Manag. 2011;7:577–84. https://doi.org/10.2147/vhrm.s24603.
105. Buijs RM, la Fleur SE, Wortel J, et al. The suprachiasmatic nucleus balances sympathetic and parasympathetic output to peripheral organs through separate preautonomic neurons. J Comp Neurol. 2003;464:36–48. https://doi.org/10.1002/cne.10765.
106. de Zambotti M, Trinder J, Silvani A, et al. Dynamic coupling between the central and autonomic nervous systems during sleep: a review. Neurosci Biobehav Rev. 2018;90:84–103. https://doi.org/10.1016/j.neubiorev.2018.03.027.
107. Beesley S, Noguchi T, Welsh DK. Cardiomyocyte circadian oscillations are cell-autonomous, amplified by beta-adrenergic signaling, and synchronized in cardiac ventricle tissue. PLoS One. 2016;11:e0159618. https://doi.org/10.1371/journal.pone.0159618.
108. Anea CB, Merloiu AM, Fulton DJR, et al. Immunohistochemistry of the circadian clock in mouse and human vascular tissues. Vessel Plus. 2018;2. https//doi.org/10.20517/2574-1209.2018.46
109. Solocinski K, Gumz ML. The circadian clock in the regulation of renal rhythms. J Biol Rhythm. 2015;30:470–86. https://doi.org/10.1177/0748730415610879.
110. Young ME. Temporal partitioning of cardiac metabolism by the cardiomyocyte circadian clock. Exp Physiol. 2016;101:1035–9. https://doi.org/10.1113/ep085779.
111. Xie Z, Su W, Liu S, et al. Smooth-muscle BMAL1 participates in blood pressure circadian rhythm regulation. J Clin Invest. 2015;125:324–36. https://doi.org/10.1172/jci76881.
112. Douma LG, Holzworth MR, Solocinski K, et al. Renal Na-handling defect associated with PER1-

dependent nondipping hypertension in male mice. Am J Physiol Renal Physiol. 2018;314:F1138–44. https://doi.org/10.1152/ajprenal.00546.2017.
113. Thompson S, Lupi D, Hankins MW, et al. The effects of rod and cone loss on the photic regulation of locomotor activity and heart rate. Eur J Neurosci. 2008;28:724–9. https://doi.org/10.1111/j.1460-9568.2008.06388.x.
114. Niijima A, Nagai K, Nagai N, et al. Effects of light stimulation on the activity of the autonomic nerves in anesthetized rats. Physiol Behav. 1993;54:555–61.
115. Khalsa SB, Jewett ME, Cajochen C, et al. A phase response curve to single bright light pulses in human subjects. J Physiol. 2003;549:945–52. https://doi.org/10.1113/jphysiol.2003.040477.
116. Mason IC, Boubekri M, Figueiro MG, et al. Circadian health and light: a report on the National Heart, Lung, and Blood Institute's workshop. J Biol Rhythm. 2018;33:451. https://doi.org/10.1177/0748730418789506.
117. Ohayon MM, Milesi C. Artificial outdoor nighttime lights associate with altered sleep behavior in the American general population. Sleep. 2016;39:1311–20. https://doi.org/10.5665/sleep.5860.
118. Kim HO, Kim JM, Woo JS, et al. Circadian distribution of acute myocardial infarction in different age groups. Am J Cardiol. 2018;121:1279–84. https://doi.org/10.1016/j.amjcard.2018.02.006.
119. Fabbian F, Bhatia S, De Giorgi A, et al. Circadian periodicity of ischemic heart disease: a systematic review of the literature. Heart Fail Clin. 2017;13:673–80. https://doi.org/10.1016/j.hfc.2017.05.003.
120. Salles GF, Reboldi G, Fagard RH, et al. Prognostic effect of the nocturnal blood pressure fall in hypertensive patients: the ambulatory blood pressure collaboration in patients with hypertension (ABC-H) meta-analysis. Hypertension. 2016;67:693–700. https://doi.org/10.1161/hypertensionaha.115.06981.
121. Willich SN, Levy D, Rocco MB, et al. Circadian variation in the incidence of sudden cardiac death in the framingham heart study population. Am J Cardiol. 1987;60:801–6.
122. Grimaldi D, Carter JR, Van Cauter E, et al. Adverse impact of sleep restriction and circadian misalignment on autonomic function in healthy young adults. Hypertension. 2016;68:243–50. https://doi.org/10.1161/hypertensionaha.115.06847.
123. Morris CJ, Purvis TE, Hu K, et al. Circadian misalignment increases cardiovascular disease risk factors in humans. Proc Natl Acad Sci U S A. 2016;113:E1402–11. https://doi.org/10.1073/pnas.1516953113.
124. James SM, Honn KA, Gaddameedhi S, et al. Shift work: disrupted circadian rhythms and sleep-Implications for health and well-being. Curr Sleep Med Rep. 2017;3:104–12. https://doi.org/10.1007/s40675-017-0071-6.
125. Morris CJ, Purvis TE, Mistretta J, et al. Circadian misalignment increases C-reactive protein and blood pressure in chronic shift workers. J Biol Rhythm. 2017;32:154–64. https://doi.org/10.1177/0748730417697537.
126. Silvani A. Sleep disorders, nocturnal blood pressure, and cardiovascular risk: A translational perspective. Auton Neurosci. 2019;218:31–42.

Part VII

Pain and Heart

When the Heart Hurts

37

Pain Perception and Cardiovascular Control

Elena G. Bignami and Alberto Castella

Contents

Abstract

The relationship between the sensation of pain and cardiovascular system has been investigated only over the past decades, highlighting significant connections between various areas of our central nervous system and the heart, putting such organs at a very close distance.

The nociceptive pathways lead painful stimuli across the nervous system to specifically designated areas, involving the phenomena of transduction, transmission, perception, and modulation.

The autonomic response to pain is able to determine a series of systemic effects, and the cardiovascular system is primarily involved, through the rise in heart rate (HR), arterial

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*,
https://doi.org/10.1007/978-3-030-28008-6_39

blood pressure (BP), together with respiratory rate and muscle tension.

Acute postoperative pain is a good example of how powerful stimuli, if not properly treated, may seriously affect the whole organism, leading in the end to increased cardiac workload and potentially lethal imbalance between oxygen demand and supply. This becomes even more evident in case patients become chronically exposed to pain.

The positive impact of analgesia on cardiovascular control, finally, indicates that this heart-brain relationship is real and can be a therapeutic target in order to improve not only the patients' symptoms but also their cardiovascular health.

Keywords

Pain · Cardiovascular · Autonomic system · Nociception · Acute · Chronic · Takotsubo · Analgesia

Introduction

According to the International Association for the Study of Pain (IASP) [1], pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [2]. There are, however, a few characteristics that must be highlighted:

- Pain is always a subjective feeling: as such, it may exist without depending on the ability of each individual to express it verbally; however, there are specific neurophysiological pathways that have to be understood beyond the verbal communication, in order for physicians to target the symptom and treat it successfully. For example, a sedated and intubated patient is surely able to feel pain but has no means to directly transfer this information to the clinician; therefore, it is the clinician's task to collect all those indirect signs of pain (e.g., increased blood pressure, increased heart rate) that may guide the diagnosis.
- Pain is most often, but not always, due to tissue damage or any other biologic/organic/pathophysiologic causes; in those situations, where pain is reported in the absence of biologic tissue alterations, yet still regarded as a very unpleasant perception, it should be accepted as pain, even if it happens for psychological reasons.

A recent paper in 2016 proposed a revised definition [3]: "pain is a distressing experience associated with actual or potential tissue damage with sensory, emotional, cognitive and social components," in order to acknowledge that this human feeling has a substantial value through a wide range of nonverbal behaviors.

These aspects are crucial in the setting of Intensive Care Unit (ICU), especially considering the cardiac ICU, where considerable amounts of patients arrive immediately after major surgical interventions and have to be kept sedated and intubated for at least 12–24 h.

Nearly half of patients interviewed after ICU hospitalization report moderate to severe pain, at rest and during routinary procedures; pain in the ICU may have multiple etiologies that can be either related to the underlying illness, performed surgery, invasive procedures, incisions, penetrating tubes and catheters. Moreover, daily patient care procedures such as tracheal suctioning, turning, mobilization, and dressing changes are pain sources, often underappreciated by caregivers. Immobility may cause musculoskeletal stiffness and wasting or pressure ulcers. Mechanical ventilation, sleep deprivation, and delirium may further enhance physical and psychological discomfort, leading to an even higher perception of pain [4].

Pain assessment in the ICU is often suboptimal, with infrequent evaluations, poor documentation, and discrepancy in the evaluation methods; as a matter of fact, this symptom has huge interindividual variability in terms of intensity, threshold, and linearity between injury and severity.

To address these challenges, validated assessment tools exist to objectively quantify and qualify pain for critically ill patients. Self-reporting is the gold standard for pain assessment: The Numerical Rating Scale (NRS) permits patients

to rate pain on a numeric axis from 0 (absence of pain) to 10 (highest level of pain) [4].

Vital signs (blood pressure, heart rate, and respiratory rate) are widely used by clinicians for pain assessment, but they can increase, decrease, or remain stable due to physiologic conditions unrelated to pain. In circumstances where self-reporting is not possible, pain assessment tools that incorporate behaviors and physiologic variables can be used. Of those developed and validated for ICU use, the behavioral pain scale (BPS) and the critical-care pain observation tool (CPOT) have the strongest evidence for reliability and validity. Both scales can be used in patients with artificial airways. The BPS evaluates three behavioral domains: facial expression, movement of upper limbs, and compliance with ventilation in response to movement and painful stimuli. Each behavioral domain is rated from one (no response) to four (full response), with a composite score ranging from 3 to 12. The CPOT evaluates four behavioral domains: facial expressions, movements, muscle tension, and ventilator compliance. Each component is rated from 0 to 2 with a composite score ranging from 0 to 8. If patients do not have an artificial airway, the BPS and CPOT include a vocalization domain to be assessed [4].

Nociception

Although now conceived as a wider and more complex entity, involving also emotional and cognitive elements, the biologic pathways through which a painful sensation is evoked and transmitted across the human body have been extensively studied.

The whole process defining how pain becomes a conscious experience is called "nociception."

It involves specific peripheral receptors, i.e., "nociceptors," that respond to a harmful stimulus or to a stimulus that may become harmful, if prolonged, repeated, or administered at higher intensity.

They are usually divided into chemical, mechanical, and thermal and act by collecting the stimulation and subsequently sending it to the brain through the nervous system. In the central nervous system (CNS), the stimuli are interpreted and elaborated to eventually produce the definitive symptom. Nociception is based on four main phases: transduction, transmission, perception, and modulation.

Transduction is the phase where the stimulus (thermal, chemical, or mechanical) is transformed into electrical impulses, able to be conducted across the peripheral nervous system (PNS); in this phase, the noxious trigger activates the nociceptors, causing ion channels to open and promoting the generation of action potentials. The nociceptors are characterized by the phenomenon of amplification, i.e., enhancing pain transmission by releasing chemical substances able to further involve new nociceptors; for example, prostaglandins are able to sensitize nociceptors through direct peripheral interaction and are the main target of nonsteroidal anti-inflammatory drugs (NSAIDs). Other chemicals, such as endorphins and enkephalins, are endogenous pain inhibitors.

Transmission is the process of conduction of electrical impulses along peripheral nerve axons to the CNS. Through a complex sequence of synapses, involving a number of excitatory and inhibitory interneurons, nociceptive impulses that have reached the dorsal horn of the spinal cord can ascend to the CNS along two different spinothalamic tracts. The thalamus is the main relay station of sensory stimulation, but the ascending pathways also connect to hypothalamus, limbic system, and the reticular formation. Finally, the thalamus projects nerve fibers to the somatosensory cortex, together with other areas, in order to obtain an integrated response to nociception.

Perception is defined as "decoding"/interpretation of afferent input in the brain that gives to the individual specific sensory experience [5]. It involves the cerebral cortex, therefore it is the phase of conscious awareness of pain and its interpretation, according to a number of personal, emotional, cultural, and experience-related factors; this explains why pain perception and its threshold differ so much among individuals.

Modulation, finally, is the overall process by which all sensory stimuli can be enhanced or

decreased, through the action of supraspinal impulses coming from the pons, medulla, and midbrain.

There are neurotransmitters (e.g., endothelin, enkephalin) released by supraspinal areas that can inhibit pain transmission to the thalamus and the somatosensory cortex; equally, norepinephrine and serotonin are released by the dorsal horn of the spinal cord. Modulation is able to make individuals feel the same type of stimuli with different intensity; it is thus another reason for the variability of pain threshold among human beings [5].

Autonomic Response to Pain

There is copious evidence, both experimental and clinical, that nociception and the autonomic nervous system (ANS) are closely interconnected; this is believed to be crucial for survival or, at least, adaptation to the environment.

Across the whole CNS, a complex network involving spinal and trigeminal dorsal horns, brainstem, amygdala, hypothalamus, thalamus, and insular cortex facilitates transmission of neural impulses coming from somatic and visceral sensation getting subsequently integrated and modulating autonomic responses; in other words, any painful sensation is able to initiate involuntary motor, endocrine, cardiovascular, and emotional reactions in our body [6, 7].

For example, the midbrain periaqueductal gray matter (MPAG), in its lateral component, is able to initiate fight-or-flight responses characterized by sympathetic activation, causing tachycardia, hypertension, blood flow redistributions to face and lower limbs; this whole neural output originates from well-localized nociceptive inputs from spinal and trigeminal dorsal horns [7].

Concurrently, the ventrolateral MPAG, receiving poorly localized visceral inputs, is able to originate an opposite set of responses: bradycardia, hypotension, hyporeactivity.

It is common knowledge that sympathetic nervous system (SNS) and parasympathetic nervous system (PNS), the two main branches of ANS, generally determine opposite responses; however, with regard to cardiovascular activity, SNS and PNS may interact in a more complex and structured fashion; while PNS typically influences decreased heart rate variability (HRV) and increased heart rate, SNS is mainly responsible for increasing heart rate by reducing the interval between ventricle contractions [6].

As a matter of fact, there is consistent literature supporting the link between painful stimulation and ANS arousal, rising with increasing levels of stimulus intensity. The most common signs of ANS response to pain are changes in:

- Respiration rate (usually increased)
- Muscle tension (usually increased)
- HRV
- Peripheral vasoconstriction (usually increased)

Therefore, pain may substantially affect the cardiovascular system directly, by altering the pathways regulating heart rate, and by modulating the tone of peripheral blood vessels, which has an impact on blood pressure and, ultimately, on cardiac hemodynamic balances [6].

HRV, i.e., the physiological phenomenon of variation in the time interval between heartbeats, measured by the variation in the beat-to-beat interval, in particular, attempts to unravel the relative contributions of SNS and PNS activity, therefore representing an interesting measure of ANS reactivity to painful stimuli. According to Koenig et al., HRV may also be of interest as a biomarker for specific pain-related diseases or a potential outcome parameter to monitor pain relief after specific therapies [8].

Like many organs in the body, the heart has dual innervation. Although a wide range of physiologic factors determine HR, the ANS is the most significant. Chronotropic (i.e., the timing of heart cycles) control of the heart is achieved via the complex interaction of the SNS and PNS branches of the ANS. More importantly, PNS influences HR in an inhibitory fashion. The basic data for the calculation of all the measures of HRV are the sequence of time intervals between adjacent heartbeats, known as the interbeat interval (IBI). Relative increases in SNS activity are associated with HR increases, and relative increases in PNS

activity are associated with HR decreases. Since PNS changes occur in the scale of milliseconds rather than seconds, the PNS influences are the only ones capable of producing rapid changes in the beat-to-beat timing of the heart. Despite several methods to record the IBI sequence, electrocardiography (ECG) is the most prominent. Different software solutions are available for the analysis of prerecorded IBI sequences [8].

Although mean HR has some predictive power, particularly in predicting morbidity and mortality, HRV, rather than mean HR, has a number of experimental and theoretical advantages; it is a physiologically grounded, theoretically explicated, empirically supported, and computationally tractable measure of autonomic function. Because HR is a product of the complex interplay of the two divisions of the ANS – the SNS and the PNS – changes in mean HR are only partially illuminating. HRV, on the other hand, attempts to tease out the relative contributions of SNS and PNS activity and may therefore be more appropriate to investigate underlying autonomic reactions to nociceptive stimulation [8].

Operating Room: Acute Postoperative Pain and Its Effects on Cardiovascular System

The sensation of pain was selected throughout human evolution as a mechanism of protection; it notifies tissue injury or damage and stimulates an organism to act in order to heal them. This is the case for any spontaneously occurred lesion in the body, whether it is from a disease or accidental trauma.

Surgery provokes pain, but since tissue disruption is usually more significant, painful stimuli are more sustained. Generally, any response to postoperative pain is proportionate to the extension of the tissue trauma, though with variability among individuals.

Peripherally, an acute inflammatory response breaks out after surgery, involving the release of cytokines and other types of immunomediators, causing erythema, vasodilation, and enhanced vascular permeability with edema and activation of nociceptors (peripheral hypersensitivity). An analogous phenomenon occurs in the dorsal column of the spinal cord. Sustained peripheral nociceptive signals cause accumulation of neurotransmitters, which lower the nociceptive threshold and enlarge the sensitivity territory. This brings nociceptive sensitivity to its maximum level (central hypersensitivity).

Due to specific interneuronal connections in the spinal cord, a series of reflexes is generated, enhancing sympathetic activity, which is expressed through an increase in heart rate, stroke volume, and peripheral resistance.

Vasoconstriction applies to all peripheral vessels, including visceral districts; moreover, uncontrolled skeletal muscle activity may be observed.

As a result, cardiac workload is substantially augmented, with a consistent increase in oxygen demand; in such frail conditions, tachycardia favors shortened diastolic filling and decreased coronary artery perfusion. In those patients already affected by abnormal coronary arteries, this imbalance between oxygen supply and demand becomes potentially lethal, as it can trigger myocardial ischemia. Also, extreme sympathetic stimuli of vasoconstriction, triggered by severe acute pain, may even induce coronary vasospasm and induce acute coronary syndromes, from unstable angina up to acute myocardial infarction.

Hypercoagulability has been implicated in the genesis of angina and myocardial ischemia after major surgery. Analgesia has been associated with reduction of this hypercoagulability, presumably by prevention of activation of platelets or improved fibrinolysis; for example, it has been demonstrated that epidural analgesia is able to positively interfere with the postoperative impairment in fibrinolysis, which is commonly seen after lower extremity revascularization surgery. This, in the end, leads to a lower incidence of postoperative arterial thrombosis. The pathophysiological mechanism has been hypothesized as follows: since steroids are able to increase levels of plasminogen activator inhibitor-1 (PAI-1), and high levels of PAI-1 are associated with an increased risk of postoperative thrombotic

complications (due to a weaker plasminogen activation, thus weaker fibrinolysis), analgesia, by reducing cortisol and catecholamine production in response to surgical tissue stress, may therefore have a significant impact on postoperative hemostasis [9].

Peripherally, acute pain may reduce venous blood flow, causing stasis and deep venous thrombosis, of which the well-known cardiovascular complication, i.e., pulmonary embolism, represents another threat. Reduced renal and hepatic blood flow is observed and associated with organ failure, particularly in case of preexisting pathology.

Finally, severe acute pain has an impact on the neuroendocrine system, as well; the hypothalamic-pituitary-adrenal axis is activated and the adrenal glands may contribute to sympathetic tone enhancement through the release of catecholamines in the blood.

Both result in catecholamine secretion, catabolic hormone secretion, and increased oxygen demand.

In summary, severe acute pain may exacerbate the stress response increasing perioperative morbidity and mortality, especially in patients with cardiac disease [10–12].

Chronic Pain and Cardiovascular Disease

It is well known that many cardiac diseases usually cause pain: acute myocardial infarction or pericarditis are the most common examples.

However, there is still scarce knowledge about how, on the other hand, pain from other origins can specifically affect the cardiovascular (CV) system.

In fact, this happens by multiple mechanisms, up to a point for which sudden cardiac death may occur in chronic pain patients who experience a severe pain attack. One of the goals of pain therapy should be to address the patient's CV system and stabilize its homeostasis, and it particularly applies to elderly patients, who have either overt or covert cardiovascular disease or who may be at risk of developing it.

The consequences of pain may have deleterious effects both in the case of acute settings, such as after surgery, and during the course of a chronic disease, such as rheumatic syndromes; this setting is particularly dangerous, as the exposure of the patient's body to pain is long lasting and continuous, and its negative effects may cumulate over time.

Chronic pain is a potentially disabling condition affecting one in three people through impaired physical function and quality of life; its potential connection with CV disease has been demonstrated across a spectrum of chronic pain conditions including low back pain, pelvic pain, neuropathic pain, and fibromyalgia.

So far, a number of significant consequences of chronic pain on the human CV system have been characterized: the main ones are the effect on hemodynamics, on coronary artery disease (CAD), and the effect on lipidic metabolism.

Pain causes elevation of blood pressure and pulse rate by two basic mechanisms: the sympathetic nervous system is stimulated by electrical pain signals reaching the brain, as it occurs in acute pain, during flares, or breakthrough pain. The neuroanatomic brain changes that may occur with severe chronic pain appear to produce continuous sympathetic discharge.

Some chronic pain patients have persistent tachycardia, defined as a pulse rate over 100 beats per minute. The apparent cause is continuous sympathetic discharge from rearranged neuroanatomy which imbeds the memory of pain in its circuitry. Despite aggressive analgesic treatments (opioids), and adjuvants such as antidepressants or benzodiazepine, such symptom may not cease.

Painful stimuli can also cause significant release of epinephrine from the adrenal glands, mainly through a hypothalamic-pituitary-mediated signaling pathway. This not only increases cardiac inotropism and chronotropism but also enhances peripheral vascular tone, affecting cardiac afterload.

This explains why uncontrolled pain is hazardous in patients who have arteriosclerotic heart disease; sudden and dramatic vasoconstriction, affecting coronary arteries, may cause various degrees of acute coronary syndromes, that can even be lethal in patients suffering from

severe atherosclerotic burden or other forms of preexisting cardiopathy.

Finally, chronic pain states are known to raise serum lipids. Although the mechanism is not known, there is evidence of serum cortisol elevations during uncontrolled pain and elevated cortisol is known to elevate serum lipids and glycemia. Moreover, the majority of chronic pain patients eat a diet which is overloaded with carbohydrates and which might lead to obesity and elevated lipids.

The biological credibility of a model in which chronic pain predisposes to cardiovascular disease through sympathetic stress or inflammation would be strengthened by evidence of a dose-response relationship. In a recent systematic review and meta-analysis, the authors reported that all associations between chronic pain phenotypes and cardiovascular outcomes (cardiac disease, cerebrovascular disease, and cardiovascular mortality) appeared to be stronger (i.e., larger effect size); this represents mounting evidence that chronic stress or inflammation may provide a biologically plausible pathway from pain to cardiovascular disease [13, 14].

Neurogenic Stunned Myocardium and Takotsubo Syndrome

Acute stress-induced (takotsubo) cardiomyopathy has a dramatic clinical presentation, mimicking acute myocardial infarction (MI). The takotsubo syndrome is a fairly rare event, 1:36,000. The male/female ratio is about 1:3. It is more common in postmenopausal women, without significant cardiovascular risk factors. The main characteristic of this condition is the transient balloniform modification of the left ventricle, due to stimuli of neurogenic origin, due to physical or emotional stress. This deformation (clearly visible with echocardiography or magnetic resonance) makes the left ventricle assume the shape of a basket (tsubo) used by Japanese fishermen for octopus (tako) fishing. The syndrome presents with prolonged chest pain (angina), for an effort (50%) or at rest.

There is considerable variability in the ECG pattern at presentation, as it is for acute MI. The patients with takotsubo can present with a normal ECG, ST/T wave changes and ST-elevation, left bundle branch block (transient), and/or arrhythmias. Coronary angiography showed no significant stenosis. Laboratory tests (such as troponin) reveal an alteration of myocardial necrosis indices, but the values never reach high levels.

An important characteristic of takotsubo is the spontaneous recovery of the left ventricular ejection fraction, which returns to normal in all patients over a variable period of time (days to weeks) [15, 16].

Pain Therapy

Considering the significant connection between pain and the heart, it becomes crucial to analyze the effects of pain relief on cardiac homeostasis and hemodynamics.

We have seen that the heart is a major target of the adrenergic cascade of pain response, and it is easily affected in case of preexisting pathology.

Although any clinical scenarios would be suitable, particular interest is found in the setting of cardiac surgery, where the heart itself undergoes substantial stress and structural changes, becoming even more vulnerable to pain and its consequences.

In this setting, not only is the heart manipulated and traumatized but also the whole body goes through a massive release of proinflammatory mediators and adrenergic stimuli, triggered by a number of factors: sternotomy, thoracotomy, bone fracture and dislocation, artery dissection, tissue retraction, vein harvesting, and the need for numerous vascular catheters and thoracic drains, which usually have to be kept in place for several days.

Such clinical background represents a valid model of how pain relief may affect cardiac health.

Therapeutic Options

Postoperative pain (POP) after cardiac surgery is more intense within the first 2 days after surgery, and it is perceived stronger by younger

people, females, and patients who suffer from preoperative pain.

There are a number of therapeutic strategies to treat POP, but they may generally be divided into two main categories: systemic drugs and regional techniques.

Systemic Drugs

This category includes a series of pharmacological treatments that are usually administered intravenously; they spread through the whole body and have different targets, according to the type of molecule, and, consequently, a series of systemic side effects, due to the wide distribution of the drug.

Paracetamol is one of the most frequently used analgesic drugs; however, its mechanism of action is not totally understood. Paracetamol does not appear to inhibit the function of any cyclooxygenase (COX) enzyme outside the central nervous system, but it selectively inhibits COX activities in the brain, which may contribute to its ability to treat fever and pain [17].

Nonsteroidal anti-inflammatory drugs (NSAIDs) act as nonselective inhibitors of COX, inhibiting both the cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) isoenzymes. COX catalyzes the formation of prostaglandins and thromboxane from arachidonic acid. Prostaglandins act (among other things) as messenger molecules in the process of inflammation [18].

Opioids bind to specific receptors in the nervous system and other tissues. There are three principal types of opioid receptors, μ, κ, δ (mu, kappa, and delta), although up to 17 have been reported, and include the ε, ι, λ, and ζ (epsilon, iota, lambda, and zeta) receptors [19].

Regional Techniques of Analgesia

This category includes various techniques, usually through an invasive approach, that provide the administration of local anesthetics and/or opioids into predetermined areas; they allow selective targeting of confined anatomical sectors, thus a lower global dosage of drugs and their side effects. Compared to systemic drug administration, they require specific expertise, both for placement and for the following management.

Thoracic epidural analgesia (TEA) is the placement of a catheter in the epidural space, through which local anesthetics and opioids can be infused; according to the chosen vertebral space, different dermatomes may be involved.

Intrathecal morphine is the administration of low doses of morphine in the subarachnoid space; being morphine quite hydrophilic, it spreads across the cerebrospinal fluid, allowing a central and long-lasting (up to 24 h) analgesic effect.

*Local peripheral blocks (*e.g.*, parasternal, paravertebral, intrapleural)* provide the release of local anesthetics directly into the peripheral nerves or close to the surgical wound. They can be performed either as a single-injection procedure or as continuous drug infusion through a previously placed catheter.

The Impact of Analgesia on the Heart

Given the wide variety of pharmacological and technical options for analgesia, there is still no definitive consensus upon their impact on main cardiovascular outcomes.

This, at least, with regard to the setting of cardiac surgery.

Paracetamol seems effective at reducing pain, but it usually needs to be combined with another drug to obtain significant pharmacological synergy. NSAIDs have also been poorly studied so far, and their potential efficacy is counterbalanced by the widespread fear for the well-known side effects, among which bleeding, acute kidney injury, and increased risk for acute myocardial infarction (AMI) are worth reminding. Indeed, the link between NSAIDs and AMI represents a strong limitation to their use, but no definitive results are yet available; for example, it has been demonstrated that some molecules belonging to this class of drugs, such as ibuprofen, are not able to increase the risk of AMI significantly after cardiac surgery. In general, severe side effects

due to NSAIDs (and including AMI) do not seem to be significantly likely after cardiac surgery, but these results derive from a few small studies, and further data are necessary to confirm them. On the other hand, long-term use of NSAIDs, as it applies to the setting of chronic rheumatologic or immunologic diseases, is more clearly associated to severe cardiovascular complications, including hypertension, AMI, and atrial fibrillation; however, a potential confounding factor is the underlying chronic disease, which usually causes increased cardiovascular damage per se [20].

Opioids are traditionally used for analgesia in this surgical setting and are certainly better known for their respiratory side effects; however, recent evidence has come to attention about the potential link between opioids and the risk of coronary artery disease and cardiovascular death, again, in the setting of chronic diseases. Interesting hypotheses have been formulated to explain it: opioid receptors have been described in human myocardial cells and their chronic use or higher doses may increase ischemia and oxidative stress; remifentanil in rat myocardium demonstrated dose-dependent increased susceptibility to reperfusion injury. Chronic methadone and oxycodone use has been linked to prolongation of QT intervals and torsade's de pointes. Other studies have found increased inflammatory markers such as CRP and accelerated atherosclerosis in chronic opioid users. Methadone also increased platelet aggregation, decreasing protective effects of aspirin [21].

On the side of regional analgesia techniques, thoracic epidural analgesia (TEA) is the one showing the most promising results in terms of clinical benefits for the heart, being associated with a number of positive systemic effects besides the decrease of pain symptom itself. Various studies showed that TEA may improve respiratory and metabolic function, through the reduction of pulmonary atelectasis and through a better postoperative metabolic management with a lower degree of "stress hyperglycemia," respectively. Pulmonary and metabolic functions are directly connected to cardiovascular homeostasis and any positive impact on them may reflect on cardiac improvement as well.

However, TEA may also have specific and direct positive effects on cardiac performance, as it has been associated to increased stroke volume index and increased central venous oxygenation. Such benefits are probably due to the effect of TEA on systemic vascular resistance (SVR), which is usually decreased through the attenuation of sympathetic activity, mediated by local anesthetics [22, 23].

Systemic drugs and regional techniques, therefore, may certainly have a positive impact on the heart; the attenuation of adrenergic stimuli, obtained by the mitigation of pain symptoms, plays a key role. Moreover, treatments like TEA have shown potential further beneficial effects, both direct and indirect, on the heart.

Anyway, all current analgesic therapies have not yet shown a significant positive impact on major clinical outcomes, such as the length of stay in hospital, and may even determine severe adverse cardiovascular effects, especially if used in the long term.

Conclusions

In conclusion, it is now possible to investigate the close connection between the heart and the nervous system. There are various patterns of response to pain that determine different systemic effects, and the cardiovascular system is primarily involved. Acute pain and, above all, chronic pain, may carry on such stimulation, generating important consequences. The positive impact of analgesia on the cardiovascular system can be employed as a therapeutic target in order to improve specifically the patients' cardiovascular function and wellness.

References

1. Treede RD. The International Association for the study of pain definition of pain: as valid in 2018 as in 1979, but in need of regularly updated footnotes. Pain Rep. 2018;3(2):e643.
2. Macintyre PE, Schug SA, Scott DA. Acute pain management: the evidence grows. Med J Aust. 2006;184(3):101–2.

3. Williams AC, Craig KD. Updating the definition of pain. Pain. 2016;157(11):2420–3.
4. Sigakis MJG, Bittner EA. Ten myths and misconceptions regarding pain management in the ICU. Crit Care Med. 2015;43(11):2468–78.
5. Ellison DL. Physiology of pain. Crit Care Nurs Clin North Am. 2017;29(4):397–406. https://doi.org/10.1016/j.cnc.2017.08.001. Epub 2017 Sep 23. Review
6. Kyle BN, McNeil DW. Autonomic arousal and experimentally induced pain: a critical review of the literature. Pain Res Manag. 2014;19(3):159–67. Epub 2014 Feb 14
7. Benarroch EE. Pain-autonomic interactions. Neurol Sci. 2006;27:S130–3.
8. Koenig J, Jarczok MN, Ellis RJ, Hillecke TK, Thayer JF. Heart rate variability and experimentally induced pain in healthy adults: a systematic review. Eur J Pain. 2014;18(3):301–14.
9. Rosenfeld BA, Beattie C, Christopherson R, et al. The effects of different anesthetic regimens on fibrinolysis and the development of postoperative arterial thrombosis. Perioperative Ischemia Randomized Anesthesia Trial Study Group. Anesthesiology. 1993;79(3):435–43.
10. Tetzlaff JE. Cardiovascular consequences of severe acute pain. Practical Pain Management. www.praticalpainmanagement.com.
11. Liu S, Carpenter RL, Neal JM. Epidural anesthesia and analgesia. Their role in postoperative outcome. Anesthesiology. 1995;82:1474–506.
12. Rosenfeld BA, Beattie C, Christopherson R. The effects of different anesthetic regiments on fibrinolysis and the development of postoperative arterial thrombosis. PIRAJ Study Group. Anesthesiology. 1993;79:435–43.
13. Fayaza A, Ayisb S, Panesar SS, et al. Assessing the relationship between chronic pain and cardiovascular disease: a systematic review and meta-analysis. Scand J Pain. 2016;13:76–90.
14. Tennant F. Treat the pain...save a heart. Practical Pain Management. www.practicalpainmanagement.com. 2011.
15. Dawson DK. Acute stress-induced (takotsubo) cardiomyopathy. Heart. 2018;104(2):96–102.
16. Templin C, Ghadri JR, Diekmann J, Napp LC, Bataiosu DR, Jaguszewski M, et al. Clinical features and outcomes of takotsubo (stress) cardiomyopathy. N Engl J Med. 2015;373(10):929–38. https://doi.org/10.1056/NEJMoa1406761.
17. Ghanem CI, Pérez MJ, Manautou JE, Mottino AD. Acetaminophen from liver to brain: new insights into drug pharmacological action and toxicity. Pharmacol Res. 2016;109:119–31. https://doi.org/10.1016/j.phrs.2016.02.020.
18. Botting RM. Inhibitors of cyclooxygenases: mechanisms, selectivity and uses. J Physiol Pharmacol. 2006;57(Suppl 5):113–24.
19. Raynor K, Kong H, Chen Y, Yasuda K, Yu L, Bell GI, Reisine T. Pharmacological characterization of the cloned kappa-, delta-, and mu-opioid receptors. Mol Pharmacol. 1994;45(2):330–4.
20. Bignami E, Castella A, Pota V, Saglietti F, Scognamiglio A, Trumello C, Pace MC, Allegri M. Perioperative pain management in cardiac surgery: a systematic review. Minerva Anestesiol. 2018;84(4):488–503.
21. Khodneva Y, et al. Prescription opioid use and risk of coronary heart disease, stroke, and cardiovascular death among adults from a prospective cohort (REGARDS Study). Pain Med. 2016;17:444–55. https://doi.org/10.1111/pme.12916.
22. Jakobsen CJ, Bhavsar R, Nielsen DV, Ryhammer PK, Sloth E, Greisen J. High thoracic epidural analgesia in cardiac surgery. Part 1 – high thoracic epidural analgesia improves cardiac performance in cardiac surgery patients. J Cardiothorac Vasc Anesth. 2012;26(6):1039–47.
23. Nielsen DV, Bhavsar R, Greisen J, Ryhammer PK, Sloth E, Jakobsen CJ. High thoracic epidural analgesia in cardiac surgery. Part 2 – high thoracic epidural analgesia does not reduce time in or improve quality of recovery in the intensive care unit. J Cardiothorac Vasc Anesth. 2012;26(6):1048–54.

Neuromodulation for Chronic Refractory Angina

38

Philippe Mavrocordatos, Gustavo Rodrigues Costa Lages, and Lucian Mihai Macrea

Contents

Abstract

Angina pectoris is not a proportional indicator of the severity of occlusive coronary disease or myocardial ischemia; however, it is a key symptom of coronary artery disease. In a subgroup of patients suffering from long-lasting angina-type pain in the presence of myocardial ischemia, symptoms cannot be controlled by a combination of medical therapy, angioplasty, and coronary bypass surgery. Despite a relatively low mortality, these patients suffer high morbidity and frequent hospital admissions. This "refractory angina syndrome" is associated with important biopsychosocial issues and should be considered and treated as "chronic pain."

Considering refractory angina pain as a chronic pain syndrome implies re-examining the entire neurophysiological pain pathways and questioning the Cartesian model. This also opens the gate to different hypothesis, including rethinking the symptom "angina" as a marker of ischemia only and looking at abnormal modulation processes involving pain pathways.

Keywords

Heart · Pathophysiology · Refractory angina · Neuromodulation · Spinal cord stimulation · Neurological mechanisms · Alternative interventions · Interventional · Treatment · Non-pharmacological

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*,
https://doi.org/10.1007/978-3-030-28008-6_44

Introduction

Angina pectoris is not a very sensitive marker of myocardial ischemia; however, it is a key symptom of coronary artery disease. In this regard, in the presence of myocardial ischemia, complaints of angina are often expressed late, inconsistently, or may be even completely absent in 30% of patients [1]. Moreover, angina is not a proportional indicator of the severity of occlusive coronary disease [2].

The perception of pain from visceral nociceptive stimuli is complex, and the severity of symptoms is often disproportionate to the degree of ischemia [3]. So, angina should not be considered as a reliable maker of the underlying pathological process of atherosclerosis. However, it remains an important clinical guide of the therapeutic effect of the treatment.

In this chapter we will focus on persistent forms of cardiac pain. This so-called refractory angina syndrome is debilitating and requires the understanding of the interplay of ischemic, metabolic, and neuropathophysiological mechanisms contributing to these clinical problems [4]. Like other types of persistent pain, cardiac pain is a complex, subjective experience with sensory-discriminative, motivational-affective, and cognitive-evaluative components. Each of these dimensions, subserved by specialized systems in the brain (i.e., limbic, reticular, neocortical areas), contributes to the overall patient experience of pain and the related individual responses [4]. Within the concept of the pain matrix (the extensive network of brain regions involved in pain processing pain) [5], there are multiple levels at which abnormal modulation of afferent signals from the heart can lead to the establishment and maintenance of a chronic cardiac pain syndrome. These same structures are also potential targets for neuromodulation treatments (Table 1).

Refractory angina (RA), end-stage coronary artery disease, "no-option" coronary vascular disease, or intractable chronic angina have been used frequently to describe this clinical syndrome. Refractory angina is described as chronic (>3 month) angina-type pain in the presence of myocardial ischemia which cannot be controlled by a combination of medical therapy, angioplasty, and coronary bypass surgery [7, 8]. This definition is important for building up an appropriate framework for basic science and clinical research, increasing awareness among clinicians [7].

With an aging population and increased survival from coronary artery disease, clinicians will increasingly encounter these complex patients in routine clinical practice [7, 8].

However, exact numbers on patients suffering from refractory angina are difficult to obtain because no large epidemiological study has focused on RA alone [9]. Moreover, the condition of refractory angina may represent at least four different anatomo-pathological phenotypes [10].

Registries suggest that between 5% and 15% of patients investigated for symptomatic angina are unsuitable for revascularization and therefore fulfil the definition of refractory angina [7, 11, 12]. A second indicator derives from stable angina prevalence and the estimated proportion of refractory angina cases [9]. From this approximation, it is estimated that 3–7 per 1,000 patients aged 45–74 years suffer from refractory angina [12]. It is estimated that in the USA, between 600,000 and 1.8 million patients suffer from RA. In Canada, about 500,000 patients live with angina. The number of new diagnosis for year is approximately

Table 1 Examples of therapies targeting the transmission pathway for angina pain

Level of transmission	Pathways targeted	Therapies
Periphery	Sympathetic ganglia	Stellate ganglion block
Periphery	Sympathetic afferent pathways	Surgical sympathectomy (neuroablation technique)
Central/spinal cord	Spinal cord synapses	TENS e SCS
Central/supraspinal	Thalamic centers	Modulatory antidepressants (low-dose tricyclics)
Central/supraspinal	Higher cortical centers	CBT

Adapted from Sainsbury et al. [6]
TENS transcutaneous electrical stimulation, *SCS* spinal cord stimulation, *CBT* cognitive behavioral therapy

75,000 in the USA and 30,000–50,000 in Europe [13]. Reynolds et al. studied the economic burden of chronic angina in a 2004 systematic review [14]. Among the 47 selected studies, 10 directly addressed the cost. The annual direct costs ranged from $1,937 for medically managed patients to almost 10 times that amount for patients with advanced illness and refractory angina ($18,467 in 1997). Severity of illness clearly matters. Two other studies by Schofield in 1999 and Kandzari in 2001 focused on "severe angina" patients. These two studies also found that costs were much higher than for patients with "medically managed" chronic angina [15, 16].

Refractory angina patients suffer a rather high morbidity considering the occurrence of acute coronary syndrome, hospital admissions, and concomitant diseases, despite a relatively low mortality (5–7% per year) rate [17].

Angina is the symptom of myocardial ischemia and chronic refractory angina (RA). These painful disorders share some clinical features but differ significantly in their underlying mechanisms [17].

Patients experience a significantly limitation by persistent debilitating chest discomfort and often relate their chest pain with a signal of a life-threating cardiac event. This leads to a progressive decline in their mental well-being, to pessimistic health beliefs, to negative behaviors, and to impaired quality of life [8, 9].

In these conditions, simply treating the expressed pain alone is important as it may improve exercise tolerance and quality of life [18]. RA ought to be conceptualized as a chronic pain disorder and treated as such, integrating physical, psychological, and educational modalities run by a multidisciplinary team [18–20].

Neuropathophysiology and Segmental Neuromodulation

Pathophysiology of angina goes far beyond "myocardial oxygen supply/demand imbalance," and therefore multiple levels of neuromodulative mechanisms may be available to control angina pain [21].

Currently the visceral pain symptoms related to angina pectoris are described as precordial pain, diffuse, poorly localized, and regional tissue tenderness. These symptoms can refer to somatic structures as the neck, jaw, or arm and associated with autonomic manifestations as sweating and nausea [22]. However, the correlation between pain perception and the extent of coronary disease is poor. The spectrum of pain modulation is extremely broad and can range from the complete cessation out of perceived pain sensations to feelings of extreme pain with little stimulus. Examples range from silent myocardial ischemia to that of a functional pain syndrome of cardiac syndrome X (the sensitive heart). The wide variability of complains described by the patients is another intriguing finding [22].

Throughout the late eighteenth and early nineteenth century, several correlations were made between coronary obstruction and the symptomatology of angina through postmortem studies as well as the description of the cardiac and extracardiac symptoms of angina [23, 24]. In 1902, Colbeck described differential stretching of the myocardium and coronary spasm as potential mechanical causes of angina-related pain [25]. Thirty years later, Lewis proposed the actual electrical hypothesis to contrast the mechanical theory and found to be accurate. He suggested that the angina pain resulted from the release of pain chemical mediators in the myocardium during ischemia [26].

The sensory nerve endings in the myocardium are formed by the endings of mixed myelinated A δ and unmyelinated C fibers, forming bundles that can be traced through the septa. Gradually these fibers form nerve branches that coalesce into the cardiac sympathetic and vagal components [22].

Physiological neuromodulation happens at different levels of the somatosensory system. These levels are also potential therapeutic targets for neuromodulation (Table 1 and Fig. 4).

Peripheral Pathophysiology and Modulation

Both chemosensitive and mechanosensitive nerve endings founded primarily in the epicardium with the vagal fibers are generally close to the

epicardium and especially in the infero-posterior wall. The substances released during ischemia such as bradykinin, potassium ions, prostaglandins, leukotrienes, and adenosine excite the receptors of the sympathetic and vagal afferent pathways [27]. Adenosine specially plays an important role in the physiological regulation of the coronary microcirculation and is considered to be responsible for the bulk of pain signaling from the heart to the spinal cord and the brain [22]. In patients with refractory angina, the high-threshold receptors in the myocardium become low-threshold receptors. The subsequent sensitization of these receptors in the myocardium results in an altered angina threshold [28].

More recently, the transient receptor potential vanilloid-1 (TRPV1) has gained significant interest. TRPV1 receptors respond to capsaicin, heat, and hydrogen ions at the myocardial and dorsal root ganglion (DRG) level. Activation of these receptors leads to an influx of cations and to a release of calcitonin gene-related peptide (CGRP) and substance P. Substance P has a synergic role together with adenosine in cardiac pain nociception [29–31].

Afferent sympathetic neurons travel through the myocardium to either the superior or inferior cardiac plexus and progress, without synapsing, through the sympathetic ganglion chain to end in the dorsal horn of the spinal cord. The cell bodies of sympathetic afferent fibers are in the dorsal root ganglia of the C8 to T9 spinal segments, especially T2–T6. In the dorsal horn, they connect predominantly to neurons in lamina I, with additional connections in lamina V [6].

Experimental pathological perturbations on the anterior surface of the heart lead to an increase nociceptive afferent traffic-inducing pain. This process is accompanied by some sympathetic efferent reflexes resulting in tachycardia and/or hypertension. Surgical sympathectomy can alleviate pain and these sympathetic reflex symptoms. Nonetheless, pathological perturbations involving the inferior-posterior surface of the heart are characterized by vagal efferent reflexes, resulting in bradycardia and/or hypotension. In this situation, it appears that the vagus nerve plays a major role in the transmission of pain. In these experimental studies, vagotomy generally abolishes such cardiovascular reflexes. Lower cervical and upper thoracic sympathectomies are not effective in the relief of pain and vagal reflexes from angina [32].

High levels of adrenergic activity can be evoked in response to cardiac ischemia, leading to a vicious cycle that increases myocardial oxygen demand, worsens ischemia, and produces more angina [33]. There are data suggesting a reflexive coronary vasoconstriction evoked by the original chest pain. High central sympathetic tone is also proarrhythmic, in addition to any local myocardial proarrhythmic effects of ischemia [18, 22, 34]. The sympathetic cardiac efferent fibers are located in the stellate ganglion [35]. The block of this ganglion can relieve cardiac pain.

Therapy Related to Peripheral Neuromodulation

Epidural Blockade with Local Anesthetics

The antianginal effect is a result of blockade of afferent and efferent cardiac sympathetic fibers leading to a reduction in myocardial ischemia, probably associated with reduced myocardial oxygen consumption.

Richter et al. conducted a pilot study [36] evaluating the effect of long-term (3-year follow-up) use of tunneled epidural catheter in RA patients. They were trained to provide self-administration through the catheter at home. Bupivacaine 0.25% were injected in an average dose of 3 ml, two to five times per day (median, 2). They demonstrated a significant improvement in angina class reducing from a mean class of 3.6 to 1.7 after 1 week and 1.3 after 6 months. The mean number of anginal attacks per week also decreased significantly. In addition, there was a significant improvement in quality of life. They had no serious complications. Ten years later, the same group published a similar study that confirmed these findings. The observational designs of these studies limit the conclusions that can be drawn, but the high benefits demonstrated lower mortality, reduced angina episodes, and significantly improvement in quality of life, and low rates of complications make the technique to be considered [37].

Stellate Ganglion Block (SGB)

Treating cardiac chest pain by modulation of sympathetic afferents was first postulated by Frank in 1899. Sympathetic neuronal blockade is presupposed to interrupt adrenergic hypersensitivity and positive feedback circuits that ordinarily augment central excitability [38].

Although the effect of this block is considered generally transient, long-term relief has been described with stellate block [39]. A potential way to prolong the effect is the use of radio-frequency ablation [40]. With the use of ultrasound-guided blocks, the technique becomes much safer. It is associated with some potential complications including intravascular injection, hematoma, retropharyngeal hematoma, hoarseness dysphagia, phrenic paralysis, and esophageal rupture [41]. The development of transient Horner's syndrome (miosis, partial ptosis, and ipsilateral anhidrosis) is a traditional marker of success for SGB. It is also frequently accompanied by ipsilateral increase in blood flow and skin temperature [38].

A recent prospective study has shown SGB to be both safe and efficacious in the management of RA, with a mean pain relief duration of 3.5 weeks. SBG can be considered as an alternative neuromodulation invasive strategy in patients suffering from intractable anginal symptoms. However, the evidence for this procedure to treat angina is lacking, and further RCTs are needed to establish whether it should be incorporated into routine clinical practice [38].

Surgical Cervical and Upper Thoracic Sympathectomies

These procedures include removal of the superior cervical and stellate ganglia or removal of the cervicothoracic trunk and the sympathetic chain. About 50–60% of patients report complete relief from angina, whereas 30–40% report partial relief, and approximately 10–20% report no relief at all [32].

Central Pathophysiology and Modulation: Spinal Level

The extensive connections among cardiac sympathetic plexus, sympathetic ganglion chain, and spinal cord (from the upper cervical ganglion to the sixth or seventh thoracic segment) explain why angina is so widely expressed. Incoming somatic nociceptive fibers synapse with the same lamina I neurons (besides their own connections on the lamina II and III), resulting in "crosstalk" which occurs between somatic and visceral afferent pathways and therefore the referred somatic pain typically associated with characterizes angina pectoris (Fig. 1). This convergence of visceral-somatic input to spinothalamic cells involving fibers of C5 and C6 explains pain referred to the upper arm and at level of C1 and C2 explains the associated jaw and neck pain. As the receptive fields were located primarily in deep muscle rather than cutaneous tissue, the referred pain is often described as deep [28, 42].

A part of these second neuron afferents cross the spinal cord in front of the anterior white commissure and then ascend near the spinothalamic tracts (STT). However, the majority of this tract intertwined with somatic neurons [22, 42].

Kreiner et al. demonstrated in a study that 6% of patients with cardiac ischemia presented with craniofacial pain as the only complaint and 32% presented it as one of the symptoms. It is believed that this transmission is made by the cardiac branch of the left vagus nerve [43]. The afferent fibers of the vagus nerve ascend to the nucleus of the solitary tract and directly or indirectly modulate the neurons of C1 and C2 that also receive somatic sensory information from the neck and the jaw [21]. Since only 6% of the vagal afferents project directly to the C1–C2 spinal neurons, the rest most likely ascend into the nucleus tractus solitarius of the medulla and then descend to synapse on the spinothalamic tract cells with axons projecting to the C1–C2 segments. Transmission of pain signals via the cardiac branch of the left vagus nerve is the mechanism postulated for the development of neck or jaw pain after sympathectomy for relieving retrosternal pain. This post-procedure pain is generally more tolerable than the presenting retrosternal pain [28] (Fig. 2).

Therapy Related to Central Neuromodulation: Spinal Level

In 1965, Melzack and Wall developed the "gate theory" [44] which presented the notion that afferent pain signals traffic could be controlled at the spinal

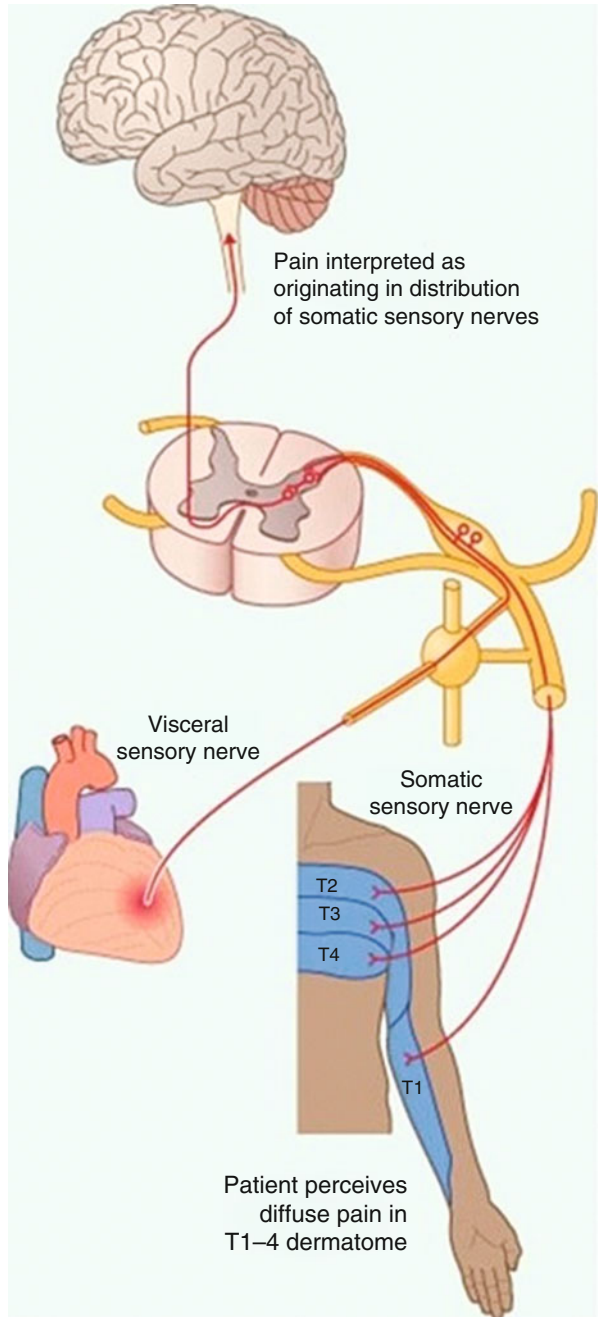


Fig. 1 Convergence of visceral-somatic input. (Source: https://slideplayer.com/slide/5332097/. Access in 10/10/2018)

level. Stimulating the dorsal columns activates the large afferent fibers, which in turn activate neuronal mechanisms in the spinal cord gray matter. In this way, large afferent fibers can decrease the amount of information coming from the nociceptive afferent nerves to reduce the nociceptive sensation. Important subsequent discoveries included that of endorphins and enkephalins, acting via spinal and central opiate receptors, Perl's report of the sensitization of nerve terminals by inflammatory mediators, and the finding of long-term potentiation at the hippocampal level by Bliss and Lomo in 1973 [22, 45].

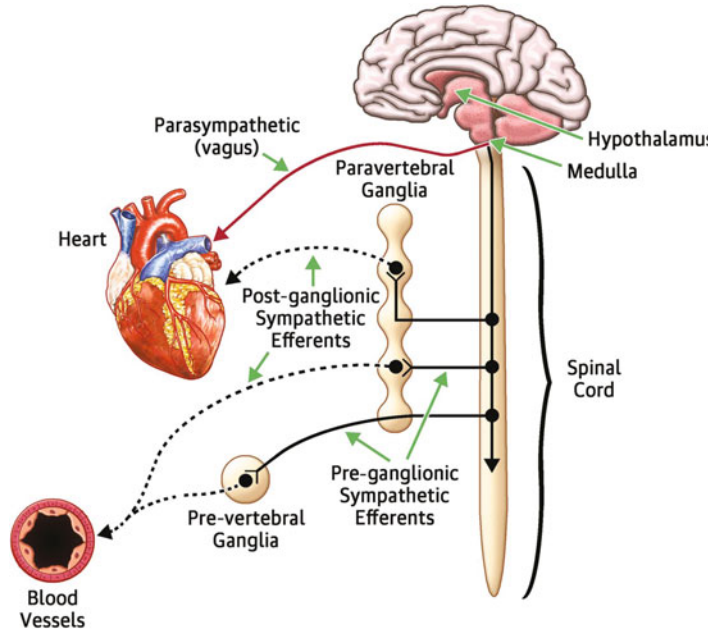


Fig. 2 Autonomic efferents pathways. (Source: https://www.sciencedirect.com/science/article/pii/B9780124047068000061. Access in 10/10/2018)

The rationale of the "gate control theory" [44] initiated the development of electrical neuromodulation techniques such as transcutaneous electrical neuromodulation (TENS) and spinal cord neuromodulation (SCN). Both of these techniques utilize low-voltage electric current to modulate nociceptive signaling and replace pain sensations with paresthesia without masking the symptom of acute myocardial infarction. Both are recommended by ESC as options to treat RA. TENS through pads is placed over the skin, and SCS through electrodes is implanted in the spine cord [38, 46, 47].

Transcutaneous Electrical Stimulation (TENS)

Some case-related reports have shown good results with TENS for the treatment of RAP. The trial dose is 1 h, one to three times a day. Long-term results with significant pain relief and even pain-free patients have been published. The mechanism of action is probably a combination of analgesia per se and inhibition of sympathetic nervous stimulation of the heart [48]. TENS may be considered to ameliorate symptoms of invalidating RA; beyond pain, it has been related to increased work capacity, decreased ST segment depression, reduced frequency of anginal attacks, and reduced consumption of short-acting nitroglycerin per week, its recommendation IIb, and level of evidence, C [46].

Spinal Cord Stimulation (SCS)

The spinal cord stimulation (SCS) is a therapy consisting of the placement of electrodes in the perineural space. Linked to a generator, the electrodes produce an electrical field inducing paresthesia at the desired region. To be effective, paresthesia must "cover" the pain region. In neuropathic and visceral pain states, it may significantly reduce pain. The first case was described in 1967 by Shealy [49, 50].

Electrodes are placed midline in patients under light sedation. An intraoperative test confirms the good placement. The devices are placed with the minimally invasive "Seldinger" technique after identification of the epidural space. Once it is in place, they are fixed to the interspinous ligament. The system is tested with an externalized battery over 2–4 weeks as an outpatient. If a pain reduction of >50% is achieved, the system is implanted with an internal battery. Depending on the power consumption, a standard (life span 2–4 years) or a rechargeable battery (life span >10 years)

is implanted subcutaneously in the abdominal or gluteal region. The battery will deliver the power for the continuous therapy (50 Hz, plus width 100–800 μs) with an adjustable intensity of stimulation depending on patient's preference [51, 52].

The epidural space contains extensive venous plexus vulnerable to damage during needle puncture and mobilization of SCS leads. Large needles and stiff-styletted leads are needed to enable directional control of SCS leads. In many cases, the technique correlates with minimal tissue trauma. However, in some clinical settings, the procedure may be laborious, with greater manipulation in the epidural space to reach to position properly the leads [53].

Significant evidence exists supporting the use of aspirin for secondary prophylaxis for cardiovascular disease [54]. Discontinuation of this medication to perform safely interventional procedures may be associated with significant risk [55]. P2Y12 receptor inhibitors are used in combination with aspirin as a "dual antiplatelet therapy," to reduce thrombotic events in the setting of acute coronary syndromes and in patients who undergo percutaneous coronary intervention. For trial of SCS, the antiplatelets drugs should be stopped and the trial kept to the minimum duration possible [53].

Oral anticoagulation must be interrupted before SCS implantation. Whether or not to bridge with heparin is a clinical common practice although with limited evidence. New observational studies and a recent large randomized trial [56] have noted significant perioperative or periprocedural bleeding rates without reduction in thromboembolism when bridging is employed [57]. Although bridging anticoagulation may be necessary for those patients at highest risk for thromboembolic events (TE), for most patients it produces excessive bleeding, longer length of hospital stay, and other significant morbidities while providing no clear prevention of TE. While awaiting the results of additional randomized trials, physicians should carefully reconsider the practice of routine bridging and whether periprocedural anticoagulation interruption is even necessary. Results from randomized trials are needed, especially for patients with mechanical heart valves [58].

The decision to stop the anticoagulants medications should be shared between the pain physician and the referring physician, cardiologist, neurologist, or primary care physician.

In Table 2 is presented a summary of recommendations for the management of anticoagulants drugs for SCS implantation [59].

Due to the consistently positive therapeutic response and the risks associated with the multiple comorbidities of patient with chronic refractory angina pectoris, we often do not undergo a trial phase and proceed to the permanent system implantation. The best placement of the electrodes is over the levels T1–T4 [59] where the induced paresthesia is optimally overlapping with the area of angina attacks. An alternative placement of electrodes is at the cervical level C1–C2 where stimulation produces a sympathetic and vagal modulation of pain of cardiac origin [21].

Today it is well known that only the sole activity of large fibers (gate theory) is not enough to explain the SCS mechanisms of pain reduction. The large fibers are not capable of "shutting down the gate" and stopping the nociceptive input in the small pain fibers. This is particularly evident in the case of acute nociceptive pain where SCS is not effective, but SCS can considerably diminish the intensity of maladaptive pain. This is also true for acute pain symptoms elicited during myocardial infarction that are not masked by SCS [47, 60–62].

In pathological pain states (e.g., animal models of mononeuropathy), the amount of GABA (gamma-aminobutyric acid) in spinal dorsal horn is decreased, and administration of $GABA_B$ agonist baclofen can revert the tactile hypersensitivity thought to trigger cardiac pain [63, 64]. An important effect of SCS on pain perception is likely to occur through the activation of inhibitory GABAergic and cholinergic spinal interneurons. Stimulation of sympathetic efferents by SCS causes vasodilation due to the antidromic release of calcitonin gene-related peptide (CGRP) and possibly nitric oxide linked to the transient receptor potential V1 (TRPV1) [45, 65].

Table 2 Time to stop the anticoagulation therapy before SCS implantation

Drug	When to stop	When to restart
Aspirin	Primary prophylaxis: 6 days Secondary prophylaxis: shared assessment and risk stratification	24 h
NSAIDs	5 half-lives	24 h
Diclofenac	1 day	
Etodolac	2 days	
Ibuprofen	1 day	
Indomethacin	2 days	
Ketorolac	1 day	
Meloxicam	4 days	
Naproxen	4 days	
Piroxicam	10 days	
Phosphodiesterase inhibitors		
Cilostazol	2 days	24 h
Dipyridamole	2 days	
P2Y12 inhibitors		
Clopidogrel	7 days	12–24 h
Prasugrel	7–10 days	12–24 h
Ticagrelor	5 days	12–24 h
PO anticoagulants		
Coumadin	5 days, normal INR	24 h
Acenocoumarol	3 days, normal INR	24 h
New PO anticoagulants		
Dabigatran	4–5 days Patients with impaired renal function: 6 days	24 h
Rivaroxaban	3 days	24 h
Apixaban	3–5 days	24 h
Anticoagulants		
IV heparin	4 h	24 h
Subcutaneous heparin	8–10 h	2 h
LMWH prophylactic	12 h	12–24 h
LMWH therapeutic	24 h	12–24 h
Fondaparinux	4 days	24 h

The nervous system is activated during chronic ischemia episodes [66], and this state corresponds most likely to the neuropathic state. The injection of bradykinin in the heart or chronic coronary occlusion induces an activation of the sympathetic nervous system and an increased activity in the spinothalamic tract cell contributing to chronic pain [67, 68]. These effects could be reversed by SCS stimulation [69]. In this way, SCS result in antinociceptive activation of spinal afferent neurons and inhibit sympathetic efferents, attenuating vasoconstriction and reducing ischemia [3].

There are differences in the mechanisms of action of SCS in ischemic and neuropathic pain. SCS also has an effect on rebalancing the myocardial oxygen demand which is an important role to improving overall cardiac function and reducing angina. During myocardial ischemia, SCS seems to have important effect on exercises test [69], long-term ECG monitoring [70], decreased O_2 demand, and lactate metabolism [71, 72]. These reduce sympathetic nerve system overactivity which produces overall pain reduction. The stabilization of the intrinsic cardiac nervous system seems to produce important antiischemic effects through the activation of spinal A1 receptors [73]. Although SCS improves the rate-pressure product (heart rate × systolic blood

pressure) [42, 74], it has no impact on the left ventricle dynamics (pressure-volume relationship), on overall coronary blood flow, or the distribution between ischemic and nonischemic zones [75, 76].

SCS inhibits the sympathetic flow or blocks the reflex arc after the onset of pain, thus reducing this sympathetic activity and producing an anti-ischemic [60] end antiarrhythmic [77, 78] effect and improving myocardial function during the acute ischemia [79]. In patients with heart failure disease, associated biomarkers showed a small but significant increase due to SCS delivered 12 h/day at the level of T2–T4 segments. This modest increase is not likely to be clinically relevant per se but may indicate a possible adverse cardiac effect of SCS in humans with heart failure (without chronic pain) [80]. There are several proposed SCS mechanism of action which include the release of neuromodulators (dynorphin), the blunting of the sympatho-excitation, and the altering of preganglionic neurons. Clinical trials in patients with heart failure need to be tested [80–82].

Stimulation of the upper cervical spinal cord C1–C2 showed in clinical trials a reduction in pain symptoms, similar to the stimulation over the usual high thoracic levels (T2) [78]. Experimental studies could prove an inhibition in the proximal and distant spinal cord neurons and also in the somatic afferents [81]. The mechanism is an antidromic activation of large fibers with a consecutive release of dynorphin [82] (κ-opioid peptide) suppressing the neuronal activity in the upper thoracic segments and reducing, for example, the amount of substance P released [83].

The direct SCS stimulation of the dorsal column were shown to reduce the firing of the spinothalamic tract cells [69].

The influence of SCS on the wide dynamic range (WDR) interneurons, through GABAergic connections, is well known from the neuropathic pain. This mechanism helps to explain the diminution of hypersensitivity when the paresthesia is delivered in the pain area [83] (Fig. 3).

"Illustration showing how spinal cord stimulation (SCS) of primary afferent fibers in the low thoracic-lumbar dorsal columns (here L1) activates neural mechanisms producing vasodilatation in peripheral vasculatures. SCS activates ERK-containing GABAergic interneurons (inset). These interneurons antidromically activate a presynaptic mechanism exciting Ad and C dorsal root afferent fibers that release calcitonin gene-related peptide (CGRP) and nitric oxide from the endothelium. SCS also activates interneurons that decrease activity of sympathetic preganglionic neurons and, in turn, reduces release of catecholamines mainly acting on alpha-1 adreno-receptors from sympathetic postganglionic neurons [83]."

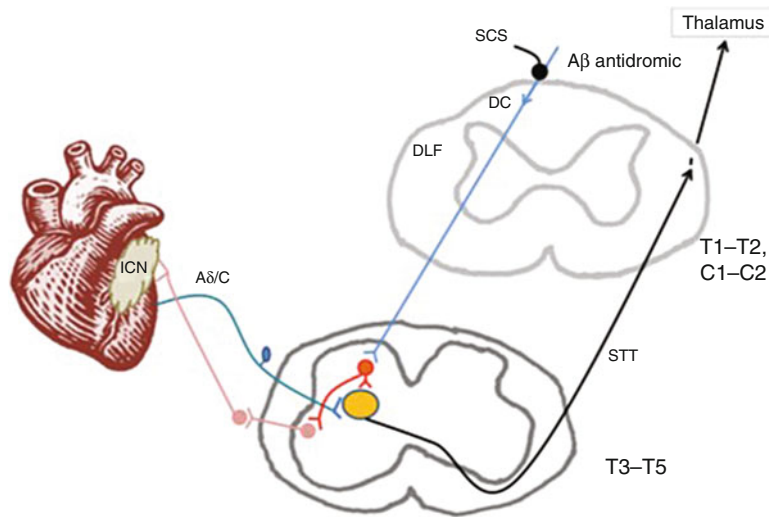
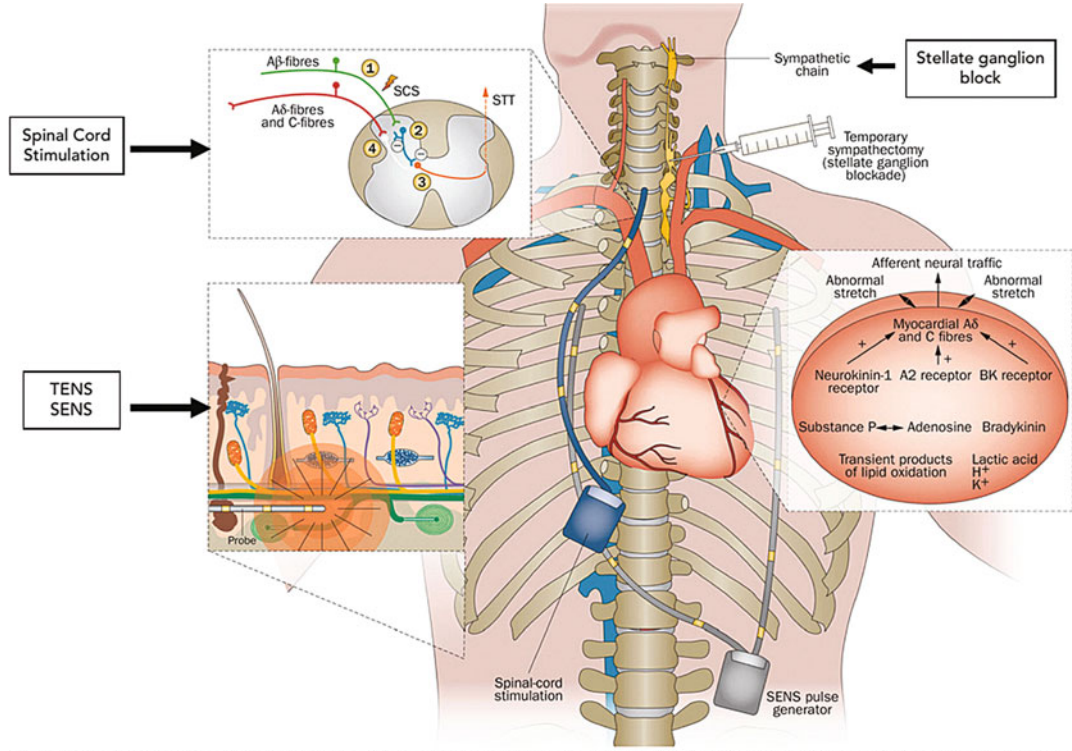


Fig. 3 Neuronal mechanisms of spinal cord stimulation. (Source: https://slideplayer.com/slide/5332097/. Access in 10/10/2018)



SCS = spinal cord stimulation; SENS = subcutaneous electrical nerve stimulation; STT = spinothalamic tract; TENS = transcutaneous electrical nerve stimulation. Figure adapted from Henry et al. Nat Rev Cardiol *2014;11(2):78–95 with permission from Macmillan Publishers Ltd, copyright (2014).*

Fig. 4 Targets for neuromodulation in RA. *SCS* spinal cord stimulation, *SENS* subcutaneous electrical nerve stimulation, *STT* spinothalamic tract, *TENS* transcutaneous electrical nerve stimulation. (Source: https://www.ecrjournal.com/articles/management-refractory-angina-pectoris. Access in 10/10/2018)

The SCS therapy is one of the best adjuvant therapies for cardiac-origin pain, and this therapeutic option can be recommended as evidence level 2b with a degree B for recommendation [46]. Success rates achieved with SCS for angina pectoris are in excess of 80% [70, 84].

The severity and frequency of anginal episodes are reduced, and, in some cases, episodes are eliminated. In addition to pain relief, SCS demonstrate reduction in disease perception, reduction in short-acting nitrate consumption, improved Canadian Cardiovascular Society class, increases in exercise tolerance (controversy) [85], improvements in ischemia-related electrocardiographic changes (ST segment), and improvements in the quality of life [42, 74]. SCS can stabilize these neurons for prolong periods even after the stimulus has been stopped. This indicates that a cardioprotective benefit may persist even after discontinuing SCS therapy for long term [66, 86]. Anyway, adequate sham-controlled RCTs to confirm efficacy and cost-effectiveness are needed [3] (Fig. 4).

Central Pathophysiology and Modulation: Supraspinal Level

Sympathetic afferent fibers advance predominantly via the dorsal columns to the ventral posterolateral nucleus of the thalamus (VPL). VPL also receive visceral afferent inputs via the spinothalamic tracts. Vagal fibers mainly connect to the nucleus of the solitary tract and from there to the parabrachial nucleus in the pons, which in turn have efferent connections to the hypothalamus and amygdala and to posterior thalamus. Rostral to the thalamus, cardiopulmonary inputs

have been shown to activate neurons in the insular cortex. The insula is also connected to medial prefrontal cortical regions. There is good evidence that the insula is involved in the monitoring of common visceral sensations and in modifying and integrating autonomic responses. Additionally, there are projections from the insula to the primary somatosensory cortex [22].

Studies with positron emission tomography (PET) have shown increased regional cerebral blood flow in the hypothalamus, periaqueductal gray, bilaterally in the thalamus and lateral prefrontal cortex, and left inferior antero-caudal cingulate cortex in angina compared with the resting state. In the study by Rosen et al. [87], he noted that angina symptoms were stopped within minutes after stopping the dobutamine infusion. He also noted that when the patients no longer experienced angina and the electrocardiographic changes had resolved, thalamic, but not cortical activation, could be demonstrated. Hence, they proposed that the central structures activated the pathways for perception of anginal pain. The persistence of thalamic activation after the cessation of the symptoms and signs of myocardial ischemia initiated the theory on "gate alterations of painful signals" might occur at the thalamic level. As an extension, the proposed mechanisms of silent myocardial ischemia are abnormal central processing of afferent pain messages, gate regulation at the thalamic level, and the presence of an autonomic neuropathy. Low-dose tricyclic antidepressants could modulate the angina pain in the thalamus [16, 87]. Nociceptive signals are relayed from the thalamus to the primary and secondary somatosensory areas and to subsequent brain regions linked to visceral sensation (i.e., insula), emotion (i.e., limbic system), attention (i.e., anterior cingulate), and cognition (i.e., prefrontal cortex). The brain also exerts descending modulation on nociceptive processing via subcortical structures such as periaqueductal gray (PAG), rostroventral medulla (RVM), hypothalamus, parabrachial nucleus, and nucleus tractus solitarius [28].

Mood, cognition (including expectation/anticipation, belief, and empathy), context, structural, and neurochemical factors have all been shown to contribute to the modulation of pain perception. Regardless of etiology or anatomy, patients with refractory symptoms commonly believe that their chest discomfort is due to pain from their heart and that it may predict a life-threatening cardiac event. This underpins the fear-driven psychological response whereby pain begets pain, leading to the development of persistent symptoms, negative health beliefs, and behavior. Cognitive behavioral therapy (CBT) could have a modulatory effect in higher cortical centers, especially for those demonstrating catastrophization [3, 16, 38, 82]. Patients with cardiac syndrome X demonstrate the interaction between the heart and brain. These patients present angina pectoris with ischemic-like changes on the stress ECG but with no angiographically coronary arteries anomaly. Functional neuroimaging studies with PET during high-dose dobutamine infusion demonstrated greater right anterior insular activity, being maybe a specific marker for a perception of myocardial pain without ischemia, characterizing a functional cardiac pain syndrome, and an abnormal central handling of afferent pain signals [3, 88, 89].

Therapy Related to Central Neuromodulation: Supraspinal Level

Acupuncture

Chronic pain is the most frequent indication for acupuncture in the Western world. Although the mechanism of action of acupuncture for pain relief is not completely understood, it appears to evolve a wide range of central nervous structures at spinal and supraspinal (subcortical and cortical structures) levels including periaqueductal gray, nucleus raphe magnus, locus coeruleus, arcuate nucleus, amygdala, and nucleus accumbens. Acupuncture modulate pain over both the ascending facilitatory pathways (*N*-methyl-D-aspartate receptors, substance P, and interleukin-1) and the descending inhibitory pain pathways (endogenous opioids, serotonin, and norepinephrine). Output of spinal neuron is dependent on ascending input from the periphery and modulated by spinal interneurons (endogenous opioidergic system) and descending projections from supraspinal centers. The dynamic balance between these three

pathways determine the final output generated by secondary neurons, which project upward to the relay centers and ultimately to the cerebral cortex for pain perception. Numerous animal studies suggest that acupuncture leads to analgesia via powerful central pain modulatory mechanisms [89].

Acupuncture also plays a role in the autonomic nervous system (regulating circulation). Some studies have shown some effectiveness in relief angina pectoris. Its beneficial influence has been demonstrated during coronary arteriography. It improves the working capacity of the heart in patients with RA as showed in some controlled studies (by placebo or standard medications, such as glyceryl trinitrate). Dilation of the coronary artery during acupuncture has been shown to be comparable with that observed during intracatheter injection of isosorbide dinitrate [90].

The main points used to treat cardiac disorders are Neiguan (pericardium 6), Tongli (heart 5), Xinshu (urinary bladder 15), Pishu (urinary bladder 20), and Zusanli (stomach 36). The beneficial effect of acupuncture at these points has been demonstrated by serial equilibrium radionuclide angiography. Acupuncture also produces hemorrheological improvement [90]. Ritcher et al. randomized in a crossover study 21 patients to 4 weeks under traditional Chinese acupuncture or placebo tablet treatment. During the acupuncture period, the number of anginal attacks per week was reduced from 10.6 to 6.1 compared with placebo (P less than 0.01); the performance before onset of pain during exercise test also increased significantly. The intensity of pain at maximal workload as well as ST-segment depressions decreased after acupuncture. A life quality questionnaire confirmed improved feeling of well-being [91].

Therapy Related to Central Neuromodulation: Spinal Level

Tricyclic Antidepressants

Low-dose tricyclic antidepressant as imipramine and amitriptyline can be used successfully in some patients with RA, improving symptoms in individuals with abnormal pain perception. It acts via its modulation of norepinephrine uptake, besides its anticholinergic and alpha-agonist effect [92].

Cognitive Behavioral Therapy (CBT)

CBT is often used to help patients manage their symptoms more effectively. It has a sustainable impact on improving quality of life [93]. The focus of sessions is to help patients develop more effective coping strategies. Patients' understanding of angina can be evaluated and misconceptions corrected. For example, to have the notion that stable angina in itself is not life-threating. Patients are educated on the concept that management is not solely limited to pharmacotherapy and revascularization but also involves a fundamental alteration in thought processes involved with symptom recognition and interpretation [94].

Through learning cognitive-behavioral self-management techniques and challenging negative health beliefs, quality of life and psychological well-being can improve substantially [3]. Self-management programs for chronic angina result in fewer episodes of angina per week and reduction in usage of glyceryl trinitrate (GTN) [38].

Lifestyle adaptations that can significantly impact on patients' symptoms (e.g., learning how to pace oneself, setting realistic goals, relaxation exercises), adoption of behaviors to reduce cardiovascular risk (e.g., smoking cessation, weight loss, sleep quality enhancement, and exercise), and adherence to primary and secondary prevention should be emphasized [3].

McGillion et al. conducted a meta-analysis based on seven small RCTs about self-management programs in RA. It showed that psychoeducational intervention may result in significantly less angina episodes, reduced nitrate consumption, and improved quality of life [95].

It has been postulated that the maladaptive cognitive responses to chronic pain may be ameliorated through mindfulness meditation. A standardized program has been shown to have a positive impact on pain management and clinical sequelae in patients with chronic pain [13]. With a growing body of evidence for chronic pain, mindfulness meditation can be an interest possibility in

the management of RA. Although its role in the context of RA is yet to be established [96].

Conclusion

Although the cornerstone of antianginal treatments remains pharmacological, current therapies are limited, and new approaches are needed. Non-pharmacological interventions are therefore required. A multimodal approach is clearly the way for optimal care.

As for other chronic pain states, considering pain pathways as therapeutic targets will broaden the spectrum. Although evidence is not here yet, it seems logical to consider the entire system of afferent and efferent pathways as well as the intrinsic inhibitory mechanisms that target and coordinated therapy. As we move forward, pain is not as only a symptom but also as pathological processing of afferent input which may help "modulate" the incoming information. Mixed therapeutic approaches may be used concurrently to either augment the intrinsic analgesia mechanisms or inhibit excitatory mechanisms.

References

1. Deedwania PC, Carbajal EV. Silent ischemia during daily life is an independent predictor of mortality unstable angina. Circulation. 1990;81:748–56.
2. Mavrocordatos P, Söderström D, de Jongste MJL. Chronic refractory angina. In: Hayek SM, Desai MJ, Shah BJ, Chelimsky TC, editors. Pain medicine: an interdisciplinary case-based approach. 3rd ed. New York: Oxford; 2015. p. 303–21.
3. Cheng K, Sainsbury P, Fisher M, de Silva R. Management of refractory angina pectoris. Eur Cardiol Rev. 2016;11(2):69–76.
4. McGillion M, Rthur HM. Persistent cardiac pain: a burgeoning science requiring a new approach. Can J Cardiol. 2012;28:S1–2.
5. Ianetti GD, Mouraux A. From the neuromatrix to the pain matrix (and back). Exp Brain Res. 2010;205 (1):1–12.
6. Sainsbury PA, Fisher M, de Silva R. Alternative interventions for refractory angina. Heart. 2017;103: 1911–22.
7. Mannheimer C, Camici P, Chester MR, Collins A, de Jongste M, Eliasson T, et al. The problem of chronic refractory angina. Report from the ESC Joint Study Group on the Treatment of Refractory Angina. Eur Heart J. 2002;23:355–70.
8. Cheng K, de Silva R. New advances in the management of refractory angina pectoris. Eur Cardiol Rev. 2018;13(1):70–9.
9. Khan SN, Dutka P. A systematic approach to refractory angina. Curr Opin Support Palliat Care. 2008;2:247–51.
10. Jolicoeur EM, Cartier R, Henry TD, Barsness GW, Bourassa MG, McGillion M, L'Allier PL. Patients with coronary artery disease unsuitable for revascularization: definition, general principles, and a classification. Can J Cardiol. 2012;28(2 Suppl):S50–9.
11. Williams B, Menom M, Satran D, Hayward D, Hodges JS, Burke MN, et al. Patients with coronary artery disease not amenable to traditional revascularization: prevalence and 3-year mortality. Catheter Cardiovasc Interv. 2010;75:886–91.
12. Cosin J, Asín E, Marrugat J, Elousa R, Arós F, de los Reyes M, et al. Prevalence of angina pectoris in Spain. PANES Study group. Eur J Epidemiol. 1999;4:323–30.
13. McGillion M, Arthur HM, Cook A, Carrol SL, Victor JC, L'Allier PL, et al. Management of patients with refractory angina: Canadian Cardiovascular Society/Canadian Pain Society joint guidelines. Can J Cardiol. 2012;28(2 Suppl):S20–41.
14. Reynolds MW, Frame D, Scheye R, et al. A systematic review of the economic burden of chronic angina. Am J Manag Care. 2004;10:S347–57.
15. Schofield PM, Sharples LD, Caine N, Burns S, Tait S, Wistow T, et al. Transmyocardial laser revascularisation in patients with refractory angina: a randomised controlled trial. Lancet. 1999;353:519–24.
16. Kandzari DE, Lam LC, Eisenstein EL, Clapp-Channing FJT, Califf RM, et al. Advanced coronary artery disease: appropriate end points for trials of novel therapies. Am Heart J. 2001;142:843–51.
17. TenVaarwerk IA, Jessurun GA, de Jongste MJL, Andersen C, Mannheimer C, Eliasson T, et al. Clinical outcome of patients treated with spinal cord stimulation for therapeutically refractory angina pectoris. Heart. 1999;82(1):82–8.
18. Dobias M, Michalek P, Neuzil P, Stritesky M, Johnston P. Interventional treatment of pain inrefractory angina. A review. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2014;158(4):518–27.
19. Waltenberger J. Chronic refractory angina pectoris: recent progress and remaining challenges. Eur Heart J. 2017;38(33):2256–558.
20. Pak N, Devcich DA, Johnson MH, Merry AF. Is refractory angina pectoris a form of chronic pain? A comparison of two patient groups receiving spinal cord stimulation therapy. N Z Med J. 2014; 127(1391):52–61.
21. Foreman RD, Chao Q. Neuromodulation of cardiac pain and cerebral vasculature: neural mechanisms. Cleve Clin J Med. 2009;76(Supl 2):575–9.
22. Rosen SD. From heart to brain: the genesis and processing of cardiac pain. Can J Cardiol. 2012; 28:S7–S19.

23. Parry CH. An inquiry into the symptoms and causes of the syncope anginosa, commonly caused angina pectoris. Bath R. Cruttwell; 1799. https://wellcomecollection.org/works/hm4zfbtq, Francis A. Countway Library of Medicine.
24. Warren J. Remarks on angina pectoris. N Engl J Med Surg. 1812;1:1–11.
25. Colbeck EH. Angina pectoris: a criticism and a hypothesis. Lancet. 1903;161:793–5.
26. Lewis T. Pain in muscular ischemia – its relation to anginal pain. Arch Intern Med. 1932;49:713–27.
27. De Decker K, Beese U, Staal MJ, de Jongste MJL. Electrical neuromodulation for patients with cardiac diseases. Neth Heart J. 2013;21:91–4.
28. Foreman RD. Mechanisms of cardiac pain. Annu Rev Physiol. 1999;61:143–67.
29. Lapointe K, Altier C. The role of TRPA in visceral inflammation and pain. Channels. 2011;5(6):525–9.
30. Wu M, Komori N, Qin C, et al. Roles of peripheral terminals of transient receptor potential vanilloid-1 containing sensory fibers in spinal cord stimulation-induced peripheral vasodilatation. Brain Res. 2007; 1156:80–92.
31. Hua F, Ricketts BA, Reifsteck A, et al. Myocardial ischemia induces the release of substance P from cardiac afferent neurons in rat thoracic spinal cord. Am J Physiol Heart Circ Physiol. 2004;286:H1654–64.
32. Meller ST, Gebhart GF. A critical review of the afferent pathways and the potential chemical mediators involved in cardiac pain. Neuroscience. 1992;48(3):501–24.
33. Svorkdal N. Treatment of inoperable coronary disease and refractory angina: spinal stimulators, epidurals, gene therapy, transmyocardial laser, and counterpulsation. Semin Cardiothorac Vasc Anesth. 2004;8(1):43–58. https://doi.org/10.1177/108925320400800109
34. Kasparov S, Teschemacher AG. Altered central catecholaminergic transmission and cardiovascular disease. Exp Physiol. 2008;93:725–40. Rosen SD. From heart to brain: The genesis and processing of cardiac pain. Can J Cardiol. 2012;28:S7–19.
35. Kuo DC, Oravitz JJ, DeGroat WC. Tracing of afferent and efferent pathways in the left inferior cardiac nerve of the cat using retrograde and transganglionic transport of horseradish peroxidase. Brain Res. 1984; 321(1):111–8.
36. Richter A, Caderholm I, Jonasson L, Mucchiano C, Uchto M, Janerot-Sjöberg B. Effect of thoracic epidural analgesia on refractory angina pectoris: long-term home self-treatment. J Cardiothorac Vasc Anesth. 2002;16(6):679–84.
37. Richter, Cederholm I, Fredrikson M, Mucchiano C, Tärff S, Janerot-Sjoberg B. Effect of long-term thoracic epidural analgesia pectoris: a 10-year experience. J Cardiothorac Vasc Anesth. 2012;26(5):822–8.
38. Ali N, Patel P. Non-pharmacological interventions in refractory angina. Heart Res Open J. 2018;5(1):1–7.
39. Chester M, Hammond C, Leach A. Long-term benefits of stellate ganglion block in severe chronic refractory angina. Pain. 2000;87:103–5.
40. Kim ED, Yoo WJ, Kim YN, Park HJ. Ultrasound-guided pulsed radiofrequency treatment of the cervical sympathetic chain for complex regional pain syndrome. Medicine. 2017;96:1–5.
41. Stanton-Hicks M. Complications of sympathetic blocks for extremity pain. Tech Reg Anesth Pain Manag. 2007;11(3):148–51.
42. Foreman RD. Neurological mechanisms of chest pain and cardiac disease. Cleve Clin J Med. 2007; 74(Suppl 1):S30–3.
43. Kreiner M, Okeson JP, Michelis V, Lujambio M, Isberg A. Craniofacial pain as the sole symptom of cardiac ischemia: a prospective multicenter study. J Am Dent Assoc. 2007;138:174–9.
44. Melzack R, Wall P. Pain mechanisms: a new theory. Science. 1965;150:971–99.
45. Prager JP. What does the mechanism of spinal cord stimulation tell us about complex regional pain syndrome? Pain Med. 2010;11(8):1278–83.
46. Task Force Members, Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the task force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J. 2013;34: 2949–3003.
47. Andersen C, Hole P, Oxhoj H. Does pain relief with spinal cord stimulation for angina conceal myocardial infarction? Br Heart J. 1994;71:419–21.
48. West PD, Colquhoun DM. TENS in refractory angina pectoris. Three case reports. Med J Aust. 1993; 158(7):488–9.
49. Shealy CN, Mortimer JT, Reswick JB. Electrical inhibition of pain by stimulation of the dorsal columns: preliminary clinical report. Anesth Analg. 1967;46:489–91.
50. Shealy CN, Taslitz N, Mortimer JT, Becker DP. Electrical inhibition of pain: experimental evaluation. Anesth Analg. 1967;46:299–305.
51. Deer TR, Thomson S, Pope JE, Russo M, Luscombe F, Levy R. International neuromodulation society critical assessment: guideline review of implantable neurostimulation devices. Neuromodulation. 2014;17:678–85.
52. Deer TR, Mekhail N, Provenzano D, et al. The appropriate use of neurostimulation of the spinal cord and peripheral nervous system for the treatment of chronic pain and ischemic diseases: the neuromodulation appropriateness consensus committee. Neuromodulation. 2014;17:515–50.
53. Narouze S, Benzon HT, Provenzano DA, Buvanendran A, De Andres J, Deer TR. Interventional spine and pain procedures in patients on antiplatelet and anticoagulant medications guidelines from the American Society of Regional Anesthesia and Pain Medicine, the European Society of Regional Anaesthesia and Pain Therapy, the American Academy of Pain Medicine, the International Neuromodulation Society, the North American Neuromodulation Society, and the World Institute of Pain. Reg Anesth Pain Med. 2015;40(3):182–212.

54. Smith SC Jr, Benjamin EJ, Bonow RO, Braun LT, Creager MA, Franklin BA, et al. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation. Circulation. 2011;124: 2458–73.
55. Oscarsson A, Gupta A, Fredrikson M, et al. To continue or discontinue aspirin in the perioperative period: a randomized, controlled clinical trial. Br J Anaesth. 2010;104:305–12.
56. Douketis JD, Spyropoulos AC, Kaatz S, Becker RC, Caprini JA, Dunn AS, et al. Perioperative bridging anticoagulation in patients with atrial fibrillation. N Engl J Med. 2015;373:823–33.
57. Rechenmacher SJ, Fang JC. Bridging anticoagulation. J Am Coll Cardiol. 2015;66:1392–403.
58. Sjögren V, Grzymala-Lubranski B, Renlund H, Sevensson PJ, Själander A. Safety and efficacy of bridging with low-molecular-weight heparin during temporary interruptions of warfarin: a register-based cohort study. Clin Appl Thromb Hemost. 2017; 23(8):961–6.
59. Van Kleef M, Staats P, Mekhail N, Huygen F. 24. Chronic refractory angina pectoris. Pain Pract. 2011;11:476–82.
60. Sanderson JE, Ibrahim B, Waterhouse D, Palmer RB. Spinal electrical stimulation for intractable angina - long-term clinical outcome and safety. Eur Heart J. 1994;15:810–4.
61. Zipes DP, Svorkdal N, Berman D, Boortz-Marx R, Henry T, Lerman A, et al. Spinal cord stimulation therapy for patients with refractory angina who are not candidates for revascularization. Neuromodulation. 2012;15:550–8.
62. Mannheimer C, Eliasson T, Augustinsson LE, Blomstrand C, Emanuelsson H, Larsson S, et al. Electrical stimulation versus coronary artery bypass surgery in severe angina pectoris: the ESBY study. Circulation. 1998;97:1157–63.
63. Ibuki T, Hama AT, Wang XT, Pappas GD, Sagen J. Loss of GABA-immunoreactivity in the spinal dorsal horn of rats with peripheral nerve injury and promotion of recovery by adrenal medullary grafts. Neuroscience. 1997;76:845–58.
64. Stiller CO, Cui JG, O'Connor WT, Brodin E, Meyerson BA, Linderoth B. Release of gamma-aminobutyric acid in the dorsal horn and suppression of tactile allodynia by spinal cord stimulation in mononeuropathic rats. Neurosurgery. 1996;39: 367–75.
65. Myerson BA, Linderoth B. Mechanisms of spinal cord stimulation in neuropathic pain. Neurol Res. 2000;22:285–92.
66. Armour JA, Linderoth B, Arora RC, et al. Long-term modulation of the intrinsic cardiac nervous system by spinal cord neurons in normal and ischaemic hearts. Auton Neurosci. 2002;95:71–9.
67. Blair RW, Weber RN, Foreman RD. Responses of thoracic spinothalamic neurons to intracardiac injection of bradykinin in the monkey. Circ Res. 1982;51:83–94.
68. Ammons WS, Girardot MN, Foreman RD. Effects of intracardiac bradykinin on T2–T3 medial spinothalamic cells. Am J Physiol. 1985;249:R147–52.
69. Chandler MJ, Brennan TJ, Garrison DW, Kim KS, Schwartz PJ, Foreman RD. A mechanism of cardiac pain suppression by spinal cord stimulation: implications for patients with angina pectoris. Eur Heart J. 1993;14:96–105.
70. de Jongste MJ, Haustvat R, Hillege H, Lie K. Efficacy of spinal cord stimulation as adjuvant therapy for intractable angina pectoris: a prospective, randomized clinical study. J Am Coll Cardiol. 1994;23:1592–7.
71. Eliasson T, Jern S, Augustinsson L-E, Mann-heimer C. Safety aspects of spinal cord stimula-tion in severe angina pectoris. Coron Artery Dis. 1994;5:845–50.
72. Mannheimer C, Eliasson T, Andersson B, Bergh CH, Augustinsson LE, Emanuelsson H, et al. Effects of spinal cord stimulation in angina pectoris induced by pacing and possible mechanisms of action. BMJ. 1993;307:477–80.
73. Norrsell H, Eliasson T, Mannheimer C, Augustinsson LE, Bergh CA, Andersson B, et al. Effects of pacing-induced myocardial stress and spinal cord stimulation on whole body and cardiac norepinephrine spillover. Eur Heart J. 1997;18:1890–6.
74. González-Darder JM, Canela P, González-Martinez V. High cervical spinal cord stimulation for unstable angina pectoris. Stereotact Funct Neurosurg. 1991;56: 20–7.
75. Kingma JG, Linderoth B, Ardell JL, Armour JA, de Jongste MJ, Foreman RD. Neuromodulation therapy does not influence blood flow distribution or left-ventricular dynamics during acute myocardial ischemia. Auton Neurosci. 2001;91:47–54.
76. Norrsell H, Eliasson T, Albertsson P, Augustinsson LE, Emanuelsson H, Eriksson P, et al. Effects of spinal cord stimulation on coronary blood flow velocity. Coron Artery Dis. 1998;9:273–8.
77. Lopshire JC, Zhou X, Dusa C, Ueyama T, Rosenberger J, Courtney N, et al. Spinal cord stimulation improves ventricular function and reduces ventricular arrhythmias in a canine post-infarction heart failure model. Circulation. 2009;120:286–94.
78. Naar J, Jaye D, Linde C, et al. Spinal cord stimulation in heart failure: effect on disease-associated biomarkers. Eur J Heart Fail. 2017;19:283–6.
79. Howard-Quijano K, Takamiya T, Dale EA, Kipke J, Kubo Y, Grogan T, et al. Spinal cord stimulation reduces ventricular arrhythmias during acute ischemia by attenuation of regional myocardial excitability. Am J Physiol Heart Circ Physiol. 2017;313:H421–31.
80. Naar J, Jaye D, Linde C, et al. Effects of spinal cord stimulation on cardiac sympathetic nerve activity in patients with heart failure. Pacing Clin Electrophysiol. 2017;40:504–13.

81. Qin C, Farber JP, Linderoth B, Shahid A, Foreman RD. Neuromodulation of thoracic intraspinal visceroreceptive transmission by electrical stimulation of spinal dorsal column and somatic afferents in rats. J Pain. 2008;9:71–8.
82. Ding X, Hua F, Sutherly K, Ardell JL, Williams CA. C2 spinal cord stimulation induces dynorphin release from rat T4 spinal cord: potential modulation of myocardial ischemia-sensitive neurons. Am J Physiol Regul Integr Comp Physiol. 2008;295: R1519–28.
83. Foreman RD, Linderoth B. Neural mechanisms of spinal cord stimulation. In: Hamani C, Moro E editors. Emerging horizons in neuromodulation. New frontiers in brain and spine stimulation, vol 107. ScienceDirect; 2012. p. 87–119. International Review of Neurobiology. Academic Press. ISSN 0074-7742, ISBN 9780124047068, https://doi.org/10.1016/B978-0-12-404706-8.00006-1. http://www.sciencedirect.com/science/article/pii/B9780124047068000061.
84. Pak N, Devcich DA, Johnson MH, et al. Is refractory angina pectoris a form of chronic pain? A comparison of two patient groups receiving spinal cord stimulation therapy. N Z Med J. 2014;127(1391):52–61.
85. Pan X, Bao H, Si Y, Xu C, Clen H, Gao X, et al. Spinal cord stimulation for refractory angina pectoris. Clin J Pain. 2017;33(6):543–51.
86. Andréil P, Yu W, Gersbach P, Gillberg L, Pehrsson K, Hardy I. Long-term effects of spinal cord stimulation on angina symptoms and quality of life in patients with refractory angina pectoris. Results from the European Angina Registry Link Study (EARL). Heart. 2010;96:1132–6.
87. Rosen SD, Paulesu E, Fritch CD, et al. Central neural correlates of angina pectoris as a model of visceral pain. Lancet. 1994;344:147–50.
88. Rosen S, Paulesu E, Wise R, Camici P. Central neural contribution to the perception of chest pain in cardiac syndrome X. Heart. 2002;87:513–9.
89. Kong J-T, Schnyer RN, Johnson KA, Mackey S. Understanding central mechanisms of acupuncture analgesia using dynamic quantitative sensory testing: a review. Evid Based Complement Alternat Med. 2013;2013:Article ID 187182, 12 pages https://doi.org/10.1155/2013/187182.
90. The world Health Organization (WHO). Acupuncture: review and analysis of reports on controlled clinical trial. 1996. https://www.iama.edu/OtherArticles/acupuncture_WHO_full_report.pdf
91. Richter A, Herlitz J, Hjalmarson A. Effect of acupuncture in patients with angina pectoris. Eur Heart J. 1991;12(2):175–8.
92. Bartley EJ, Rhudy JL. The influence of pain catastrophizing on experimentally induced emotion and emotional modulation of nociception. J Pain. 2008;9:388–96.
93. Wasson L, Emeruwa O, Davidson KW. Tricyclic antidepressant for refractory angina pain. In: Lemos JA, Omland T, editors. Chronic coronary artery disease: a companion to Braunwald's heart. 1st ed. Philadelphia: Elsevier; 2018. p. 303–21.
94. Lewin RJ, Furze G, Robinson J, et al. A randomized controlled trial of a self-management plan for patients with newly diagnosed angina. Br J Gen Pract. 2002;52:194–6, 199–201.
95. McGillion M, Arthur H, Victor JC, et al. Effectiveness of psychoeducational interventions for improving symptoms, health-related quality of life, and psychological well being in patients with stable angina. Curr Cardiol Rev. 2008;4:1–11.
96. La Cour P, Petersen M. Effects of mindfulness medication on chronic pain: a randomized controlled trial. Pain Med. 2015;16(4):641–52.

Analgesic Control During Acute Pain to Protect Heart Function

39

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Contents

Abstract

Pain activates a general hormonal and inflammatory reaction is a main determinant in post-surgical patient's recovery that may negatively affect the CV system, especially in high-risk patients. Pain can also become chronic, increasing the risk for CV dysfunctions.

Epidural analgesia has various beneficial effects on patient's outcome, including the reduction of stress response and sympathetic activation after surgery. Some data suggest a protective role of EA on CV morbidity, especially on ischemia and dysrhythmias. However, serious CV complications may be expected with neuraxial anesthesia.

Traditional CV drugs such as alpha-2 agonists and beta-blockers display important role in pain treatment. Clonidine may also protect from CV morbidity perioperatively, by improving hemodynamic and sympathetic stabilities and

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*,
https://doi.org/10.1007/978-3-030-28008-6_42

reducing stress response, while beta-blockers display beneficial effects in cardiac surgery but may be deleterious in noncardiac surgery.

On the other hand, common drugs that are effective for analgesia may also improve the risk for CV morbidity. COX-2 inhibitors are contraindicated for chronic use in pain patients; however, they may not be unsafe in the perioperative setting. Available data are sparse to conclude that short-time administration of COX-2 inhibitors in the perioperative setting is associated to higher risk of CV morbidity, except for patients at higher risk for cardiac events. As well, new data suggest that acetaminophen, which is traditionally considered safe in terms of CV risk, may not be as safe as believed. Opioids are safe, but can harm CV homeostasis in specific cases or when associated with other drugs; neuraxial opioids may protect from hemodynamic impairment and positively affect analgesia.

Protecting heart function during pain flares means acting on nociceptive stimulus and on the organic response to pain; the concept should be to stabilize and bring homeostasis to a pain patient's CV system, always balancing beneficial and detrimental effects of any treatment.

Keywords

Postoperative analgesia · Surgical outcome · Surgical stress · Cardiovascular complications · Myocardial infarction · Stroke · NSAIDs · Acetaminophen · Alpha-2 agonists · Beta-blockers

Introduction

Pain has negative impact on the cardiovascular (CV) system and the heart, and complications may occur in acute pain patients, as well as in chronic pain patients, who experience a severe pain flare. Hormonal and metabolic changes immediately follow surgical trauma, with a wide range of endocrine, immunological, and hematologic effects, which are primarily activated by afferent neural inputs from the injured area [1]; tissue injury is responsible for the inflammatory reaction and physiologic stress response observed during the perioperative period [2].

This inflammatory reaction has a major influence on a patient's recovery trajectory since it is involved in a variety of adverse outcomes besides acute pain [3]: fatigue and delirium, cardiovascular and thromboembolic events, metabolic deregulation (i.e., insulin resistance or activation of a catabolic state), and immune impairment [1]. This is the so-called surgical stress syndrome that was therefore identified as the main determinant of perioperative morbidity in various surgical settings [4].

One of the goals of intra- and postoperative analgesia should be to minimize the effect of surgical stress, including the effects on heart and CV function, meaning to stabilize and bring homeostasis to a pain patient's CV system. This is particularly the case in older patients, who display either previously diagnosed or unknown CV disease, or who may be at higher risk of developing it.

Pain Pathways and Nociception

Nociceptors are the specialized sensory receptors responsible for the detection of noxious stimuli, transforming the stimuli into electrical signals, and then conducting them to the central nervous system (CNS). Distributed throughout the body, they can be stimulated by mechanical, thermal, or chemical stimuli. Inflammatory mediators are released from damaged tissue and can activate nociceptors by reducing the activation threshold: this process is called *peripheral sensitization*.

Nociceptors are the free nerve endings of primary afferent Aδ and C fibers; the so-called *nociceptive* fibers that are mainly responsible for acute postoperative pain are as follows:

- Aδ fibers are lightly myelinated. They respond to mechanical and thermal stimuli, carrying rapid, sharp pain. They are responsible for the initial reflex response to acute pain, especially to dynamic stimuli.

- C fibers are unmyelinated and are also the smallest type of primary afferent fiber. Hence, they demonstrate the slowest conduction. C fibers are polymodal, responding to chemical, mechanical, and thermal stimuli, leading to slow, burning pain.

Aδ and C fibers synapse with *secondary afferent neurons* in the dorsal horn of the spinal cord. Primary afferent terminals release a number of excitatory neurotransmitters, and complex interactions occur in the dorsal horn between afferent neurons, interneurons, and descending modulatory pathways. These interactions determine activity of the secondary afferent neurons. The pathways interacting in this complex network may be schematically divided in ascending (excitatory) and inhibitory (spinal and supraspinal) pathways.

Ascending pathways carry nociceptive signals to higher centers in the brain: secondary afferent neurons ascend in the contralateral thalamus; *third order neurons* then ascend to terminate in the somatosensory cortex. However, the experience of pain is complex and subjective, and is affected by factors such as cognition (distraction or catastrophising), mood, beliefs, and genetics. The somatosensory cortex is important for the localization of pain, but projections to the periaqueductal gray matter (PAG) and other important structures in the CNS exist. Imaging techniques such as functional magnetic resonance imaging have demonstrated that a large brain network (often called the "pain matrix") is activated during the acute pain experience [5]: the commonest areas activated include the primary and secondary somatosensory, insular, anterior cingulate and prefrontal cortex, and the thalamus, demonstrating that these areas are all important in both the discriminative and emotional aspects of pain perception.

Meanwhile, other mechanisms act to inhibit pain transmission at the spinal cord level. These mechanisms are characterized by descending inhibition from higher centers. Two of them deserve special attention:

- Gate control theory (GCT) of pain: GCT describes a process of inhibitory pain modulation at the spinal cord level. It explains why when we hurt any part of our body, it feels better when we rub it. By activating Aβ fibers (non-noxious, myelinated fibers responsible of pressure and tactile sensation) with tactile, non-noxious stimuli inhibitory interneurons in the dorsal horn are activated leading to inhibition of pain signals transmitted via C fibers.
- Descending inhibition: the periaqueductal gray in the midbrain and the rostral ventromedial medulla (RVM) are two important areas of the brain involved in descending inhibitory modulation. Descending pathways project to the dorsal horn and inhibit pain transmission. These pathways are monoaminergic, utilizing noradrenaline and serotonin as neurotransmitters, as well as high concentrations of opioid receptors and endogenous opioids.

Pain pathways are also connected with the autonomic system, and such relationship is the main mechanism underlying CV morbidity.

The Autonomic Nervous System (ANS)

The autonomic nervous system is a control system that acts largely unconsciously and regulates body functions such as the heart rate, digestion, respiratory rate, pupillary response, urination, and sexual arousal. Within the brain, the autonomic nervous system is mainly regulated by the hypothalamus.

The autonomic nervous system is divided into the *sympathetic* nervous system and *parasympathetic* nervous system. The sympathetic nervous system is often considered the "fight or flight" system, while the parasympathetic nervous system is considered the "rest and digest" system. In many cases, both of these systems have "opposite" actions where one system activates a physiological response and the other inhibits it.

Both systems coexist in a steady state, which can be altered by both pain and anesthetic techniques. Once pain stimuli reach the CNS, a stress reaction is triggered via the hypothalamic–pituitary–adrenal (HPA) axis; the autonomic system is therefore unbalanced toward a sympathetic activation, mainly mediated by the increased catecholamine's

production. Efferent messages can trigger changes in different parts of the body simultaneously, especially influencing CV function (see below).

As well, neuraxial administration of anesthetic compounds (especially local anesthetics) can block pre- to postganglionic communication in paravertebral ganglia, reducing sympathetic tone and unbalancing the system toward the parasympathetic component.

Both mechanisms underlie a loss-of-balance that may favor some CV side effects and complications.

Effects of Pain on Cardiovascular System

Pain influences the CV system by multiple mechanisms, and also affects other physiologic pathways that are involved with CV morbidity.

Pain causes elevation of *blood pressure* and *pulse rate* by two basic mechanisms that may simultaneously operate [6–11].

The sympathetic (autonomic) nervous system is stimulated by electrical pain signals that reach the central nervous system. Pain activates the hypothalamic–pituitary–adrenal axis: adrenocorticotropin hormone (ACTH) is released centrally, which stimulates the adrenal glands to release adrenalin with subsequent elevation of pulse rate and blood pressure [12]. A hallmark complication of uncontrolled pain is vasoconstriction due to increased sympathetic tone, as well. A step-up in heart rate and blood pressure due to autonomic sympathetic stimulation can be a terminal event in a patient who has existing heart disease or vascular compromise.

Recognition of sympathetic stimulation is a useful clinical tool to guide therapy and diagnose uncontrolled pain. Besides hypertension and tachycardia, sympathetic discharge also produces mydriasis (dilated pupil), diaphoresis (sweating), hyperactive reflexes, nausea, diarrhea, vasoconstriction (cold hands and feet), anorexia, and insomnia.

Protecting the CV system during pain requires to block (or at least reduce) the elevation of heart rate and blood pressure stimulated by pain, especially in patients at risk or with reduced functional reserve.

Persistent Pain May Affect CV Morbidity

Usually acute postoperative pain is supposed to resolve in a variable timespan according to the type of surgery. However, pain can sometime last longer than expected, and configure the so-called persistent postsurgical pain (PPSP). Some patients can experience pain for months or year after surgery, leading to reduction in the quality of life and patient's performance [13].

Persistent postsurgical pain (PPSP) probably relies on a dysfunction of the mechanisms underlying secondary hyperalgesia and sensitization [14]. Physiologic, adaptive, and typically *transient* modifications within the central nervous system (CNS) in response to pain stimulus becomes *permanent*, leading to a persistent state of activation within the CNS, which becomes constantly hyperreactive [13]. At present, the cause of this dysfunction is not known, as well as why only some patients develop PPSP while others do not. However, some patients (even with heart or vascular comorbidities) can develop persistent pain after surgery: the aberrant, neuroanatomic changes that may occur with constant pain appear to be capable of producing *continuous sympathetic discharge* [15–17].

Some intractable pain patients have chronic tachycardia. The apparent cause is continuous sympathetic discharge from rearranged neural anatomy, which imbeds the memory of pain in its circuitry [15–17]. Despite aggressive opioid and other treatments – such as antidepressants or benzodiazepine – the tachycardia may not abate. Severe fibromyalgia patients are particularly prone to this phenomenon.

The relationship between hypertension and chronic pain is still not clear, but pain and cardiovascular modulatory pathways are overlapped and connected [18–20]. Some studies on chronic pain patients have reported a positive correlation between blood pressure and pain sensitivity in chronic pain conditions, as well as an increased

prevalence of hypertension in chronic pain population [21], suggesting chronic pain as a risk factor for hypertension [18]. Recent data further argue in favor of a high blood pressure-pain intensity association, with hypertensive patients being more prone to suffer higher levels of PPSP [22], reflecting a pathologic, maladaptive mechanism in the common adrenergic pathway (pain and blood pressure), leading to hypertension and central sensitization (and persistent pain).

Chronic pain states are known to raise serum lipids [23, 24]. Although the mechanism is somewhat unclear, serum cortisol elevations occur during uncontrolled pain and elevated cortisol is known to elevate serum lipids and glucose. Finally, drugs used for chronic pain management, like NSAIDs or Opioids, are associated with consistent (including CV) side effects.

Since uncontrolled postoperative pain is one of the main risk factors for PPSP, effective acute pain control may reduce CV morbidity besides the immediate perioperative period, by reducing the negative impact of chronic sympathetic discharge and pain medications.

Analgesic Strategies and Their Effect on CV Morbidity

The aim that should be always pursued to protect the CV system from pain is to provide effective analgesia. Effective acute pain treatment should be based on multimodal analgesia (different drugs aimed to different mechanisms that create and maintain pain are used in order to improve effectiveness and reduce side effects). Multiple drugs and techniques are used for this purpose that can be variously combined; however, some of them are worth to be mentioned in the perspective of heart protection (namely regional anesthesia with local anesthetics and alpha-2 agonist clonidine), because they are associated with specific beneficial effects for the CV system. On the other hand, some of them deserve special attention, since they are largely used in clinical practice because of their efficacy, but also display potential side effects on heart function and CV morbidity (NSAIDs and acetaminophen, beta-blockers).

Regional Anesthesia and Local Anesthetics

Regional anesthesia (RA) involve segmental block of a specific body region according to the source of pain. RA can be performed at the neuraxis, by administering a mixture of local anesthetics (LA) (and eventually adjuvants) in the epidural space (epidural analgesia) or in the subarachnoid space within the CSF (spinal anesthesia). Nevertheless, anesthetic mixture can also be placed on specific points along peripheral nerve's course, configuring the so-called peripheral nerve blocks. Both strategies can be prolonged over time with catheters insertion, allowing continuous regional anesthesia.

Regional anesthesia is considered as the "gold-standard" analgesic technique in many surgical settings, due to the ability of providing strong blockade of pain signals and leading to a wide range of benefits. RA globally preserves the homeostasis comparing to other analgesic approaches, and is a major item in "fast-track" methodologies to reduce perioperative complications and enhance patients' recovery after surgery [25]; many data suggest that RA is generally associated with improved short- and long-term outcome in patients receiving surgery [26, 27].

RA can modulate the stress response mainly by: (1) the direct anti-inflammatory effect of local anesthetic and (2) the effective block of neural afferents and sympathetic activation.

Local anesthetics (LA) are a major component of RA techniques and display some direct and indirect anti-inflammatory properties. Interruption of nociceptive transmission by sodium channel blocking reduces "neurogenic inflammation" (i.e., the release of inflammatory mediators by stimulated neurons); the interruption of neurogenic inflammation modulates both peripheral and central sensitizations processes as local neurogenic inflammation contributes to the general inflammatory response [28].

Neuraxial anesthesia provides an effective block of neural afferents and reduces sympathetic activation in response to pain; further, the administration of LA in the spinal canal at thoracic level provides sympathetic block directly on the

thoracic sympathetic trunk. Sympathetic blockade and lower activation in response to pain by neuraxial anesthesia reduces myocardial oxygen demand and improves myocardial oxygen supply by coronary dilatation [29–31]; thoracic epidural analgesia (TEA) also directly reduces pulmonary vascular resistance in pulmonary hypertension [32]. Recent data on chronic patients with dilated cardiomyopathy show that epidural infusion (when combined with conventional medical treatment) may reverse myocardial fibrosis and improve cardiac function [33].

Available data on the protective effect of regional anesthesia on CV morbidity are sparse and far from giving conclusive evidence. However, some initial suggestions of benefits coming from the adoption of RA are available, especially regarding the occurrence of myocardial ischemia.

Some data show that cardiac morbidity was generally lower among patients treated with epidural analgesia. A recent meta-analysis, including 11 randomized studies and involving 1173 patients [34], showed a significant reduction in perioperative myocardial infarction in patients treated with thoracic epidural analgesia in comparison with control groups. A Cochrane study in 2016 from a review of 15 clinical trials concluded that epidural analgesia significantly reduces the number of people who suffer heart damage, and improves other important perioperative outcomes, including time to return of unassisted respiration, gastrointestinal bleeding, and ICU length of stay, but without reducing death rates at 30 days [35]. When considering ischemic patients undergoing elective major abdominal cancer surgery, Mohamed et al. concluded that lumbar epidural anesthesia combined with general anesthesia provided better pain relief, but ischemic cardiac events were similar in both groups [36].

In agreement with previous data, a very recent randomized controlled trial [36] added additional evidence that perioperative thoracic epidural analgesia reduces cardiac events in patients suffering from coronary artery disease and subjected to major surgery; a significant reduction in overall adverse cardiac events (myocardial injury, arrhythmias, angina, heart failure, and nonfatal cardiac arrest) was observed in patients receiving epidural analgesia, and there was a significant reduction in intraoperative mean arterial pressure and heart rate.

Dysrhythmias are also common complications in the immediate postoperative period, even more common after upper abdominal and thoracic surgeries. The occurrence of arrhythmias can be explained by many factors such as preexisting cardiac pathology, intraoperative events, and arrhythmia triggers. Autonomic imbalance after operation has been implicated as a possible trigger, and is thought to be characterized by increased sympathetic tone and lower vagal tone [37].

The first randomized evaluation of the impact of perioperative epidural analgesia on outcome in a large series of 400 patients with normal ventricular function undergoing coronary artery bypass grafting showed a reduction in the incidence of supraventricular arrhythmias [38]. In this study, epidural analgesia resulted in a better optimization of heart rate and mean arterial pressure during the intra- and postoperative period in comparison with intravenous anesthesia. This result showed the advantage of epidural analgesia by means of decreased heart rate and improved coronary blood flow.

However, results from further trials have provided conflicting evidence: methodological bias or discrepancies between studies may account for nonuniform results.

Kessler et al. compared heart rate either with or without TEA during coronary artery bypass grafting performed on a beating heart and reported that HR with TEA was lower than preoperatively, during sternotomy and anastomosis. In that study, esmolol was administered in the group that received GA because of a high HR.

Kopeika et al. showed TEA provided superior postoperative pain control than intramuscular opioid administration after pulmonary resection, and found only a “tendency” of less frequent postoperative atrial fibrillation among those who received TEA [39].

Oka et al. compared TEA with bupivacaine and TEA with morphine for postoperative analgesia for pulmonary resection and found that occurrence of atrial fibrillation and supraventricular tachycardia within 3 days after surgery was less

for TEA with bupivacaine [40]. This should reinforce the concept of high sympathetic block as the major protective mechanism from arrhythmias, but this study was biased by the fact that patients in the bupivacaine group received a higher dose of indomethacin than those in the morphine group.

In a recent study, the occurrence of atrial fibrillation, atrial flutter, and supraventricular tachycardia increased after the TEA catheter was removed; however, TEA was continued only until 2–3 days after surgery, which is the time of frequent occurrence of atrial arrhythmia [41], and the occurrence of atrial arrhythmia after discontinuation of TEA could be just coincidence rather than a causal relationship.

Other studies have even displayed conflicting evidence, suggesting that TEA may be not protective (or even harmful). Jiang et al. compared the incidence of supraventricular arrhythmia within 48 h after pulmonary resection between patients having TEA with a combination of local anesthetic and opioid for intra- and postoperative analgesia and those who received intravenous patient-controlled analgesia with opioids. These authors observed significantly less supraventricular tachycardia and a tendency of less frequent atrial fibrillation among patients who received intravenous patient-controlled analgesia [42]. Ahn et al. compared intravenous patient-controlled analgesia with fentanyl plus ketorolac vs TEA for postoperative analgesia among esophageal surgery patients and found that the occurrence of arrhythmia until 3 days after surgery was similar between the groups [38]. Conversely, TEA was not associated with reduced occurrence of postoperative atrial arrhythmia in other studies [43]. Apart from differences in the populations and the specific analgesic regimens studied, differences in the way arrhythmia was diagnosed, duration of observation after the surgery, and use of nonsteroidal anti-inflammatory drugs, which are potentially protective against atrial arrhythmia, could be possible explanations of conflicting outcomes [43].

Despite the possible beneficial outcomes, immediate CV side effects are related with the use of neuraxial anesthesia. The preganglionic neurons of the sympathetic system originate from the thoracolumbar region of the spinal cord (T1 to L2–L3), and travel to paravertebral ganglia, where they synapse with a postganglionic neuron. The physiologic effects of neuraxial anesthesia are the result of blockade of sympathetic component, the compensatory reflexes, and of unopposed parasympathetic tone.

Hypotension occurs as a result of a decrease in systemic vascular resistance and peripheral blood pooling with decreased venous return to the heart, or both. In addition, block of cardio-accelerator nerve fibers (originating from T1 to T4 nerve roots) with high subarachnoid block can contribute to hypotension through a decrease in heart rate and cardiac output. Mechanisms for bradycardia are direct (blockade of sympathetic cardio-accelerator fibers) and indirect. Indirect mechanisms include decreased output of the myocardial pacemaker cells due to decrease in venous return, stimulation of low-pressure baroreceptors in the right atrium and vena cava, and stimulation of mechanoreceptors in the left ventricle resulting in bradycardia (paradoxical Bezold-Jarisch reflex). Hypotension and bradycardia are frequent during neuraxial anesthesia and can eventually evolve in major events such cardiac arrest. Some patient populations are at higher risk, because of either higher sensibility to local anesthetics/high spinal block or because of coexisting comorbidities leading to a dramatic decrease in cardiac output (elderly, pregnant women, hypovolemic patients, patients with major mitral or aortic stenosis, pulmonary hypertension, low cardiac output, and/or hypertrophic left ventricle).

Peripheral nerve blocks are a valuable alternative for patients at risk of complications with neuraxial anesthesia: since they are performed away from the neuraxis, the impact on sympathetic tone and CV homeostasis is far less pronounced, except in case of rare complications associated with specific nerve blocks. Such complications are mainly related to the migration of local anesthetics to the neuraxis or to local anesthetic systemic toxicity (LAST).

Epidural or intrathecal spread during lumbar plexus blocks is often observed but is rarely clinically significant; however, unintended neuraxial block can lead to cardiac or respiratory arrest

[44]. This is one of the most feared complications for anesthesiologists; since it is unpredictable and there are no validated strategies to avoid it, alternative techniques are often used and suspicion is always maintained when a lumbar plexus block is performed [45].

LAST results from intravascular injection or from massive reabsorption of local anesthetics. It has variable presentation, but encompasses neurologic symptoms (tinnitus, lightheadness, perioral numbness, peripheral tremors up to seizures in severe cases) and/or CV symptoms (arrhythmias up to ventricular fibrillation and cardiac arrest). Specific guidelines are available for treatment, while specific approaches are adopted to avoid LAST (ultrasound guidance, use of lower doses of local anesthetics, intermittent aspiration before injection, epinephrine as marker of early intravascular injection) [46].

Except for these rare events, the impact of hypotension, bradycardia, or major adverse CV complications is reduced with the use of peripheral techniques.

Clonidine and Beta-Blockers

Clonidine is a centrally acting imidazolin α2-adrenergic agonist, analog of norepinephrine. The presynaptic stimulation of α2-receptors is coupled via G-protein to several effectors including inhibition of adenylate cyclase and effects on potassium and calcium channels that finally restricts the release of norepinephrine in the central nervous system. This drug has been largely studied in anesthesia, suggesting a place for analgesia, antiemesis, bleeding reduction, induction time reduction, hemodynamic and hormonal stability, reduction of oxygen consumption, renal protection, anesthetics-sparing effect, anxiolysis, sedation, antishivering, recovery time reduction, and myocardial protection.

Evidence from metanalysis on 57 studies and nearly 15,000 patients shows that clonidine has several protective effects on heart function in the perioperative period: generally speaking, clonidine improves hemodynamic and sympathetic stabilities [47].

Clonidine is a well-known analgesic, which helps reducing postoperative pain; furthermore, clonidine attenuates blood pressure and heart rate increase after intubation and insufflation, that are key moments in anesthesia and during laparoscopic surgery (which is increasingly adopted in clinical practice): sympathetic activation may be deleterious, and heart rate and blood pressure stability is helpful, especially in patients with previous CV morbidity and higher risk for complications when CV homeostasis is not carefully maintained. Despite result being less clear, some studies also claim a role for clonidine in reducing epinephrine release and stress response after surgical manipulation, as well as oxygen consumption, with the cumulative result to reduce perioperative metabolic demands [47]. Clonidine can also be used as an adjuvant to local anesthetics in neuraxial anesthesia. Epidural clonidine demonstrates greater anti-inflammatory effects in terms of reduction in systemic pro-inflammatory cytokine expression than local anesthetics [48, 49].

A recent RCT has questioned the role of clonidine in reducing myocardial infarction [50], but data on this specific outcome are sparse and methodological discrepancies hinder any firm conclusion on the topic [47].

In contrast, it is important to keep in mind that nonfatal bradycardia/nonfatal cardiac arrest and hypotension have been described with the use of clonidine. Despite no report of sequels, it should be assumed that not enough data concerning bradycardia/nonfatal cardiac arrest are available to formally conclude about their safety. However, clonidine-induced hypotension has not been specifically described to be associated with adverse events linked to hypotension (worse renal or cardiac outcomes). Even if not formally demonstrated by available large-scale data, hypotension due to other factors than clonidine (e.g., hypovolemic shock) is problematic, but not necessarily if specifically due to clonidine, and clonidine can be considered as safe. Further, findings are compatible with the belief that α2-adrenergic agonists depress baseline sympathetic activity but that clonidine leaves, at least partially, unaffected the response to environmental or circulatory challenges such as hypotension [51].

Of course, clonidine should be used carefully used in the elderly patient [52], as in predicted hypotensive response as after tourniquet deflation [53], and considering the different impact on heart rate and blood pressure according to the route of administration (being more likely associated to hypotension and bradycardia when injected in the neuraxis rather than systemically) [54]. Beta-blockers are drugs that attenuate stress response, as well, which results in reduced heart rate and blood pressure. These effects are desirable to fight the stress response, but if pronounced, they may cause very low blood pressure, a very low pulse, and ultimately stroke or death.

Beta-blockers are extremely effective as analgesics: a systematic review and meta-analysis investigating the effect of beta-adrenergic antagonist on perioperative pain in RCTs showed that perioperative esmolol and propranolol decrease postoperative pain and analgesic consumption when given as an adjuvant to general anesthesia. Adverse effects were rarely reported in RCTs, but notably, most of them were cardiovascular alterations [55].

A large Cochrane review on 88 randomized controlled trials with 19,161 participants recently gave more detailed clues on the risk/benefit profile of this class of drugs. Data show that perioperative application of beta-blockers still plays a pivotal role in cardiac surgery, as they can substantially reduce the burden of supraventricular and ventricular arrhythmias in the postoperative period. Their influence on mortality, myocardial infarction, stroke, congestive heart failure, hypotension, and bradycardia in this setting remains unclear [56].

However, evidence shows opposite relationship between beta-blockers and CV outcomes in noncardiac surgery, namely an association of beta-blockers with increased all-cause mortality. Data from trials further suggest an increase in stroke rate. As the quality of evidence is still low to moderate, more evidence is needed before a definitive conclusion can be drawn; however, the beneficial reduction in supraventricular arrhythmias and myocardial infarction in noncardiac surgery seems to be offset by the potential increase in mortality and stroke [56].

NSAIDs and Acetaminophen

NSAIDs and Acetaminophen/Paracetamol are extensively used in clinical practice, and are a cornerstone for postoperative analgesia in nearly all surgical setting. Despite the undisputed efficacy, all of them have potential side effect that may limit their use in some clinical situations. Side effects are a concern both when they are administered chronically or for few days in the immediate postoperative period.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

All of NSAIDs' side effects are associated with the intrinsic ability of this class of drugs of blocking cyclooxygenase activity: Cyclooxygenase-1 (COX-1 – innate) and Cyclooxygenase-2 (COX-2 – induced by surgical stimulus).

COX-1 and COX-2 inhibitors are both effective as analgesics, but COX-2 selective inhibitors have been introduced because of their higher selectivity on trauma-induced COX, with reduced platelet impairment and being less aggressive on gastric mucosae.

Traditionally, NSAIDs main side effects were considered to be gastric toxicity, bleeding, and kidney failure. However, new interest has emerged in the last 10 years on the potential CV risk associated with NSAIDs, especially with selective COX-2 inhibitors.

Several explanations of CV toxicity have been proposed. The more likely theory is that the inhibition of COX-1 and COX-2 induces an unbalance between thromboxane (TXA) and the prostaglandin (PGI2) production: platelet TXA production is not inhibited if COX-1 activity is not completely blocked, while the production of endothelial PGI2 is suppressed by COX-2 inhibition. PGI2 is a powerful inhibitor of platelets aggregation and a potent vasodilator, while thromboxane is a potent vasoconstrictor and induce platelet aggregation.

Cardiovascular side effects have however been reported after a long period of selective COX-2 inhibitors, but it is not clear if the administration for few days can be harmful, as well.

Furberg et al. [57] evaluated the incidence of cerebrovascular accidents in patients undergoing

coronary artery bypass graft (CABG) and showed a three-fold higher risk of cardiovascular events compared with placebo [57]. These data have, however, not been confirmed in a recent study: 1,065 patients undergoing thoracic and cardiovascular surgery were treated with different nonselective NSAIDs, particularly diclofenac, ketorolac, and indomethacin. No difference in side effects was found between NSAIDs-treated patients and the control group [58]. The short duration of drug administration and low risk patients may have influenced the lack of cardiovascular and renal side effects. On the other hand, in a recent cohort study that has enrolled 83,677 patients the use of NSAIDs in patients with prior myocardial infarct resulted in an increased risk of death and recurrent myocardial infarction also if the drugs are used for short time [59]. Taken together, these data may suggest that the higher risk of CV toxicity may be limited to high-risk patients, i.e., patients with prior CV morbidity.

However, the current idea that a great difference in CV risk exists between combined NSAIDs (COX-1 + COX-2) and COX-2 selective inhibitors should be revisited. Nonselective NSAIDs inhibit both COX-1 and COX-2 enzymes; selective COX-2 inhibitors still act on both COX isoforms, but producing lower effect on COX-1. For this reason, difference in cardiovascular risk between the two drugs is more hypothetical than real.

As abovementioned, the CV adverse profile is related with the degree of TXA synthesis and PGI inhibition: a reduction in TXA production greater than 95% produces cardiovascular protection as low-dose aspirin does. The incomplete block of TXA production provided by COX-2 selective inhibitors, as well as by many nonselective NSAIDs does not reduce TXA production in significant percentage, predisposing to CV complications, regardless of the type of NSAIDs and their selectivity [60]. The increase in CV risk not only depends on the TXA/PGI2 inhibition ratio, but also on other mechanisms (including blood pressure elevation and COX-independent mechanisms) [61]; available clinical data indicate that the entire substance group of NSAIDs may cause a little but increased risk for cardiovascular/thromboembolic events [62], independently on COX-1/-2 selectivity.

Most of data about toxicity are drawn from chronic patients, which are administered with NSAIDs for a long period of time. Projecting the same results on acute pain patients, i.e., those receiving NSAIDs for a brief timespan (days) after surgery, may lead to wrong conclusions. Actually, few studies exist on NSAIDs-associated CV risk in patients treated for postoperative pain according to COX selectivity.

The administration of paracoxib and valdecoxib in the immediate postoperative period of coronary surgery increased the risk of cardiovascular events (risk ratio 3.7 [63]). However, the nonselective NSAIDs ketorolac, when administered in the postoperative period of cardiac surgery has not showed an increase of cardiovascular risk [64]. As for previous data, COX-2 selective inhibitors only showed to increase CV side effects in high-risk patients with previous CV comorbidities. No significant increase in the incidence of postoperative myocardial infarction was retrieved in more than 10,000 patients undergoing total joint replacement: 0.8% for patients that received meloxicam or ketorolac, 1.3% for patients that received celecoxib, and 1.8% in subjects who does not receive NSAIDs [65].

Data on postoperative patients are somewhat conflicting; however, given the best available evidence, the European Medicine Agency Committee for Medicinal Products for Human Use decided that COXIBs but not nonselective inhibitors should be contraindicated in patients with cardiovascular disease [66]. The possible increase of cardiovascular adverse events has been receipted by the Food and Drug Administration that stated that, in the characteristics of the drugs, a boxed warning about the risk of cardiovascular disease is reported.

Noteworthy, most of data are transferred from the chronic pain population to the completely different setting of acute pain; further, when considering postoperative pain patients, a distinction should be made for noncardiac and cardiac surgery (where the risk for CV major events is probably mostly not related to the type of patient and surgery, but rather to NSAIDs administration).

Currently, despite unclear evidence existing on NSAIDs CV toxicity for short-time administration (perioperatively), the most rational approach for acute pain seems to base the choice of NSAIDs on the type of patient and surgery that we are dealing with. Patients with no CV comorbidities can be treated with both selective and non-selective drugs; when gastric toxicity/bleeding are feared, COX-2 inhibitors are probably the better choice, while it should be avoided in patients with higher risk for cardiac events (due to the type of surgery or to patient's medical history comorbidities) [67, 68].

Acetaminophen/Paracetamol

Paracetamol is the most widely used over-the-counter and prescription analgesic worldwide [69]. It is the first step on the WHO pain ladder and is currently recommended as first-line pharmacological therapy by a variety of international guidelines for a multitude of acute and chronic painful conditions, including multimodal analgesia for mild to severe postoperative pain. Irrespective of its efficacy, paracetamol is generally considered to be safe than other commonly used analgesics such as nonsteroidal anti-inflammatory drugs [70, 71].

However, the analgesic benefit of paracetamol has recently been called into question in the management of chronic painful condition (like osteoarthritis) [72], and a recent systematic review of studies investigating the association between paracetamol and major adverse events in the general adult population gave clues on the unexpected paracetamol-associated CV toxicity [73]. Comparing paracetamol use versus no use, a dose–response and an increased relative rate of mortality was reported in patients receiving paracetamol [74, 75]. Further, one study reporting cardiovascular adverse events showed an increased risk ratio of all cardiovascular adverse events (confirmed or probable nonfatal myocardial infarction, nonfatal stroke, fatal coronary heart disease, or fatal stroke) [76].

While many limitations exist to the interpretation of these results that are important to consider, the striking trend of dose–response is a consistent finding across multiple outcomes and studies. There is also evidence from the case–control literature supporting the dose–response seen in the abovementioned review, and a similar toxicity profile is demonstrated in systematic reviews of short-term RCTs [72]. However, these data come from the chronic pain population; evidence from the available literature show that adverse events associated with paracetamol in the postoperative period (in patients with short-time administration) are trivial [77].

Despite the true risk of paracetamol, prescription may be higher than that currently perceived in the clinical community for chronic pain patients; it is still a cornerstone in postoperative analgesia and should still be considered as the safest available drug in the postsurgical setting.

Opioids

Opioids bind to opioid-specific receptors that are located in the central nervous system (CNS). However, the same opioid receptors are available in many other organs, including cardiovascular tissue [78]. Opioid receptors are linked to G proteins, and activation of the opioid receptor leads to membrane hyperpolarization. Opioids may differently impact the CV system when given acutely rather than chronically [79]; in the acute and intraoperative setting, opioids can are a mainstay for surgical anesthesia and for postoperative analgesia, but they are also responsible for important side effects; some of them (nausea, vomiting, pruritus, ileus, respiratory depression) can prolong and complicate perioperative recovery. In some cases, paradoxical opioid-related hyperalgesia (associated to intraoperative or preoperative opioid use) can increase postoperative pain and analgesic consumption [80]; tolerance is a major concern, as well, and opioids in the perioperative period seem to predispose to chronic abuse [81, 82]. Opioid abuse in the pre- and perioperative period has generally been linked to poorer outcomes and higher rate of readmission [83, 84].

Opioids can also cause CV damage. Opioids administered as part of an anesthetic are thought to have modest direct effects on the heart, especially as an isolated drug. When administered

alone, opioids (other than high doses of meperidine) do not depress cardiac contractility. Intravenous fentanyl leads to minimal changes to cardiovascular function, heart rate, and blood pressure [85]. Nevertheless, while cardiac contractility may not be affected, opioids can impact other aspects of the cardiovascular system: several opioids can cause vagus nerve-mediated bradycardia. In addition, acute administration of opioids can lead to vasodilation and decreased sympathetic tone. Tramadol administration can lead to serotonin syndrome [86], which can lead to cardiac arrhythmias; cardiac side effects may range from agitation and palpitations to rhythm abnormalities, conduction defects, and cardiac arrest [87]. Morphine, hydromorphone, hydrocodone, and meperidine can lead to histamine release, and as a result can cause significant decreases in systemic vascular resistance and blood pressure, which may require the administration of vasopressors and intravenous fluids. However, opioids are rarely the sole anesthetic agent used, and when combined with other medications they are associated with significant changes in cardiac function. When administered with benzodiazepines, opioids can significantly decrease cardiac output, and significant CV effects can be observed when opioids are administered with inhaled anesthetics.

Opioids have been found to have minimal effect on coronary vessel vasomotor tone. Studies on the influence of opioids on perioperative ischemia have suggested that they can mimic ischemic preconditioning, reducing infarct size. Mechanisms are not completely understood, and opioid-based anesthesia has not been shown to reduce intraoperative ischemia, postoperative myocardial infarction, or death [88].

Finally, opioids can be given into the neuraxis, either by epidural and intrathecal route. In these cases, they are administered as adjuvants to local anesthetics: morphine, fentanyl, and sufentanyl have all demonstrated to prolong sensitive block and postoperative analgesia comparing to local anesthetics alone. Neuraxial opioids reduce the amount of anesthetics required for surgical anesthesia, and have lower effects on the sympathetic tone than local anesthetics: neuraxial opioids are a cornerstone to reduce hemodynamic impairment associated with neuraxial techniques, reducing the risk for major CV events (especially in high-risk patients). Concerns exist on other side effects (nausea, vomiting, pruritus, sedation), but neuraxial opioids are more protective than harmful on the CV homeostasis.

Conclusion

Pain has negative impact on the cardiovascular (CV) system and the heart because it activates a systemic stress response with generalized sympathetic activation. Unbalancing the homeostasis of the CV system may lead to major complications, especially in patients with previous comorbidities or risk factors.

Several drugs and techniques are available that can be combined in multimodal strategies to achieve optimal pain control. Some of them display specific advantages, while others may be associated with adverse outcomes. In some cases, evidence of risk/benefits is stronger while in other case available data should be interpreted with caution (because they are extrapolated from chronic pain patients and no distinction is made according to the type of surgery).

However, further studies are recommended because current data suggest, at least, that even short-term administration of specific drugs, as well as the perioperative adoption of specific analgesic strategies may influence CV morbidity, especially in high-risk situations.

References

1. Desborough JP. The stress response to trauma and surgery. Br J Anaesth. 2000;85(1):109–17.
2. Nicholson G, Hall GM. Effects of anaesthesia on the inflammatory response to injury. Curr Opin Anaesthesiol. 2011;24(4):370–4.
3. Buvanendran A, Kroin JS, Berger RA, Hallab NJ, Saha C, Negrescu C, et al. Upregulation of prostaglandin E2 and interleukins in the central nervous system and peripheral tissue during and after surgery in humans. Anesthesiology. 2006;104(3):403–10.
4. Kehlet H, Wilmore DW. Multimodal strategies to improve surgical outcome. Am J Surg. 2002;183(6):630–41.

5. Tracey I. Imaging pain. Br J Anaesth. 2008;101(1):32–9.
6. Drummond PD. The effect of pain on changes in heart rate during the Valsalva manoeuvre. Clin Auton Res. 2003;13(5):316–20.
7. Heller PH, Perry F, Naifeh K, Gordon NC, Wachter-Shikura N, Levine J. Cardiovascular autonomic response during preoperative stress and postoperative pain. Pain. 1984;18(1):33–40.
8. Lewis KS, Whipple JK, Michael KA, Quebbeman EJ. Effect of analgesic treatment on the physiological consequences of acute pain. Am J Hosp Pharm. 1994;51(12):1539–54.
9. Moltner A, Holzl R, Strian F. Heart rate changes as an autonomic component of the pain response. Pain. 1990;43(1):81–9.
10. Nyklicek I, Vingerhoets AJ, Van Heck GL. Hypertension and pain sensitivity: effects of gender and cardiovascular reactivity. Biol Psychol. 1999;50(2):127–42.
11. Tousignant-Laflamme Y, Rainville P, Marchand S. Establishing a link between heart rate and pain in healthy subjects: a gender effect. J Pain. 2005;6(6):341–7.
12. Greisen J, Grofte T, Hansen PO, Jensen TS, Vilstrup H. Acute non-traumatic pain increases the hepatic amino- to urea-N conversion in normal man. J Hepatol. 1999;31(4):647–55.
13. Grosu I, de Kock M. New concepts in acute pain management: strategies to prevent chronic postsurgical pain, opioid-induced hyperalgesia, and outcome measures. Anesthesiol Clin. 2011;29(2):311–27.
14. Eisenach JC. Preventing chronic pain after surgery: who, how, and when? Reg Anesth Pain Med. 2006;31(1):1–3.
15. Apkarian AV, Sosa Y, Sonty S, Levy RM, Harden RN, Parrish TB, et al. Chronic back pain is associated with decreased prefrontal and thalamic gray matter density. J Neurosci Off J Soc Neurosci. 2004;24(46):10410–5.
16. Teutsch S, Herken W, Bingel U, Schoell E, May A. Changes in brain gray matter due to repetitive painful stimulation. NeuroImage. 2008;42(2):845–9.
17. Tracey I, Bushnell MC. How neuroimaging studies have challenged us to rethink: is chronic pain a disease? J Pain. 2009;10(11):1113–20.
18. Bruehl S, Chung OY, Jirjis JN, Biridepalli S. Prevalence of clinical hypertension in patients with chronic pain compared to nonpain general medical patients. Clin J Pain. 2005;21(2):147–53.
19. Bruehl S, Chung OY, Ward P, Johnson B, McCubbin JA. The relationship between resting blood pressure and acute pain sensitivity in healthy normotensives and chronic back pain sufferers: the effects of opioid blockade. Pain. 2002;100(1–2):191–201.
20. Maixner W, Fillingim R, Kincaid S, Sigurdsson A, Harris MB. Relationship between pain sensitivity and resting arterial blood pressure in patients with painful temporomandibular disorders. Psychosom Med. 1997;59(5):503–11.
21. Chung OY, Bruehl S, Diedrich L, Diedrich A, Chont M, Robertson D. Baroreflex sensitivity associated hypoalgesia in healthy states is altered by chronic pain. Pain. 2008;138(1):87–97.
22. Bugada D, Lavand'homme P, Ambrosoli AL, Cappelleri G, Saccani Jotti GM, Meschi T, et al. Effect of preoperative inflammatory status and comorbidities on pain resolution and persistent postsurgical pain after inguinal hernia repair. Mediat Inflamm. 2016;2016:5830347.
23. Asanuma Y, Oeser A, Shintani AK, Turner E, Olsen N, Fazio S, et al. Premature coronary-artery atherosclerosis in systemic lupus erythematosus. N Engl J Med. 2003;349(25):2407–15.
24. Ozgurtas T, Alaca R, Gulec M, Kutluay T. Do spinal cord injuries adversely affect serum lipoprotein profiles? Mil Med. 2003;168(7):545–7.
25. Carli F, Kehlet H, Baldini G, Steel A, McRae K, Slinger P, et al. Evidence basis for regional anesthesia in multidisciplinary fast-track surgical care pathways. Reg Anesth Pain Med. 2011;36(1):63–72.
26. Bugada D, Allegri M, Gemma M, Ambrosoli AL, Gazzerro G, Chiumiento F, Dongu D, Nobili F, Fanelli G, Ferrua P, Berruto M, Cappelleri G. Effects of anaesthesia and analgesia on long-term outcome after total knee replacement: a prospective, observational, multicentre study. Eur J Anaesthesiol. 2017;34(10):665–72.
27. Bugada D, Ghisi D, Mariano ER. Continuous regional anesthesia: a review of perioperative outcome benefits. Minerva Anestesiol. 2017;83(10):1089–100.
28. Pham-Marcou TA, Gentili M, Asehnoune K, Fletcher D, Mazoit JX. Effect of neurolytic nerve block on systemic carrageenan-induced inflammatory response in mice. Br J Anaesth. 2005;95(2):243–6.
29. Blomberg S, Emanuelsson H, Kvist H, Lamm C, Ponten J, Waagstein F, et al. Effects of thoracic epidural anesthesia on coronary arteries and arterioles in patients with coronary artery disease. Anesthesiology. 1990;73(5):840–7.
30. Blomberg S, Emanuelsson H, Ricksten SE. Thoracic epidural anesthesia and central hemodynamics in patients with unstable angina pectoris. Anesth Analg. 1989;69(5):558–62.
31. Kirno K, Friberg P, Grzegorczyk A, Milocco I, Ricksten SE, Lundin S. Thoracic epidural anesthesia during coronary artery bypass surgery: effects on cardiac sympathetic activity, myocardial blood flow and metabolism, and central hemodynamics. Anesth Analg. 1994;79(6):1075–81.
32. Armstrong P. Thoracic epidural anaesthesia and primary pulmonary hypertension. Anaesthesia. 1992;47(6):496–9.
33. Ma D, Liu L, Zhao H, Zhang R, Yun F, Li L, et al. Thoracic epidural anesthesia reversed myocardial fibrosis in patients with heart failure caused by dilated cardiomyopathy. J Cardiothorac Vasc Anesth. 2017;31(5):1672–5.
34. Beattie WS, Badner NH, Choi P. Epidural analgesia reduces postoperative myocardial infarction: a meta-analysis. Anesth Analg. 2001;93(4):853–8.

35. Guay J, Kopp S. Epidural pain relief versus systemic opioid-based pain relief for abdominal aortic surgery. Cochrane Database Syst Rev. 2016;(1):Cd005059.
36. Mohamad MF, Mohammad MA, Hetta DF, Ahmed EH, Obiedallah AA, Elzohry AAM. Thoracic epidural analgesia reduces myocardial injury in ischemic patients undergoing major abdominal cancer surgery. J Pain Res. 2017;10:887–95.
37. Groban L, Dolinski SY, Zvara DA, Oaks T. Thoracic epidural analgesia: its role in postthoracotomy atrial arrhythmias. J Cardiothorac Vasc Anesth. 2000; 14(6):662–5.
38. Ahn HJ, Sim WS, Shim YM, Kim JA. Thoracic epidural anesthesia does not improve the incidence of arrhythmias after transthoracic esophagectomy. Eur J Cardiothorac Surg. 2005;28(1):19–21.
39. Kopeika U, Taivans I, Udre S, Jakusenko N, Strazda G, Mihelsons M. Effects of the prolonged thoracic epidural analgesia on ventilation function and complication rate after the lung cancer surgery. Medicina (Kaunas). 2007;43(3):199–207.
40. Oka T, Ozawa Y, Ohkubo Y. Thoracic epidural bupivacaine attenuates supraventricular tachyarrhythmias after pulmonary resection. Anesth Analg. 2001;93(2):253–9, 1st contents page.
41. Roselli EE, Murthy SC, Rice TW, Houghtaling PL, Pierce CD, Karchmer DP, et al. Atrial fibrillation complicating lung cancer resection. J Thorac Cardiovasc Surg. 2005;130(2):438–44.
42. Jiang Z, Dai JQ, Shi C, Zeng WS, Jiang RC, Tu WF. Influence of patient-controlled i.v. analgesia with opioids on supraventricular arrhythmias after pulmonary resection. Br J Anaesth. 2009;103(3):364–8.
43. Komatsu R, Makarova N, Dalton JE, Sun Z, Chang D, Grandhe R, et al. Association of thoracic epidural analgesia with risk of atrial arrhythmias after pulmonary resection: a retrospective cohort study. J Anesth. 2015;29(1):47–55.
44. Allegri M, Bugada D, Grossi P, Manassero A, Pinciroli RL, Zadra N, et al. Italian Registry of Complications associated with Regional Anesthesia (RICALOR). An incidence analysis from a prospective clinical survey. Minerva Anestesiol. 2016;82(4):392–402.
45. Bugada D, Bellini V, Lorini LF, Mariano ER. Update on selective regional analgesia for hip surgery patients. Anesthesiol Clin. 2018;36(3):403–15.
46. Neal JM, Woodward CM, Harrison TK. The American Society of Regional Anesthesia and Pain Medicine checklist for managing local anesthetic systemic toxicity: 2017 version. Reg Anesth Pain Med. 2018; 43(2):150–3.
47. Sanchez Munoz MC, De Kock M, Forget P. What is the place of clonidine in anesthesia? Systematic review and meta-analyses of randomized controlled trials. J Clin Anesth. 2017;38:140–53.
48. Persec J, Persec Z, Husedzinovic I. Postoperative pain and systemic inflammatory stress response after preoperative analgesia with clonidine or levobupivacaine: a randomized controlled trial. Wien Klin Wochenschr. 2009;121(17–18):558–63.
49. Wu CT, Jao SW, Borel CO, Yeh CC, Li CY, Lu CH, et al. The effect of epidural clonidine on perioperative cytokine response, postoperative pain, and bowel function in patients undergoing colorectal surgery. Anesth Analg. 2004;99(2):502–9, table of contents.
50. Devereaux PJ, Sessler DI, Leslie K, Kurz A, Mrkobrada M, Alonso-Coello P, et al. Clonidine in patients undergoing noncardiac surgery. N Engl J Med. 2014;370(16):1504–13.
51. Parlow JL, Begou G, Sagnard P, Cottet-Emard JM, Levron JC, Annat G, et al. Cardiac baroreflex during the postoperative period in patients with hypertension: effect of clonidine. Anesthesiology. 1999; 90(3):681–92.
52. Filos KS, Patroni O, Goudas LC, Bosas O, Kassaras A, Gartaganis S. A dose-response study of orally administered clonidine as premedication in the elderly: evaluating hemodynamic safety. Anesth Analg. 1993; 77(6):1185–92.
53. Maruyama K, Takeda S, Hongo T, Kobayashi N, Kim C, Ogawa R. Oral clonidine premedication exacerbates hypotension following tourniquet deflation by inhibiting noradrenaline release. J Nippon Med Sch. 2004;71(1):44–50.
54. Eisenach JC, De Kock M, Klimscha W. Alpha(2)-adrenergic agonists for regional anesthesia. A clinical review of clonidine (1984–1995). Anesthesiology. 1996;85(3):655–74.
55. Harkanen L, Halonen J, Selander T, Kokki H. Beta-adrenergic antagonists during general anesthesia reduced postoperative pain: a systematic review and a meta-analysis of randomized controlled trials. J Anesth. 2015;29(6):934–43.
56. Blessberger H, Kammler J, Domanovits H, Schlager O, Wildner B, Azar D, et al. Perioperative beta-blockers for preventing surgery-related mortality and morbidity. Cochrane Database Syst Rev. 2018;3:Cd004476.
57. Furberg CD, Psaty BM, FitzGerald GA. Parecoxib, valdecoxib, and cardiovascular risk. Circulation. 2005;111(3):249.
58. Bainbridge D, Cheng DC, Martin JE, Novick R. NSAID-analgesia, pain control and morbidity in cardiothoracic surgery. Can J Anaesth. 2006; 53(1):46–59.
59. Schjerning Olsen AM, Fosbol EL, Lindhardsen J, Folke F, Charlot M, Selmer C, et al. Duration of treatment with nonsteroidal anti-inflammatory drugs and impact on risk of death and recurrent myocardial infarction in patients with prior myocardial infarction: a nationwide cohort study. Circulation. 2011; 123(20):2226–35.
60. Bunimov N, Laneuville O. Cyclooxygenase inhibitors: instrumental drugs to understand cardiovascular homeostasis and arterial thrombosis. Cardiovasc Hematol Disord Drug Targets. 2008;8(4):268–77.
61. Jaksch W, Dejaco C, Schirmer M. 4 years after withdrawal of rofecoxib: where do we stand today? Rheumatol Int. 2008;28(12):1187–95.
62. Trelle S, Reichenbach S, Wandel S, Hildebrand P, Tschannen B, Villiger PM, et al. Cardiovascular safety

of non-steroidal anti-inflammatory drugs: network meta-analysis. BMJ. 2011;342:c7086.
63. Nussmeier NA, Whelton AA, Brown MT, Langford RM, Hoeft A, Parlow JL, et al. Complications of the COX-2 inhibitors parecoxib and valdecoxib after cardiac surgery. N Engl J Med. 2005;352(11):1081–91.
64. Oliveri L, Jerzewski K, Kulik A. Black box warning: is ketorolac safe for use after cardiac surgery? J Cardiothorac Vasc Anesth. 2014;28(2):274–9.
65. Liu SS, Bae JJ, Bieltz M, Ma Y, Memtsoudis S. Association of perioperative use of nonsteroidal anti-inflammatory drugs with postoperative myocardial infarction after total joint replacement. Reg Anesth Pain Med. 2012;37(1):45–50.
66. European Medicine Agency concludes action on COX-2 inhibitors (press release). 2005.
67. da Costa BR, Reichenbach S, Keller N, Nartey L, Wandel S, Jüni P, Trelle S. Effectiveness of nonsteroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis. Lancet. 2017;390(10090):e21–33.
68. Bugada D, Lavand'homme P, Ambrosoli AL, Klersy C, Braschi A, Fanelli G, et al. Effect of postoperative analgesia on acute and persistent postherniotomy pain: a randomized study. J Clin Anesth. 2015;27(8):658–64.
69. Blieden M, Paramore LC, Shah D, Ben-Joseph R. A perspective on the epidemiology of acetaminophen exposure and toxicity in the United States. Expert Rev Clin Pharmacol. 2014;7(3):341–8.
70. Doherty M, Hawkey C, Goulder M, Gibb I, Hill N, Aspley S, et al. A randomised controlled trial of ibuprofen, paracetamol or a combination tablet of ibuprofen/paracetamol in community-derived people with knee pain. Ann Rheum Dis. 2011;70(9):1534–41.
71. Rahme E, Barkun A, Nedjar H, Gaugris S, Watson D. Hospitalizations for upper and lower GI events associated with traditional NSAIDs and acetaminophen among the elderly in Quebec, Canada. Am J Gastroenterol. 2008;103(4):872–82.
72. Zhang W, Nuki G, Moskowitz RW, Abramson S, Altman RD, Arden NK, et al. OARSI recommendations for the management of hip and knee osteoarthritis: part III: changes in evidence following systematic cumulative update of research published through January 2009. Osteoarthr Cartil. 2010;18(4):476–99.
73. Roberts E, Delgado Nunes V, Buckner S, Latchem S, Constanti M, Miller P, et al. Paracetamol: not as safe as we thought? A systematic literature review of observational studies. Ann Rheum Dis. 2016;75(3):552–9.
74. de Vries F, Setakis E, van Staa TP. Concomitant use of ibuprofen and paracetamol and the risk of major clinical safety outcomes. Br J Clin Pharmacol. 2010;70(3):429–38.
75. Lipworth L, Friis S, Mellemkjaer L, Signorello LB, Johnsen SP, Nielsen GL, et al. A population-based cohort study of mortality among adults prescribed paracetamol in Denmark. J Clin Epidemiol. 2003;56(8):796–801.
76. Chan AT, Manson JE, Albert CM, Chae CU, Rexrode KM, Curhan GC, et al. Nonsteroidal antiinflammatory drugs, acetaminophen, and the risk of cardiovascular events. Circulation. 2006;113(12):1578–87.
77. Mathiesen O, Wetterslev J, Kontinen VK, Pommergaard HC, Nikolajsen L, Rosenberg J, et al. Adverse effects of perioperative paracetamol, NSAIDs, glucocorticoids, gabapentinoids and their combinations: a topical review. Acta Anaesthesiol Scand. 2014;58(10):1182–98.
78. Sobanski P, Krajnik M, Shaqura M, Bloch-Boguslawska E, Schafer M, Mousa SA. The presence of mu-, delta-, and kappa-opioid receptors in human heart tissue. Heart Vessel. 2014;29(6):855–63.
79. Chen A, Ashburn MA. Cardiac effects of opioid therapy. Pain Med. 2015;16(Suppl 1):S27–31.
80. Lavand'homme P, Steyaert A. Opioid-free anesthesia opioid side effects: tolerance and hyperalgesia. Best Pract Res Clin Anaesthesiol. 2017;31(4):487–98.
81. Brat GA, Agniel D, Beam A, Yorkgitis B, Bicket M, Homer M, et al. Postsurgical prescriptions for opioid naive patients and association with overdose and misuse: retrospective cohort study. BMJ. 2018;360:j5790.
82. Sun EC, Darnall BD, Baker LC, Mackey S. Incidence of and risk factors for chronic opioid use among opioid-naive patients in the postoperative period. JAMA Intern Med. 2016;176(9):1286–93.
83. Long DR, Lihn AL, Friedrich S, Scheffenbichler FT, Safavi KC, Burns SM, et al. Association between intraoperative opioid administration and 30-day readmission: a pre-specified analysis of registry data from a healthcare network in New England. Br J Anaesth. 2018;120(5):1090–102.
84. Gupta A, Nizamuddin J, Elmofty D, Nizamuddin SL, Tung A, Minhaj M, et al. Opioid abuse or dependence increases 30-day readmission rates after major operating room procedures: a National Readmissions Database study. Anesthesiology. 2018;128(5):880–90.
85. Stanley TH, Webster LR. Anesthetic requirements and cardiovascular effects of fentanyloxygen and fentanyl-diazepam-oxygen anesthesia in man. Anesth Analg. 1978;57(4):411–6.
86. Sun-Edelstein C, Tepper SJ, Shapiro RE. Drug-induced serotonin syndrome: a review. Expert Opin Drug Saf. 2008;7(5):587–96.
87. Nair S, Chandy TT. Cardiac arrest from tramadol and fentanyl combination. Indian J Anaesth. 2015;59(4):254–5.
88. Warltier DC, Pagel PS, Kersten JR. Approaches to the prevention of perioperative myocardial ischemia. Anesthesiology. 2000;92(1):253–9.

Analgesic Drugs and Cardiac Safety

40

Giustino Varrassi, Joseph Pergolizzi, John F. Peppin, and Antonella Paladini

Contents

Abstract

Acute pain may become very dangerous for the cardiac function. Its rapid and efficacious treatment is important to prevent serious cardiac complications, especially in patients with pre-existing cardiovascular problems. At the same time, the use of analgesics may become harmful for the cardiovascular system. In fact, all the drugs used for treating pain have effects on heart and vascular system.

In this chapter, the authors deeply analyze the quality and quantity of the side effects of analgesics on heart's safety. They start reminding that opioid receptors are present in every part of the cardiovascular system and may have a deep influence on its function. Such receptors have effects on the parasympathetic system, but also on the inotropic and chronotropic heart activities. They affect the heart electrophysiology and may be responsible for arrhythmias. At the same time, they may protect the heart activity, as it is the case with the well-known efficacy of morphine administration to treat coronary syndromes. Lastly, the authors report data on potential cardio-protective effects of opioids "conditioning" myocardial responses both in

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*,
https://doi.org/10.1007/978-3-030-28008-6_43

physiological conditions and during post-ischemic phase.

Large part of the chapter is dedicated to the effects of NSAIDs on cardiovascular functions. The authors start reminding the different actions of cyclooxygenases (COX1 and COX2) on the cardiovascular system. Then, they make clear that not all the NSAIDs affect such functions in an equal entity. Lastly, they deeply analyze the effects of both NSAIDs and Coxibs on ischemic cardiovascular risk, on heart failure, on stroke, and on renal function and arterial hypertension. At the end, they present a list of questions still open for scientific discussion, and conclude that, from the cardiovascular perspective, there are no "safe" NSAIDs, and the best solution is always to use such drugs in a wise way, at their minimal efficacious dosage, for the shortest time necessary.

The chapter is closed with the presentation of the cardiovascular effects of paracetamol and adjuvant drugs. In particular, authors report the effects of antidepressants, gabapentinoids and few other adjuvant drugs frequently used in pain patients.

They conclude reminding the readers that pain management is always difficult and very challenging for the clinicians. A deep knowledge of the drugs used as analgesics, both for the effects on pain and for their side effects, is absolutely crucial if the physicians want to help more than to harm the patients.

Keywords

Cardiovascular system · Cardiovascular safety · Analgesics · Opioids · NSAIDs · Paracetamol · Analgesic adjuvants

Introduction

To the body, acute pain is interpreted as a defense mechanism; however, it also has multiple deleterious effects on specific physiologic processes, especially the cardiovascular system (CVS). These effects can be both direct and indirect. Related directly to the entity of the tissue damage, these effects can become extremely dangerous, especially in multi-traumatized patients. The traumatic injury is locally responsible for erythema, vasodilation, activation of pain receptors, and other local physiologic processes, e.g., local increase in neurotransmitters, recruitment of inflammatory cells, mastocyte activation, and neuroinflammation [1]. Pain signals, transmitted by peripheral nerves, arrive at the spinal cord and then the brain. If these signals become prolonged and are not blocked, they alter the process of normal transmission. Sustained local vasodilation, altered capillary permeability, and edema with the resultant peripheral hypersensitivity all contribute to this process. The same occurs in the dorsal column of the spinal cord, where the persistent arrival of nociceptive stimuli is responsible for accumulation of neurotransmitters with reduction of pain thresholds and production of central hypersensitivity, i.e., central sensitization [2].

Immediately after the tissue lesion and nociceptive stimulus production, the CVS is affected at a local level, with recruitment of segmental spinal reflexes and increased sympathetic activity. This latter response is responsible for increased heart rate, stroke volume, peripheral resistance, arterial pressure, myocardial work, and oxygen demand [3]. This reaction is a direct result of the initial traumatic lesion; however, its consequences may be very different if the CVS of the affected patient had some preexisting anatomic and pathological disorder. Untreated acute pain is responsible for reduced peripheral blood flow and impaired fibrinolysis, with a concomitant increased risk of venous thrombosis [3–5]. This process is highly associated with increased general morbidity and mortality and especially with pulmonary embolism.

The local reactions to acute pain are significant, but the systemic reactions are even more profound; they include neuroendocrine, cellular, and immunological consequences. Initially, there is the activation of the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system by the adrenal glands. Among other responses, this results in an increased myocardial oxygen demand [6]. Moreover, the epicardial blood flow is reduced by the higher resistance consequent to

alpha-receptor stimulation [7]. In normal patients the stress reactions are compensated, but this is not possible in those with coronary artery disease [8]. In these patients there is a paradoxical vasoconstriction of the coronary arteries, after this sympathetic stimulation, instead of the normal physiologic vasodilatation [8]. This risk is significantly reduced by an efficacious and aggressive analgesia [9].

There are data suggesting that the stress responses per se are limiting pain perception, in normal individuals [10], but without good analgesia, this is not enough to prevent potential side effects of pain on cardiovascular balance. In other terms, an efficacious and aggressive analgesia is a "bodyguard" for the CVS, especially in patients with cardiac disease. Nevertheless, analgesic drugs (as any other efficacious drugs) have many side effects, including a certain number on the CVS [11]. This will be the focus of this chapter, in order to make clear why and how much analgesics may be responsible for protection or damage on the heart and vascular system. This chapter will emphasize the most relevant data in the literature on this specific topic. Additionally, we will also describe the currently known pathophysiological mechanisms of these cardiovascular effects.

Pharmacological Treatment of Pain

Both acute and chronic pain are, in general, treated with a wide group of drugs known broadly as "analgesics." The most frequently used are opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), paracetamol, adjuvants (e.g., anti-epileptic agents, alpha agonists, etc.), and other agents (e.g., ketamine, etc.) or combinations. These last agents also affect the CVS as well [12], but will not be treated in this chapter because of less frequent clinical use.

Opioids

Opioid peptide receptors (OPR), in all their subtypes, are ubiquitous in the CVS and especially in the heart per se [13, 14]. These receptors modulate vascular tone, alter excitation-contraction coupling, and may even be involved in cardiogenesis [15]. There are data showing these receptors' ability to protect the myocardial muscle from ischemia-reperfusion injury [16, 17], to participate in protective conditioning responses [18], to reduce cardiac hypertrophy and fibrosis [19], and to trigger positive cardiac adaptation to exercise [20, 21]. Large quantities of endogenous opioid peptide precursors have been found in both ventricular and atrial myocytes [22]. This is responsible for myocardial synthesis of the major opioid endogenous peptides, e.g., dynorphin. Endogenous opioid production can be elevated under both physiological and pathological conditions, e.g., aging [23], physical exercise [24], ischemia [25], and protective conditioning stimuli [26]. Even though both opioid receptors and endogenous peptides are present in the myocardial muscle, their effects and roles on cardiovascular physiology are still not completely understood.

A clear interaction between endogenous enkephalins and catecholamines has been demonstrated [27]. Enkephalins decrease systemic vascular resistance, ventricular contractility, and heart rate [27]. Acute myocardial ischemia and/or infarction is responsible for a marked increase in cardiac enkephalins [28]. This seems helpful in reducing sympathetic input, improving vagal activity, and improving myocardial energy balance [23, 28–31].

Vagal effects. Endogenous and exogenous opioids have a crucial role in parasympathetic activity and modulation, resulting in a finely tuned role in adjustment of heart rate and cardiac performance; such effects are also neuromodulated by endogenous enkephalins [32]. Vagal stimulation is responsible for reduced heart rate and blood pressure; this effect is reversed by enkephalins and restored by their antagonists [33]. The vagolytic action of enkephalins mitigates the intensity of bradycardia, thus reducing the impact of sympathetic control of atrial excitability [34]. Remifentanil is definitely responsible for bradycardia in hypnotic and non-hypnotic patients [35].

Inotropic activity. OPRs' activity is also involved in the inotropic myocardial activity. For instance, alfentanil is responsible for dose-dependent reductions in contractile force in human right atrial trabeculae [36]. This effect has been

demonstrated also for other opioids [37]. However, the results cannot be considered definitive, because other authors have reported positive inotropic actions of the opioids [38].

Chronotropic effects of opioids are debated. However, direct influence of some enkephalins on the SA node has been demonstrated, together with its reversal by naloxone [39].

QT prolongation. Much better knowledge exists on the effects of some opioids on QT prolongation. Methadone (but not morphine or other commonly used opioids) rapidly induces concentration-dependent QT prolongation [40, 41], which can lead to *torsade de pointes* [42]. This has also been demonstrated in young patients [43]. Meperidine is responsible for QT prolongation, and this is correlated with the drug itself and its metabolites [44].

Electrophysiology and arrhythmias. The anti- or pro-arrhythmic properties of opioids depend upon the metabolic state and activity of the heart. Morphine has a very strong effect on vagal activation and enhance the ventricular fibrillation threshold [45]. Also, fentanyl that is selective for the μ-receptors augments the threshold for ventricular fibrillation, partially increasing vagal efferent activity and partially reducing the sympathetic outflow [46, 47]. Loperamide abuse has been associated with cardiac dysrhythmias [48, 49] and death [50]. Buprenorphine has a dose limitation in the United States of America (USA), because it was believed to increase the risk of arrhythmias; such risk has not been demonstrated in "real-world" use [51]. However, there is equivocal data suggesting that buprenorphine may have effects on the QTc [52]. This topic becomes very important when related to the effects of opioids on myocardial ischemia and infarction. Nevertheless, the existing data on the effects of opioids and OPRs on electrophysiology and arrhythmias are conflicting, and the topic would deserve further research, both experimentally and clinically.

Vascular effects. Hypotension is the better-known effect of opioids on the CVS. This is certainly the most frequently observed non-analgesic effect of this class of drugs [53]. There are still controversies on its pathophysiology and on which subgroup of OPRs is responsible. OPR-mediated vasodilatation/OPR-mediated vasodepression depends upon OPR subtypes targeted and the relative levels of agonisms applied [54]. The provoked hypotension may also be refractory to treatment and be associated with arrhythmias in cases of overdose [53].

Myocardial protection. Myocardial survival is very plastic and depends upon many factors. For instance, it is reduced by age and some specific diseases and enhanced by preconditioning, caloric restriction, and exercise. The protective actions may all involve the OPRs, and this is particularly well known for the effects of morphine in acute coronary syndrome [55]. Preconditioning responses are the most studied cardioprotective modalities [56]. Ischemic preconditioning triggers local G protein-coupled receptors (GPCR), including OPRs, which can be selectively targeted to replicate the benefits during future ischemic episodes [57, 58]. All the data on conditioning responses of myocardial muscle to ischemia demonstrate important roles for opioids and OPRs [56, 59]. Recent studies demonstrate that κ- and δ-OPRs (but not μ-receptors) [60] or κ-OPRs alone [61] mediate the protection of ischemic postconditioning. In early reperfusion, drug agonism of δ- and κ-OPRs provides a significant cardiac protection [62, 63]. Myocardial infarction may also be reduced by remote control mediated via opioid receptors [56, 64], and data suggest that OPRs can enhance cardiac stress resistance interacting with other receptors [65, 66]. This mechanism seems very promising from a clinical point of view [67].

Effects of age, diseases, and activity. Age and chronic diseases seem to have a detrimental effect on the CVS, whereas exercise has a positive effect and involves the intrinsic OPRs' signaling. Physical activity increases serum level of endogenous opioids [24] and myocardial expression of opioid-related genes and improves cardiac ischemic tolerance [20]. These effects are opposed by OPRs' antagonism [21].

Opioid system and cardiac pathologies. The opioid system is influenced by heart acute and chronic pathologies and may contribute to the cardiovascular manifestation of disease [68]. For instance, cardiomyopathy and heart failure enhance negative inotropic and lusitropic

responses to κ- and δ-OPRs' stimulation [69]. Proenkephalin has different actions in heart failure [70]. Cardiac μ-opioid receptor stimulation has a cardioprotective effect in chronic heart failure [71]. Intrathecal fentanyl influences the $\dot{V}O_2$ kinetics during moderate-intensity exercise in heart failure [72]. Endorphins may alter inotropic and chronotropic activities in other pathological conditions [73]. For example, obstructive cholestasis seems associated with naltrexone-sensitive bradycardia [74]. Enhanced OPR-mediated chronotropy is significantly associated with hypertension [75]. K-opioid receptor stimulation has a protective effect in hypoxic pulmonary hypertension [76]. Thus, different disease states are linked to either enhanced or repressed OPR-dependent control of cardiac activities [77].

Conclusion. Ongoing research is focusing on non-analgesic effects of opioids, especially on the CVS [68]. Opioid receptors and their effects mediate a wide range of potentially useful cardiovascular responses, including clear cardioprotection in the case of myocardial infarction. Indeed, data supports opioid receptor involvement in intrinsic ischemic tolerance and "conditioning" responses. Existing data on opioid receptor cardioprotection are even more reinforced by the last data on post-ischemic efficacy of their effects. Ongoing investigation of the physiological roles of opioid receptors in the heart and vascular system and their changes with age and diseases may open the way to new opioidergic therapies. Certainly, from the data we have at the moment, a correct use of normal pharmacological doses of opioids does not seem to be responsible for cardiovascular damages.

NSAIDs

The nonsteroidal anti-inflammatory drugs (NSAIDs) are a chemically heterogeneous group of compounds very frequently used in the clinical practice, including in cancer patients [78], mainly as analgesics. Recently, there are suggestions that the use of NSAID prodrugs may provide analgesia with a better side effect profile [79]. NSAIDs' efficacy has been extensively demonstrated not only in pain treatment [80] but also as powerful anti-inflammatory and antipyretics [81]. The first representative, of this group, was salicylic acid, a natural product, converted to acetylsalicylic acid at the end of the nineteenth century and soon after followed by many other synthetic versions [82]. Chemically, they are very different, and this structural difference is responsible for their relatively different action and side effects. Actually, the older drugs were classified based on their origin or chemical structure; the newer ones are in general classified for their modality of action, e.g., the "selective COX-2 inhibitors" or "coxibs" (Table 1). The acronym "coxib" is used to identify COX-2

Table 1 Classification of NSAIDs and their COX-1/COX-2 selectivity

Chemical class	COX-1 selective and nonselective	COX-2 selective
Salicylates	Aspirin, diflunisal	
Sulfonanilides		Nimesulide, flosulide
Anthranilic acid derivatives (fenamates)	Mefenamic acid, meclofenamic acid, flufenamic acid, tolfenamic acid	Esters and amides of meclofenamate
Acetic acid derivatives	Aceclofenac, diclofenac, ketorolac, indomethacin, nabumetone, sulindac, tolmetin	Etodolac, lumiracoxib
Enolic acid (oxicam) derivatives	Droxicam, isoxicam, lornoxicam, phenylbutazone, piroxicam, tenoxicam	Meloxicam
Propionic acid derivatives	Dexketoprofen, dexibuprofen, fenoprofen, flurbiprofen, ibuprofen, ketoprofen, loxoprofen, naproxen, oxaproxin	
Selective COX-2 inhibitors (Coxibs)		Celecoxib, rofecoxib, valdecoxib, parecoxib, etoricoxib

inhibitors, thus defining a subclass of NSAIDs that are different both from the chemical and pharmacological point of view. For instance, meloxicam has a COX-2 selectivity very similar to that shown by celecoxib, even if they are chemically different; lumiracoxib is chemically similar to diclofenac; it however has a very different chemical profile when compared with other coxibs, e.g., celecoxib and rofecoxib [83]. Coxibs are an integral part of the NSAID group, producing the inhibition of the COX (Fig. 1), and should be better defined as "COX-1-savers," instead of COX-2 selective inhibitors or coxibs [85].

Although the NSAIDs have been in use for more than a century, their mechanism of action was only recently clarified. Vane and his group were able to demonstrate their ability to inhibit the transformation of arachidonic acid into prostaglandin by blocking the enzyme COX [86–88]. The mechanism was made even more clear a few years later, when the genes for COX expression were identified and their role in the prostaglandin pathway demonstrated [89]. Subsequent research demonstrated much of the actions of the COX pathways [90–93]. In the early 1990s, the existence of different COX isoforms was suggested [94–96]. In the late 1990s, the isoenzymes cyclooxygenase-1 and -2 (COX-1, COX-2) were identified and well defined, COX-1 being a constitutive enzyme while COX-2 was mostly inducible by inflammatory processes [97]. Research and synthesis of new molecules able to selectively block the COX-2 enzyme were then developed [98–102]. In the future it seems likely that we will see other therapeutic developments involving the COX pathways [103].

The action of the COX on lipids, including those involving arachidonic acid, gives origin to a variety of products. Most of them derive from the catabolism of prostaglandin F2 (PGF2) (Fig. 2). The final products derived from COX-1 activity (thromboxane and prostanoids) have their own actions, especially on the gastrointestinal and CVS. They also contribute to the development of fever, inflammation, and pain [87, 97]. Hence, blocking the action of COX-1 and COX-2 will result in the reduction of fever, inflammation, and pain. COX-1 however also reduces the physiological protective effect of the prostanoids on the gastric mucosa.

Despite the clear therapeutic efficacy of the NSAIDs, their clinical use is frequently affected by the incidence of side effects, most frequently gastrointestinal [104, 105]. Moreover, the COX plays an important role within the CVS. Thromboxane A2, mostly derived from the COX-1 activity at the platelet level, is responsible for platelet aggregation, vasoconstriction, and smooth muscle proliferation [106]. On the contrary, prostacyclin (PGI2) synthesis, mainly mediated by COX-2 activity in macrovascular endothelial cells, opposes these effects resulting in inhibition of platelet aggregation, vasodilation, and antiproliferative effects [107].

The blockage of the COX system has a further consequence, the increase of arachidonic acid catabolized by the lipoxygenase with resultant potential consequences for the CVS (Fig. 3).

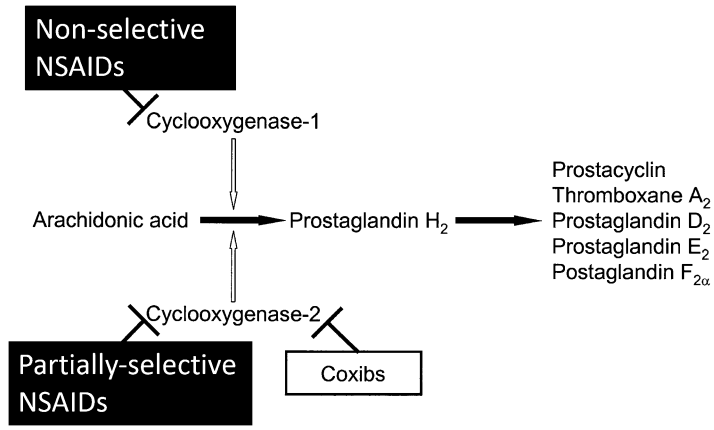


Fig. 1 Mechanism of action of NSAIDs. (Redrawn from Howard and Delafontaine [84])

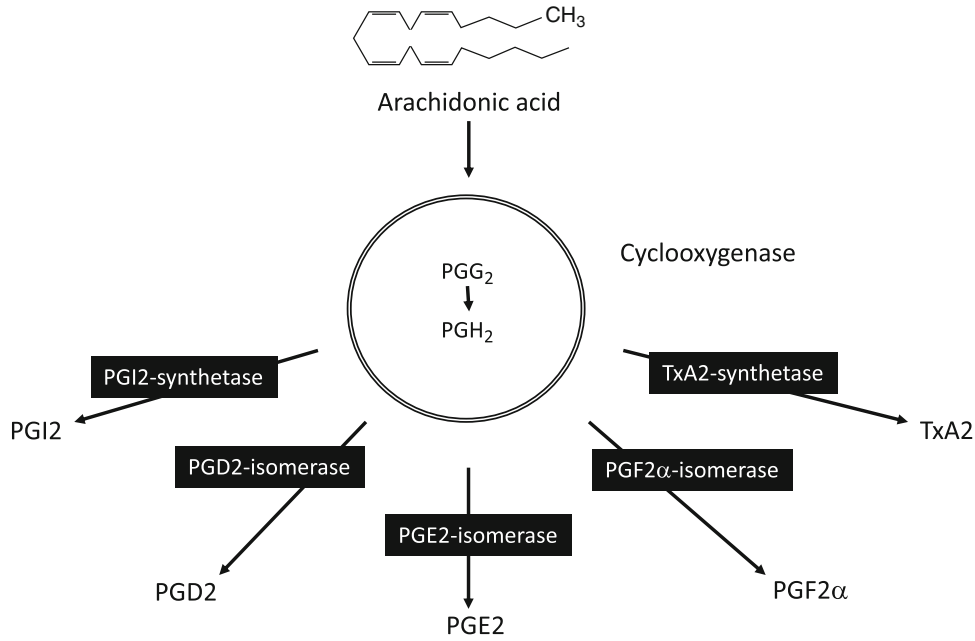
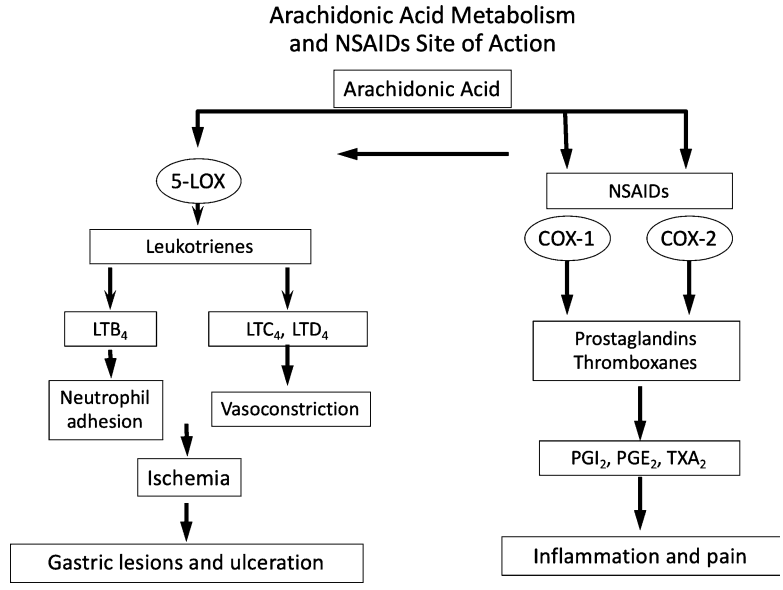


Fig. 2 Synthesis of prostanoids. PGD2 = Prostaglandin D2; PGE2 = Prostaglandin E2; PGF2 = Prostaglandin F2; PGG2 = Prostaglandin G2; PGH2 = Prostaglandin H2; PGI2 = Prostacyclin; TxA2 = Thromboxane A2

Fig. 3 Site of action of NSAIDs and increased metabolism of the arachidonic acid by the lipoxygenase (LOX)



COX and CVS

Per years, there was the general knowledge that the vascular system was only able to express COX-1, except when an inflammatory process was present, e.g., atherosclerosis [108, 109]. In fact, COX-2 is rapidly expressed in the place of a lesion and/or infection [110, 111]. At the moment, this phenomenon is still under investigation, even if there are data showing that the shear stress of the vascular endothelium is

responsible for the expression of COX-2 as well [112].

The studies on the relations between COX and CVS go back to the 1970s. In 1975, for the first time, it was shown that platelets were able to produce thromboxane A2 [113]. Prostacyclin was discovered 1 year later, when Moncada et al. [114] demonstrated that an enzyme isolated from arteries transforms prostaglandin endoperoxides, formed by COX, to an instable substance that inhibits platelet aggregation. Now we know that the vascular endothelial cells express in enormous quantity prostacyclin synthetase and platelets have thromboxane synthetase. The first has vasodilating effect, inhibits adhesion and aggregation of platelets, opposes the modifications of smooth muscles, and reduces cholesterol metabolism. On the contrary, thromboxane A2 is a vasoconstrictor and increases the metabolism of cholesterol and proliferation of vascular smooth muscle [85, 97, 99] (Table 2). The topic has been highlighted in a recent review connecting the role of prostaglandin H with all the potential cardiovascular damages caused by the COX inhibition [115].

The physiological balancing between prostacyclin and thromboxane A2 is crucial for the cardiovascular system. There are data on this, mainly deriving from the studies on the pharmacological and clinical effects of aspirin. This drug is an irreversible inhibitor of the COX. At low dosages (30–150 mg/day), it produces a selective inhibition of the platelet COX, but not of COX of the endothelial cells [106, 116, 117]. This is because platelets do not have nuclei and cannot produce new COX to replace the inhibited portion. On the contrary, endothelial cells reproduce COX, thanks to their nuclei. Moreover, platelets are exposed to high concentrations of aspirin prior to its degradation in the liver [118]. This means that low and repeated doses of aspirin are responsible for a complete block of COX-1 in platelet and less of an effect on endothelial COX. In other terms, low-dose aspirin reduces platelet thromboxane A2, with scarce effect on endothelial prostacyclin, with the consequence of a strong antithrombotic effect. This is possible just with aspirin, which is the only NSAID producing an irreversible block of COX.

Table 2 Effects induced by prostacyclin and thromboxane A2

Prostacyclin (IP receptors)	Thromboxane A2 (TP receptors)
Platelet anti-aggregating effect	Platelet aggregating effect
Platelet anti-adhesive effect	Platelet adhesive effect
Vasodilation	Vasoconstriction
Reduced myo-vascular remodeling	Increased myo-vascular remodeling
Reduced cholesterol uptake	Increased cholesterol metabolism

Inhibition of COX and Cardiovascular Risk

The beginning of this century has seen the synthesis and market introduction of new molecules able to selectively block COX-2 [99–101]. The selective block of the "inducible COX" was immediately seen as a potential in reducing the side effects of the less-selective NSAIDs, especially gastroenteric side effects [119–121]. At the moment, other possible mechanisms for the blockade of COX-2 have been suggested, especially based on its "inducibility" [122]. However, previously, these drugs were not studied for potential side effects involving other organs and/or systems. The *Vioxx Gastrointestinal Outcomes Research* (VIGOR) study, a clinical trial comparing rofecoxib with naproxen in a large population, showed a significant higher incidence of myocardial infarction in the group treated with rofecoxib, compared to the one receiving naproxen [123]. These unexpected cardiovascular side effects of the study opened a "Pandora's box" [124]. The VIGOR study did not give a clear explanation for this unforeseen phenomenon and assumed that it could have been the consequence of low-dose aspirin in at-risk patients. In fact, in patients who did not have an indication for secondary prevention, the incidence of myocardial infarction was similar in the two studied groups. Another explanation could have been the protective effect of naproxen, a powerful antiplatelet aggregating drug. Moreover, it is of importance to note that the studied population was represented by

rheumatoid arthritis patients, patients that would have an increased risk of myocardial infarction [125]. Different results were obtained in a study comparing celecoxib with ibuprofen or diclofenac where the difference in cardiovascular side effects was not statistically different [126]. On the contrary, a different study, comparing placebo vs celecoxib 400 or 800 mg/day, also demonstrated a significant increase of cardiovascular events in the two active groups [127]. A further RCT, *Adenomatous Polyp Prevention on Vioxx* (APPROVe) comparing two groups treated with placebo or rofecoxib, has demonstrated an increased risk of thrombotic events after 18 months of treatment [128]. In addition, in the treated group, there were other cardiovascular side effect, e.g., heart failure, pulmonary edema, and precocious hypertension; prevention of recurrent colorectal adenomas is still under discussion [129], hopefully not with the same AEs.

This topic was not new [84], but since 2004 other data have been published related to potential cardiovascular side effects of both the NSAIDs and the coxibs. They are focused on different aspects of cardiovascular activity. In the following we will summarize the results of the best published studies.

Ischemic cardiovascular risk. Previous studies suggesting a potential protective effect of naproxen for acute myocardial infarction, when compared to rofecoxib, seem debatable. In a double-blind, randomized, multicenter study, comparing celecoxib to naproxen (*Alzheimer's Disease Anti-Inflammatory Prevention Trial*, ADAPT) the cardiovascular risk was increased in the naproxen group, and not in the celecoxib group [130]. This is proposing again the old concept of the relationship between the traditional NSAIDs and the cardiovascular risk [120]. In a 4-year case-control study [131], over 9000 patients with acute myocardial infarction have been examined. All of them were chronically using either NSAIDs (diclofenac, ibuprofen, naproxen) or COXIBs (celecoxib, rofecoxib). With some limitations, the general analysis of the data has demonstrated that all the drugs used are associated with acute myocardial infarction. The univariate analysis of the data and the correction of the OR for influencing factors have demonstrated that the chronic use of diclofenac, ibuprofen, and rofecoxib increases the risk of myocardial infarction by 24–25%; the influence of naproxen is less significant [131]. The limitation of this study is the low number of patients over 65 years of age, which is an important factor studying such side effects [132]. Similar results were obtained in a nested large case-control study [133]. A meta-analysis, evaluating over 100 trials for about 150,000 patients, has demonstrated that the high doses of ibuprofen and diclofenac are associated with a higher risk of cardiovascular events. Further the risk increased after 1-year treatment [134]. Such risk cannot even be prevented by the simultaneous use of low-dose aspirin [135, 136]. Another systematic review on the risk of myocardial infarction in patients treated with NSAIDs and coxibs has demonstrated a 10% increase in MI risk with the use of NSAIDs, with differences between the drugs; diclofenac showed an increased risk of 44% and rofecoxib an increased risk of 30% [137]. Systematic reviews on the clinical use of dexketoprofen suggest that this drug does not interfere with the CVS [138, 139]. Similar results have been obtained with the use of a fixed-dose combination of dexketoprofen and tramadol [140]. The MEDAL study, comparing etoricoxib and diclofenac, did not show any difference in the incidence of cardiovascular effects in the two studied groups [141]. In a very extensive systematic review, diclofenac was the NSAID associated to the highest risk of cardiovascular complications; naproxen does not reduce the risk; rofecoxib has a dose-dependent risk, appearing as early as 30 days of treatment; and celecoxib at lower doses does not increase the risk of unexpected cardiovascular events [142]. These data are reinforced by a more recent expert consensus, specifically designed to address benefits and gastrointestinal and cardiovascular risks with the use of NSAIDs [143].

All the previous studies are focused on patients selected as part of RCTs. The data coming from "real-life" therapy suggests different results. In studying the use of both NSAIDs and Coxibs in the population of the United Kingdom (UK) and the USA, it seems clear that the use of such

analgesics is for short periods of time and at low dosages [144]. This could partially explain the existing differences in results coming from RCTs and observational studies. The situation is similar in Finland, where a different observational study on the first episode of myocardial infarction has demonstrated its modest correlation with the use of traditional NSAIDs or coxibs [145]. A recent Bayesian meta-analysis, including about half-million patients using celecoxib, diclofenac, ibuprofen, naproxen, or rofecoxib, has reported a significant increase in the risk of myocardial infarction in the studied populations, especially when using high dosages of NSAIDs (i.e., ibuprofen and naproxen) [146]. The risk is dose, duration, and recency of exposure dependent. Recent results revealed that at moderate doses, "celecoxib was found to be noninferior to ibuprofen or naproxen with regard to cardiovascular safety" [147].

All these studies describe the epidemiology of the cardiovascular events as complications of the use of NSAIDs and coxibs. The only study designed in 2009 to specifically investigate the cardiovascular side effects with the use of long-term NSAIDs or coxibs' treatment was the PRECISION trial [148]. Its results are not final, yet.

NSAIDs and heart failure. There are several studies focused on this topic, demonstrating a relationship between the use of NSAIDs and heart failure. Till now, none of them has been able to connect the risk with the dose-response of any individual NSAID. This topic has been included as one of the outcomes of the Safety of Non-Steroidal Anti-Inflammatory Project funded by the European Commission inside of the seventh Framework Programme. The recently published results demonstrate that there is a connection between the individual studied NSAIDs and the duration of the therapy [149].

Coxibs and stroke. Data on the possible relationship between COX-2 inhibition and stroke is debated. The initial data connecting rofecoxib and etoricoxib (but not celecoxib) to an increased risk of stroke [150] is contradicted by an extensive meta-analysis of randomized, double blind, controlled only studies. This meta-analysis was not able to show any significant difference in the incidence of stroke, comparing patients using either coxibs, other drugs (including NSAIDs), or placebo [151]. Similar results were obtained in a recent randomized trial where patients on non-specific NSAID therapy were either left on their initial therapy or shifted to celecoxib use [152]. A retrospective cohort study on over 160,000 Australian patients using NSAIDs found an association with an increased risk of hospitalization for stroke, either ischemic or hemorrhagic, and recommended a careful evaluation and monitoring of the patients at risk, when prescribing either NSAIDs or coxibs [153]. Similar results are reported by a recent review article, which also explain the pathophysiology of the vascular damages caused by NSAIDs but especially by coxibs [154]. There are reasons to believe that such effects may be prevented either by picroside II which affects the expression of the COX-2 [155] or the combined therapy with 20-HETE inhibitors, a lipid mediator causing protective effects in cerebral circulation [156]. More information on this topic have been recently published in an extensive review article [157].

COX, renal function, and arterial hypertension. Reduced synthesis of prostaglandins and the action on the renin-angiotensin system caused by NSAIDs and coxibs are responsible for increases in arterial pressure and peripheral edemas [158–160]. Moreover, it has been demonstrated that the nonselective NSAIDs reduce the pharmacological responses of some antihypertensive drugs [161, 162]. Both COX isoforms are present in the kidney and are involved, together with their metabolites, in the hydro-electrolytic balance and arterial pressure maintenance [83] and the subsequent consequences [163]. In normal subjects, COX-2 inhibition does not have any consequence on blood pressure and renal function ([164, 163]). On the contrary, in elderly and chronic pain patients, coxibs may increase the blood pressure [165, 166], as may be the case with both coxibs and NSAIDs [167]. Rofecoxib has been shown to cause major increases in blood pressure [168], while celecoxib has been shown not to significantly increased blood pressure [169–171]. Unfortunately, there are no specific studies designed to investigate whether NSAIDs or coxibs are directly responsible for an increase

in arterial blood pressure. In general, this is reported as side effect of the administration of those drugs, in retrospective analyses. More clear data would be useful, especially considering the high prevalence of chronic hypertension in elderly people, frequently affected by musculoskeletal pain, and necessitating the use of efficacious analgesia, including NSAIDs and coxibs.

Open questions and conclusions. On the interaction between NSAIDs and CVS, there are still many questions to be answered [172–174]. For instance, the pro-thrombotic mechanisms of NSAIDs are not completely understood. Which isoform of COX is responsible for the production of circulating prostacyclin is still unclear. Further, the existing data does not establish the effects of long lasting non-specific NSAID administration risk on CVS. Moreover, we still do not know if the difference between non-specific NSAIDs and coxibs is only the saving effect on the COX-1 or there are other important physiologic differences. Lastly, we should be able to explain the unusual finding of why the sudden interruption of a long-lasting administration of NSAIDs is associated with an increased risk of acute myocardial infarction [175].

On the clinical use of coxibs, there is still a need for further research, data, and understanding. For instance, in relation to the side effects on the CVS, we have hypothesized a "class effect," mainly based on studies testing high dosages of coxibs [123, 127]. However, the differences between the various coxibs are enormous. Unfortunately, we do not have data on direct head-to-head comparisons between them all. Moreover, the use of coxibs is not recommended in patients at high cardiovascular risk, but we do not know if this also applies to young patients at low cardiovascular risk due to a complete absence of data. Secondary cardiovascular risk prevention with low-dose aspirin is recommended, when prescribing coxibs at high cardiovascular risk patients. However, this is not the case with the nonselective NSAIDs. In fact, ibuprofen reduces the anti-aggregating effect of low-dose aspirin, via a well-defined receptor effect. Such interference seems preventable administering aspirin at least 2 h prior to the administration of the NSAID [143, 176]. Non-specific NSAIDs should be preferred in patients at high risk for cardiovascular problems. In case they also have a high risk for gastroenteric bleeding, they should be prescribed with NSAIDs and proton pump inhibitors (PPIs). As already said, the data on cardiovascular risk following the use of coxibs is consequent to the use of high dosages of those drugs, but we do not have any idea on what would happen using the same high dosages of nonselective NSAIDs; maybe they would have exactly the same toxicity on the CVS.

In conclusion, there is no "safe" NSAID for patients in pain from a CVS perspective. The best advice would be to avoid NSAIDs, especially in those with cardiovascular problems. If necessary and the benefits outweigh the risks, they should use such drugs at the lowest possible doses and for the shortest time period possible. If NSAIDs are going to be used in a given patient, those with low risk of gastroenteric bleeding can receive a non-specific NSAIDs, possibly starting with the drugs with the lowest risk for gastrointestinal and cardiovascular lesions [177–179]. If the pain is not relieved, a careful evaluation of the risk/benefit ratio of other drugs, including the coxibs, should be made. In case patients would be at high risk for cardiovascular events, low-dose aspirin and PPI should be added to the therapy. NSAID therapy should always be the least amount of time and the lowest effective dosage, with a careful evaluation of any sign and symptom of cardiovascular complication (e.g., hypertension, peripheral edema, renal insufficiency).

Paracetamol (Acetaminophen)

Paracetamol has been used as an analgesic for many decades. It has been used either alone or in combination with other drugs, e.g., with an opioid. Its analgesic mechanism of action is still a topic of debate. However, its hepatotoxicity is now commonly accepted [180]. This potential adverse event seems to be reduced by molecular hybridization between celecoxib and paracetamol [181].

Toxicity of paracetamol is well known, especially in the UK where it represents one of the

most frequent causes of intoxication [182]. Effects on the CVS are rare [183]. However, some biomarkers recently identified seem to suggest that paracetamol intoxication may cause kidney injury [184]. This could be responsible for elevated blood pressure and other CVS AEs. The chronic administration of paracetamol and other OTC analgesics has resulted in an increase in blood pressure, which was also found in younger chronic pain patients [185–187]. In any case, low incidence of probable nonfatal myocardial infarction, nonfatal stroke, fatal coronary heart disease, or fatal stroke is always reported as a dose-response consequence [185, 188–190].

Adjuvant Drugs

Because pain is multifactorial and involves multiple neurotransmitters and pathways, treatment is frequently complex. Single agents usually do not give significant relief for those patients with chronic pain. In such a setting, the use of NSAIDs long term is problematic, as it is paracetamol for the reasons discussed above. Therefore, even powerful analgesics (opioids and NSAIDs) may necessitate of simultaneous administration of drugs that are not primarily considered "analgesics." These are the so-called "adjuvants." In pain medicine they are widely used and are a very diverse set of agents. Some of them are very useful for pain management, but as with any other drugs, they have side effects. Sometimes those drugs may affect the CVS.

Antidepressants. This class of drugs is one of the most commonly used as adjuvants, especially in chronic pain patients. They are frequently used in the setting of neuropathic pain. In general, they have different effects on CVS functionality, especially affecting intraventricular conduction (prolonged PR, QRS, and QTc intervals) [191–199], and their action may also be increased by the simultaneous administration of NSAIDs [200]. They can frequently be responsible for orthostatic hypotension [201, 202]. Tricyclic antidepressants (TCA) have a long history and experience of use. They have effects on the CVS, especially arrhythmias [203]. Further, they have significant anticholinergic and cardiovascular side effects, e.g., QRS prolongation, atrial fibrillation, atrioventricular block, and ventricular tachycardia, but reduce heart rate variability and myocardial infarction [197, 204–206]. Similar effects on the CVS are reported with many other antidepressant drugs [207]. When this class of drugs is used as adjuvants, health-care professionals should be careful and evaluate for potential cardiovascular side effects. These should be included in the risk/benefit evaluation.

Gabapentinoids, e.g., gabapentin and pregabalin, have a similar mechanism of action: they modulate the α-2-δ subunits of voltage-sensitive calcium channels in the presynaptic afferent neurons [208, 209]. Nevertheless, they have differences in pharmacokinetics and pharmacodynamics, which explain their diversities in the efficacy and adverse event profiles. Their side effects are mainly on the central nervous system, and not on the CVS. Data on the side effects of gabapentin are reported in an extensive Cochrane review, where the only interesting CVS side effect is peripheral edema [RR = 3.4 (95% CI 2.1–5.3, NNH 19)] [210]. Pregabalin has a similar side effect profile [211].

Glucocorticoids: The short-term administration of glucocorticoids (GCCs) has not been shown responsible for major CVS AEs. In an RCT on about 4500 patients, comparing the administration of dexamethasone with placebo, the administration of the active drug did not cause important AEs; both myocardial infarction and stroke were not increased [212]. Similar results were reported in a meta-analysis of 54 RCTs, comparing the administration of GCCs with placebo or no treatment [213]. This meta-analysis showed that there was no increase of mortality and myocardial or pulmonary complications. A further meta-analysis of 51 RCTs, studying the differences between patients either treated with methylprednisolone or placebo or no treatment, did not demonstrate any difference between the three groups related to major AEs [214]. Therefore, the short-term use of glucocorticoids can be effective in reducing inflammation and treating painful conditions. However, long-term use is fraught with complications, including CVS issues. Long-term use of glucocorticoids

should be avoided unless the benefit clearly outweighs the risks [215].

Use of adjuvant medications in the treatment of pain is a common and accepted therapeutic approach. There are multiple medications used as "adjuvants," only a few of which are discussed above. Other medications such as ketamine, cannabinoids, other anti-epileptic agents, NMDA blockers and modulators, and other drugs have been used as adjuvants. Each of these classes of drugs needs to be thoroughly understood before they are introduced into a patient regimen. All have side effects, many on the CVS. Consistent evaluation and re-evaluation of patients, the efficacy of therapeutic regimens, and potential CVS adverse events should always be part of a patient treatment plan.

Conclusions

Acute and chronic pain are significant public health issues and affect patients around the world. Pain has profound consequences for patients in almost every aspect of patient's lives as well as significant and long-lasting physiologic effects [216]. The treatment of chronic pain is never straightforward and is always complicated [217]. This complexity requires the application of a number of therapeutic approaches, both pharmacologic and non-pharmacologic, to help relieve patient's suffering. The appropriate use of analgesics is in line with this approach as well as with one of the major goals of medicine, i.e., the relief of suffering [218]. The goal of the cardiologist and the pain physician is similar in this regard, to relieve suffering through their individual expertise and focus. Because of the complexities involved in the treatment of chronic pain, a successful clinical approach will rarely involve a single modality or agent. Treatment, involving both pharmacologic and non-pharmacologic modalities, should be established for a coordinated approach to analgesia. As with any therapy, either pharmacologic or non-pharmacologic, there are side effects that need to be understood and considered.

Pain patients will be frequently seen by cardiologists or other specialists who may not have prescribed the analgesics in question but will still need to understand their impact on the cardiovascular health of the patient. The cardiologist and the other specialists should work in tandem with the pain physician (and vice versa) to make sure a given analgesic regimen provides good analgesia and at the same time has the lowest risk possible. Opioids, NSAIDS, paracetamol, and adjuvants all have their place in treating pain. However, each, as we have outlined, has its own set of CVS side effects that can affect a cardiologists' treatment plan and an individual patients' CVS health.

References

1. Varrassi G, Fusco M, Coaccioli S, Paladini A. Chronic pain and neurodegenerative process in elderly people. Pain Pract. 2015;15:1–3. https://doi.org/10.1111/papr.12254.
2. Fusco M, Skaper S, Coaccioli S, Paladini A, Varrassi G. Degenerative joint diseases and neuroinflammation. Pain Pract. 2017;17:522–32. https://doi.org/10.1111/papr.12551.
3. Liu S, Carpenter RL, Neal JM. Epidural anesthesia and analgesia. Their role in postoperative outcome. Anesthesiology. 1995;82:1474–506.
4. Rosenfeld BA, Beattie C, Christopherson R. The effects of different anesthetic regimens on fibrinolysis and the development of postoperative arterial thrombosis. PIRAJ Study Group. Anesthesiology. 1993;79:435–43.
5. Steele SM, Slaughter TF, Greenberg CS. Epidural anesthesia and analgesia: implications for perioperative coagulability. Anesth Analg. 1991;73:683–5.
6. Stevens RA, Beardsley D, White JL. Does the choice of local anesthetic affect the catecholamine response to stress during epidural anesthesia? Anesthesiology. 1995;81:1169–74.
7. Meissner A, Rolf N, VanAken H. Thoracic epidural anesthesia and the patient with heart disease: benefits, risks and controversies. Anesth Analg. 1997;85:517–28.
8. Nabel EG, Ganz P, Gordon JB. Dilation of normal and constriction of artherosclerotic coronary arteries caused by the cold pressor test. Circulation. 1988;77:43–52.
9. Beattie WS, Buckley DN, Forrest JB. Epidural morphine reduces the risk of postoperative myocardial ischemia in patients with cardiac risk factors. Can J Anaesth. 1993;40:532–8.
10. Bruehl S, Chung OY. Interactions between the cardiovascular and pain regulatory systems: an updated review of mechanisms and possible alterations in chronic pain. Neurosci Biobehav Rev. 2004;28:395–414.

11. Shawaqfeh MS, Harrington C. Pain: systematic review of pharmacy compounding of pain medication. Int J Pharm Compd. 2018;22(1):19–24.
12. Klivinyi C, Bornemann-Cimenti H. Pain medication and long QT syndrome. Korean J Pain. 2018;31(1): 3–9. https://doi.org/10.3344/kjp.2018.31.1.3.
13. Khademi H, Kamangar F, Brennan P, Malekzadeh R. Opioid therapy and its side effects: a review. Arch Iran Med. 2016;19(12):870–6. 0161912/AIM.0010.
14. Treskatsch S, Shaqura M, Dehe L, Roepke TK, Shakibaei M, Schäfer M, Mousa SA. Evidence for MOR on cell membrane, sarcoplasmatic reticulum and mitochondria in left ventricular myocardium in rats. Heart Vessel. 2016;31(8):1380–8. https://doi.org/10.1007/s00380-015-0784-8.
15. Headrick JP, See Hoe LE, Du Toit EF, Peart JN. Opioid receptors and cardioprotection – 'opioidergic conditioning' of the heart. Br J Pharmacol. 2015;172 (8):2026–50. https://doi.org/10.1111/bph.13042.
16. Romano MA, Seymour EM, Berry JA, McNish RA, Bolling SF. Relative contribution of endogenous opioids to myocardial ischemic tolerance. J Surg Res. 2004;118:32–7.
17. Zhang L, Guo H, Yuan F, Hong ZC, Tian YM, Zhang XJ, Zhang Y. Limb remote ischemia per-conditioning protects the heart against ischemia-reperfusion injury through the opioid system in rats. Can J Physiol Pharmacol. 2018;96(1):68–75. https://doi.org/10.1139/cjpp-2016-0585.
18. Jang Y, Xi J, Wang H, Mueller RA, Norfleet EA, Xu Z. Postconditioning prevents reperfusion injury by activating delta-opioid receptors. Anesthesiology. 2008;108:243–50.
19. Yin W, Zhang P, Huang JH, Zhang QY, Fan R, Li J, Zhou JJ, Hu YZ, Guo HT, Zhang SM, Wang YM, Kaye AD, Gu CH, Liu JC, Cheng L, Cui Q, Yi DH, Pei JM. Stimulation of kappa-opioid receptor reduces isoprenaline-induced cardiac hypertrophy and fibrosis. Eur J Pharmacol. 2009;607(1–3):135–42. https://doi.org/10.1016/j.ejphar.2009.01.050.
20. Dickson EW, Hogrefe CP, Ludwig PS, Ackermann LW, Stoll LL, Denning GM. Exercise enhances myocardial ischemic tolerance via an opioid receptor-dependent mechanism. Am J Physiol Heart Circ Physiol. 2008;294:H402–8.
21. Galvão TF, Matos KC, Brum PC, Negrão CE, Luz PL, Chagas AC. Cardioprotection conferred by exercise training is blunted by blockade of the opioid system. Clinics (Sao Paulo). 2011;66:151–7.
22. Barron BA. Cardiac opioids. Proc Soc Exp Biol Med. 2000;224:1–7.
23. Younès A, Pepe S, Barron BA, Spurgeon HA, Lakatta EG, Caffrey JL. Cardiac synthesis, processing, and coronary release of enkephalin-related peptides. Am J Physiol Heart Circ Physiol. 2000;279: H1989–98.
24. Varrassi G, Bazzano C, Edwards WT. Effects of physical activity on maternal plasma β-endorphin levels and perception of labor pain. Am J Obstet Gynecol. 1989;160(3):707–12. https://doi.org/10.1016/S0002-9378(89)80065-1.
25. Falcone C, Guasti L, Ochan M, Codega S, Tortorici M, Angoli L, Bergamaschi R, Montemartini C. Beta-endorphins during coronary angioplasty in patients with silent or symptomatic myocardial ischemia. J Am Coll Cardiol. 1993;22(6):1614–20.
26. Zatta AJ, Kin H, Yoshishige D, Jiang R, Wang N, Reeves JG, Mykytenko J, Guyton RA, Zhao ZQ, Caffrey JL, Vinten-Johansen J. Evidence that cardioprotection by postconditioning involves preservation of myocardial opioid content and selective opioid receptor activation. Am J Physiol Heart Circ Physiol. 2008;294(3):H1444–51. https://doi.org/10.1152/ajpheart.01279.2006.
27. Pepe S, van den Brink OW, Lakatta EG, Xiao RP. Cross-talk of opioid peptide receptor and beta-adrenergic receptor signaling in the heart. Cardiovasc Res. 2004;63:414–22.
28. Younès A, Pepe S, Yoshishige D, Caffrey JL, Lakatta EG. Ischemic preconditioning increases the bioavailability of cardiac enkephalins. Am J Phys. 2005;289: H1652–61.
29. Farias M, Jackson K, Yoshishige D, Caffrey JL. Bimodal δ-opioid receptors regulate vagal bradycardia in canine sinoatrial node. Am J Phys. 2003;285: H1332–9.
30. Gross ER, Hsu AK, Gross GJ. Opioid-induced cardioprotection occurs via glycogen synthase kinase b inhibition during reperfusion in intact rat hearts. Circ Res. 2004;94:960–6.
31. Jackson KE, Farias M, Stanfill AS, Caffrey JL. Transient arterial occlusion raises enkephalin in the canine sinoatrial node and improves vagal bradycardia. Auton Neurosci. 2001;94:84–92.
32. Headrick JP, Pepe S, Peart JN. Non-analgesic effects of opioids: cardiovascular effects of opioids and their receptor systems. Curr Pharm Des. 2012;18(37): 6090–100.
33. Caffrey JL, Mateo Z, Napier LD, Gaugl JF, Barron BA. Intrinsic cardiac enkephalins inhibit vagal bradycardia in the dog. Am J Phys. 1995;268:H848–55.
34. Caffrey JL. Enkephalin inhibits vagal control of heart rate, contractile force and coronary blood flow in the canine heart in vivo. J Auton Nerv Syst. 1999;76:75–82.
35. Hayashi K, Tanaka A. Effect-site concentrations of remifentanil causing bradycardia in hypnotic and non-hypnotic patients. J Clin Monit Comput. 2016;30(6):919–24.
36. Hanouz JL, Yvon A, Guesne G, Eustratiades C, Babatasi G, Rouet R, Ducouret P, Khayat A, Bricard H, Gérard JL. The in vitro effects of remifentanil, sufentanil, fentanyl, and alfentanil on isolated human right atria. Anesth Analg. 2001;93(3):543–9.
37. Wu C, Fry CH, Henry J. The mode of action of several opioids on cardiac muscle. Exp Physiol. 1997; 82:261–72.
38. Huang MH, Nguyen V, Wu Y, Rastogi S, Lui CY, Birnbaum Y, Wang HQ, Ware DL, Chauhan M, Garg

N, Poh KK, Ye L, Omar AR, Tan HC, Uretsky BF, Fujise K. Reducing ischaemia/reperfusion injury through delta-opioid-regulated intrinsic cardiac adrenergic cells: adrenopeptidergic co-signaling. Cardiovasc Res. 2009;84(3):452–60. https://doi.org/10.1093/cvr/cvp233.
39. Maslov LN, Barzakh EI, Platonov AA, Minin SM, Ovchinnikov MV. Chronotropic effect of D-Ala2, Leu5,Arg6-enkephalin (dalargin) is associated with activation of peripheral kappa-opioid receptors. Bull Exp Biol Med. 2005;140:682–6.
40. Katchman AN, Koerner J, Tosaka T, Woosley RL, Ebert SN. Comparative evaluation of HERG currents and QT intervals following challenge with suspected torsadogenic and nontorsadogenic drugs. J Pharmacol Exp Ther. 2006;316:1098–106.
41. Westermeyer J, Adabag S, Anand V, Thuras P, Yoon G, Batres-Y-Carr T. Methadone maintenance dose/weight ratio, long QTc, and EKG screening. Am J Addict. 2016;25(6):499–507. https://doi.org/10.1111/ajad.12423.
42. Krantz MJ, Lewkowiez L, Hays H, Woodroffe MA, Robertson AD, Mehler PS. Torsade de pointes associated with very-high-dose methadone. Ann Intern Med. 2002;137:501–4.
43. Anghelescu DL, Patel RM, Mahoney DP, Trujillo L, Faughnan LG, Steen BD, Baker JN, Pei D. Methadone prolongs cardiac conduction in young patients with cancer-related pain. J Opioid Manag. 2016;12(2):131–8. https://doi.org/10.5055/jom.2016.0325.
44. Keller GA, Villa Etchegoyen MC, Fernández N, Olivera NM, Quiroga PN, Diez RA, Di Girolamo G. Meperidine-induced QTc-interval prolongation: prevalence, risk factors, and correlation to plasma drug and metabolite concentrations. Int J Clin Pharmacol Ther. 2017;55(3):275–85. https://doi.org/10.5414/CP202612.
45. DeSilva RA, Vemer RL, Lown B. Protective effect of the vagotonic action of morphine sulphate on ventricular vulnerability. Cardiovasc Res. 1978;12:167–72.
46. Laubie M, Schmitt H, Canellas I, Roquebert J, Demichel P. Centrally mediated bradycardia and hypotension induced by narcotic analgesics: dextromoramide and fentanyl. Eur J Pharmacol. 1974;28:66–75.
47. Laubie M, Schmitt H, Drouillat M. Central sites and mechanisms of the hypotensive and bradycardic effects of the narcotic analgesic agent fentanyl. Naunyn Schmiedeberg's Arch Pharmacol. 1977;296:255–61.
48. Eggleston W, Marraffa JM, Stork CM, Mercurio-Zappala M, Su MK, Wightman RS, Cummings KR, Schier JG. Notes from the field: cardiac dysrhythmias after loperamide abuse – New York, 2008–2016. MMWR Morb Mortal Wkly Rep. 2016;65(45):1276–7. https://doi.org/10.15585/mmwr.mm6545a7.
49. Vaughn P, Solik MM, Bagga S, Padanilam BJ. Electrocardiographic abnormalities, malignant ventricular arrhythmias, and cardiomyopathy associated with loperamide abuse. J Cardiovasc Electrophysiol. 2016;27(10):1230–3. https://doi.org/10.1111/jce.13052.
50. Eggleston W, Clark KH, Marraffa JM. Loperamide abuse associated with cardiac dysrhythmia and death. Ann Emerg Med. 2017;69(1):83–6. https://doi.org/10.1016/j.annemergmed.2016.03.047.
51. Sessler NE, Walker E, Chickballapur H, Kacholakalayil J, Coplan PM. Disproportionality analysis of buprenorphine transdermal system and cardiac arrhythmia using FDA and WHO post-marketing reporting system data. Postgrad Med. 2017;129(1):62–8. https://doi.org/10.1080/00325481.2016.1271698.
52. Cataldo M. Arrhythmia associated with buprenorphine and methadone reported to the Food and Drug Administration. Addiction. 2016;111(9):1685–6. https://doi.org/10.1111/add.13411.
53. Cole JB, Stellpflug SJ, Smith SW. Refractory hypotension and "ventricular fibrillation" with large U waves after overdose. JAMA Intern Med. 2016;176(7):1007–9. https://doi.org/10.1001/jamainternmed.2016.2065.
54. Gursoy S, Bagcivan I, Yildirim MK, Berkan O, Kaya T. Vasorelaxant effect of opioid analgesics on the isolated human radial artery. Eur J Anaesthesiol. 2006;23:496–500.
55. Ruan X, Chiravuri S, Kaye AD. The narrative review on morphine in acute coronary syndrome: recognizing opioidergic cardioprotection. Am Heart J. 2016;180:e5–6. https://doi.org/10.1016/j.ahj.2016.07.008.
56. Heusch G. Molecular basis of cardioprotection: signal transduction in ischemic pre-, post-, and remote conditioning. Circ Res. 2015;116:674–99. https://doi.org/10.1161/CIRCRESEAHA.116.305348.
57. Kharbanda RK. Cardiac conditioning: a review of evolving strategies to reduce ischaemia-reperfusion injury. Heart. 2010;96:1179–86.
58. Zhao ZQ, Corvera JS, Halkos ME, Kerendi F, Wang NP, Guyton RA, Vinten-Johansen J. Inhibition of myocardial injury by ischemic postconditioning during reperfusion: comparison with ischemic preconditioning. Am J Physiol Heart Circ Physiol. 2003;285:H579–88.
59. Yang XC, Liu Y, Wang LF, Cui L, Wang T, Ge YG, Wang HS, Li WM, Xu L, Ni ZH, Liu SH, Zhang L, Jia HM, Vinten-Johansen J, Zhao ZQ. Reduction in myocardial infarct size by postconditioning in patients after percutaneous coronary intervention. J Invasive Cardiol. 2007;19(10):424–30.
60. Wong GT, Li R, Jiang LL, Irwin MG. Remifentanil postconditioning attenuates cardiac ischemia-reperfusion injury via kappa or delta opioid receptor activation. Acta Anaesthesiol Scand. 2010;54:510–8.
61. Guo HT, Zhang RH, Zhang Y, Zhang LJ, Li J, Shi QX, Wang YM, Fan R, Bi H, Yin W, Pei JM. Endogenous κ-opioid peptide mediates the cardioprotection induced by ischemic postconditioning. J Cardiovasc Pharmacol. 2011;58(2):207–15. https://doi.org/10.1097/FJC.0b013e318220e37f.

62. Gross ER, Hsu AK, Gross GJ. Acute methadone treatment reduces myocardial infarct size via the delta-opioid receptor in rats during reperfusion. Anesth Analg. 2009;109:1395–402.
63. Tong G, Sun Z, Wei X, Gu C, Kaye AD, Wang Y, Li J, Zhang Q, Guo H, Yu S, Yi D, Pei J. U50,488H post-conditioning reduces apoptosis after myocardial ischemia and reperfusion. Life Sci. 2011;88(1–2):31–8. https://doi.org/10.1016/j.lfs.2010.10.018.
64. Patel HH, Moore J, Hsu AK, Gross GJ. Cardioprotection at a distance: mesenteric artery occlusion protects the myocardium via an opioid sensitive mechanism. J Mol Cell Cardiol. 2002;34:1317–23.
65. Yao L, Wong GT, Xia Z, Irwin MG. Interaction between spinal opioid and adenosine receptors in remote cardiac preconditioning: effect of intrathecal morphine. J Cardiothorac Vasc Anesth. 2011;25:444–8.
66. Zhang Y, Irwin MG, Lu Y, Mei B, Zuo YM, Chen ZW, Wong TM. Intracerebroventricular administration of morphine confers remote cardioprotection – role of opioid receptors and calmodulin. Eur J Pharmacol. 2011;656(1–3):74–80. https://doi.org/10.1016/j.ejphar.2011.01.027.
67. Rentoukas I, Giannopoulos G, Kaoukis A, Kossyvakis C, Raisakis K, Driva M, Panagopoulou V, Tsarouchas K, Vavetsi S, Pyrgakis V, Deftereos S. Cardioprotective role of remote ischemic periconditioning in primary percutaneous coronary intervention: enhancement by opioid action. JACC Cardiovasc Interv. 2010;3(1):49–55. https://doi.org/10.1016/j.jcin.2009.10.015.
68. Chen A, Ashburn MA. Cardiac effects of opioid therapy. Pain Med. 2015;16:S27–31. https://doi.org/10.1111/pme.12915.
69. Bolte C, Newman G, Schultz Jel J. Kappa and delta opioid receptor signaling is augmented in the failing heart. J Mol Cell Cardiol. 2009;47:493–503.
70. Siong Chan DC, Cao TH, Ng LL. Proenkephalin in heart failure. Heart Fail Clin. 2018;14(1):1–11. https://doi.org/10.1016/j.hfc.2017.08.001.
71. He SF, Jin SY, Yang W, Pan YL, Huang J, Zhang SJ, Zhang L, Zhang Y. Cardiac μ-opioid receptor contributes to opioid-induced cardioprotection in chronic heart failure. Br J Anaesth. 2018;121(1):26–37. https://doi.org/10.1016/j.bja.2017.11.110.
72. Van Iterson EH, Johnson BD, Joyner MJ, Curry TB, Olson TP. $\dot{V}o_2$ kinetics associated with moderate-intensity exercise in heart failure: impact of intrathecal fentanyl inhibition of group III/IV locomotor muscle afferents. Am J Physiol Heart Circ Physiol. 2017;313(1):H114–24. https://doi.org/10.1152/ajpheart.00014.2017.
73. Ebrahimi F, Tavakoli S, Hajrasouliha AR, Sadeghipour H, Dehghani M, Ahmadi SH, Dehpour AR. Involvement of endogenous opioid peptides and nitric oxide in the blunted chronotropic and inotropic responses to beta-adrenergic stimulation in cirrhotic rats. Fundam Clin Pharmacol. 2006;20(5):461–71.
74. Gaskari SA, Mani AR, Ejtemaei-Mehr S, Namiranian K, Homayoun H, Ahmadi H, Dehpour AR. Do endogenous opioids contribute to the bradycardia of rats with obstructive cholestasis? Fundam Clin Pharmacol. 2002;16(4):273–9.
75. Wong SC, Ingenito AJ. Possible opioid receptor function changes in isolated atria of the spontaneously hypertensive rat. Gen Pharmacol. 1993;24:1483–90.
76. Zhou Y, Wang Y, Wang X, Tian X, Zhang S, Yang F, Guo H, Fan R, Feng N, Jia M, Gu X, Wang Y, Li J, Pei J. The protective effects of K-opioid receptor stimulation in hypoxic pulmonary hypertension involve inhibition of autophagy through the AMPK-MTOR pathway. Cell Physiol Biochem. 2017;44(5):1965–79. https://doi.org/10.1159/000485886.
77. Rawal H, Patel BM. Opioids in cardiovascular disease: therapeutic options. J Cardiovasc Pharmacol Ther. 2018;23(4):279–91. https://doi.org/10.1177/1074248418757009.
78. Strawson J. Nonsteroidal anti-inflammatory drugs and cancer pain. Curr Opin Support Palliat Care. 2018; https://doi.org/10.1097/SPC.0000000000000332.
79. Shah K, Gupta JK, Chauhan NS, Upmanyu N, Shrivastava SK, Mishra P. Prodrugs of NSAIDs: a review. Open Med Chem J. 2017;11:146–95. https://doi.org/10.2174/1874104501711010146.
80. Rasmussen S. NSAIDs are superior to paracetamol for osteoarthritic pain and function in a network meta-analysis. BMJ Evid Based Med. 2018;23(1):40–1. https://doi.org/10.1136/ebmed-2017-110878.
81. Aranda JV, Salomone F, Valencia GB, Beharry KD. Non-steroidal anti-inflammatory drugs in newborns and infants. Pediatr Clin N Am. 2017;64(6):1327–40. https://doi.org/10.1016/j.pcl.2017.08.009.
82. Desborough MJR, Keeling DM. The aspirin story – from willow to wonder drug. Br J Haematol. 2017;177(5):674–83. https://doi.org/10.1111/bjh.14520.
83. Vane JR, Warner TD. Nomenclature for COX-2 inhibitors. Lancet. 2000;356(9239):1373–4.
84. Howard PA, Delafontaine P. Nonsteroidal anti-inflammatory drugs and cardiovascular risk. J Am Coll Cardiol. 2004;43(4):519–25.
85. Warner TD, Mitchell JA. Cyclooxygenase: new forms, new inhibitors, and lesson from the clinic. FASEB J. 2004;18:790–804.
86. Ferreira SH, Moncada S, Vane JR. Indomethacin and aspirin abolish prostaglandin release from the spleen. Nat New Biol. 1971;231(25):237–9.
87. Smith JB, Willis AL. Aspirin selectively inhibits prostaglandin production in human platelets. Nat New Biol. 1971;231(25):235–7.
88. Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. Nat New Biol. 1971;231(25):232–5.
89. Rosen GD, Birkenmeier TM, Raz A, Holtzman MJ. Identification of a cyclooxygenase-related gene and its potential role in prostaglandin formation. Biochem Biophys Res Commun. 1989;164(3):1358–65.

90. Dubois RN, Abramson SB, Crofford L, Gupta RA, Simon LS, Van De Putte LB, Lipsky PE. Cyclooxygenase in biology and disease. FASEB J. 1998;12 (12):1063–73.
91. Kujubu DA, Fletcher BS, Varnum BC, Lim RW, Herschman HR. TIS10, a phorbol ester tumor promoter-inducible mRNA from Swiss 3T3 cells, encodes a novel prostaglandin synthase/cyclooxygenase homologue. J Biol Chem. 1991;266(20):12866–72.
92. O'Banion MK, Winn VD, Young DA. cDNA cloning and functional activity of a glucocorticoid-regulated inflammatory cyclooxygenase. Proc Natl Acad Sci U S A. 1992;89(11):4888–92.
93. Xie WL, Chipman JG, Robertson DL, Erikson RL, Simmons DL. Expression of a mitogen-responsive gene encoding prostaglandin synthase is regulated by mRNA splicing. Proc Natl Acad Sci U S A. 1991;88(7):2692–6.
94. Hla T, Neilson K. Human cyclooxygenase-2 cDNA. Proc Natl Acad Sci U S A. 1992;89(16):7384–8.
95. Masferrer JL, Seibert K, Zweifel B, Needleman P. Endogenous glucocorticoids regulate an inducible cyclooxygenase enzyme. Proc Natl Acad Sci U S A. 1992;89(9):3917–21.
96. Mitchell JA, Akarasereenont P, Thiemermann C, Flower RJ, Vane JR. Selectivity of nonsteroidal antiinflammatory drugs as inhibitors of constitutive and inducible cyclooxygenase. Proc Natl Acad Sci U S A. 1993;90(24):11693–7.
97. Vane JR, Bakhle YS, Botting RM. Cyclooxygenases 1 and 2. Annu Rev Pharmacol Toxicol. 1998;38:97–120.
98. Catella-Lawson F, McAdam B, Morrison BW, Kapoor S, Kujubu D, Antes L, Lasseter KC, Quan H, Gertz BJ, FitzGerald GA. Effects of specific inhibition of cyclooxygenase-2 on sodium balance, hemodynamics, and vasoactive eicosanoids. J Pharmacol Exp Ther. 1999;289(2):735–41.
99. FitzGerald GA, Patrono C. The coxibs, selective inhibitors of cyclooxygenase-2. N Engl J Med. 2001;345(6):433–42.
100. Flower RJ. The development of COX2 inhibitors. Nat Rev Drug Discov. 2003;2(3):179–91.
101. McAdam BF, Catella-Lawson F, Mardini IA, Kapoor S, Lawson JA, FitzGerald GA. Systemic biosynthesis of prostacyclin by cyclooxygenase (COX)-2: the human pharmacology of a selective inhibitor of COX-2. Proc Natl Acad Sci U S A. 1999;96(1):272–7.
102. Mitchell JA, Evans TW. Cyclooxygenase-2 as a therapeutic target. Inflamm Res. 1998;47(Suppl 2):S88–92.
103. Hara S. Prostaglandin terminal synthases as novel therapeutic targets. Proc Jpn Acad Ser B Phys Biol Sci. 2017;93(9):703–23. https://doi.org/10.2183/pjab.93.044.
104. Scarpignato C, Hunt RH. Nonsteroidal antiinflammatory drug-related injury to the gastrointestinal tract: clinical picture, pathogenesis, and prevention. Gastroenterol Clin N Am. 2010;39:433–64. https://doi.org/10.1016/j.gtc.2010.08.010.
105. Shin SJ, Noh CK, Lim SG, Lee KM, Lee KJ. Nonsteroidal anti-inflammatory drug-induced enteropathy. Intest Res. 2017;15(4):446–55. https://doi.org/10.5217/ir.2017.15.4.446.
106. Aboul-Hassan SS, Stankowski T, Marczak J, Peksa M, Nawotka M, Stanislawski R, Kryszkowski B, Cichon R. The use of preoperative aspirin in cardiac surgery: a systematic review and meta-analysis. J Card Surg. 2017;32(12):758–774. https://doi.org/10.1111/jocs.13250. Epub 2017 Dec 3.
107. Rodriguez LA. The effect of NSAIDs on the risk of coronary heart disease: fusion of clinical pharmacology and pharmacoepidemiologic data. Clin Exp Rheumatol. 2001;19(Suppl 25):S41–4.
108. Belton O, Byrne D, Kearney D, Leahy A, FitzGerald DJ. Cyclooxygenase-1 and -2-dependent prostacyclin formation in patients with atherosclerosis. Circulation. 2000;102(8):840–5.
109. Censarek P, Freidel K, Udelhoven M, Ku SJ, Hohlfeld T, Meyer-Kirchrath J, Schrör K, Weber AA. Cyclooxygenase COX-2a, a novel COX-2 mRNA variant, in platelets from patients after coronary artery bypass grafting. Thromb Haemost. 2004;92(5):925–8.
110. Bishop-Bailey D, Pepper JR, Larkin SW, Mitchell JA. Differential induction of cyclooxygenase-2 in human arterial and venous smooth muscle: role of endogenous prostanoids. Arterioscler Thromb Vasc Biol. 1998;18(10):1655–61.
111. Jimenez R, Belcher E, Sriskandan S, Lucas R, McMaster S, Vojnovic I, Warner TD, Mitchell JA. Role of Toll-like receptors 2 and 4 in the induction of cyclooxygenase-2 in vascular smooth muscle. Proc Natl Acad Sci U S A. 2005;102(12):4637–42.
112. Inoue H, Taba Y, Miwa Y, Yokota C, Miyagi M, Sasaguri T. Transcriptional and posttranscriptional regulation of cyclooxygenase-2 expression by fluid shear stress in vascular endothelial cells. Arterioscler Thromb Vasc Biol. 2002;22(9):1415–20.
113. Hamberg M, Svensson J, Samuelsson B. Thromboxanes: a new group of biologically active compounds derived from prostaglandin endoperoxides. Proc Natl Acad Sci U S A. 1975;72:2994–8.
114. Moncada S, Gryglewski R, Bunting S, Vane JR. An enzyme isolated from arteries transforms prostaglandin endoperoxides to an unstable substance that inhibits platelet aggregation. Nature. 1976;263(5579):663–5.
115. Patrono C. Cardiovascular effects of cyclooxygenase-2 inhibitors: a mechanistic and clinical perspective. Br J Clin Pharmacol. 2016;82(4):957–64. https://doi.org/10.1111/bcp.13048.
116. Patrono C. Aspirin: new cardiovascular uses for an old drug. Am J Med. 2001;110(1A):62S–5S.
117. Roth GJ, Machuga ET, Ozols J. Isolation and covalent structure of the aspirin-modified, active-site region of prostaglandin synthetase. Biochemistry. 1983;22: 4672–5.
118. Pedersen AK, FitzGerald GA. Dose-related kinetics of aspirin. Presystemic acetylation of platelet cyclooxygenase. N Engl J Med. 1984;311(19):1206–11.

119. Bjarnason I, Scarpignato C, Holmgren E, Olszewski M, Rainsford KD, Lanas A. Mechanisms of damage to the gastrointestinal tract from nonsteroidal anti-inflammatory drugs. Gastroenterology. 2018;154(3):500–514. https://doi.org/10.1053/j.gastro.2017.10.049. Epub 2017 Dec 6.
120. Cata JP, Guerra CE, Chang GJ, Gottumukkala V, Joshi GP. Non-steroidal anti-inflammatory drugs in the oncological surgical population: beneficial or harmful? A systematic review of the literature. Br J Anaesth. 2017;119(4):750–64. https://doi.org/10.1093/bja/aex225.
121. Schug SA, Parsons B, Li C, Xia F. The safety profile of parecoxib for the treatment of postoperative pain: a pooled analysis of 28 randomized, double-blind, placebo-controlled clinical trials and a review of over 10 years of postauthorization data. J Pain Res. 2017;10:2451–9. https://doi.org/10.2147/JPR.S136052.
122. Alexanian A, Sorokin A. Cyclooxygenase 2: protein-protein interactions and posttranslational modifications. Physiol Genomics. 2017;49(11):667–81. https://doi.org/10.1152/physiolgenomics.00086.2017.
123. Bombardier C, Laine L, Reicin A, Shapiro D, Burgos-Vargas R, Davis B, Day R, Ferraz MB, Hawkey CJ, Hochberg MC, Kvien TK, Schnitzer TJ, VIGOR Study Group. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. N Engl J Med. 2000;343(21):1520–8.
124. Thomas D, Ali Z, Zachariah S, Sundararaj KGS, Van Cuyk M, Cooper JC. Coxibs refocus attention on the cardiovascular risks of non-aspirin NSAIDs. Am J Cardiovasc Drugs. 2017;17(5):343–6. https://doi.org/10.1007/s40256-017-0223-6.
125. Watson DJ, Rhodes T, Guess HA. All-cause mortality and vascular events among patients with rheumatoid arthritis, osteoarthritis, or no arthritis in the UK general practice research database. J Rheumatol. 2003;30(6):1196–202.
126. Silverstein FE, Faich G, Goldstein JL, Simon LS, Pincus T, Whelton A, Makuch R, Eisen G, Agrawal NM, Stenson WF, Burr AM, Zhao WW, Kent JD, Lefkowith JB, Verburg KM, Geis GS. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. JAMA. 2000;284(10):1247–55.
127. Solomon SD, McMurray JJ, Pfeffer MA, Wittes J, Fowler R, Finn P, Anderson WF, Zauber A, Hawk E, Bertagnolli M, Adenoma Prevention with Celecoxib (APC) Study Investigators. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. N Engl J Med. 2005;352(11):1071–80.
128. Bresalier RS, Sandler RS, Quan H, Bolognese JA, Oxenius B, Horgan K, Lines C, Riddell R, Morton D, Lanas A, Konstam MA, Baron JA, Adenomatous Polyp Prevention on Vioxx (APPROVe) Trial Investigators. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. N Engl J Med. 2005;352(11):1092–102.
129. Veettil SK, Lim KG, Ching SM, Saokaew S, Phisalprapa P, Chaiyakunapruk N. Effects of aspirin and non-aspirin nonsteroidal anti-inflammatory drugs on the incidence of recurrent colorectal adenomas: a systematic review with meta-analysis and trial sequential analysis of randomized clinical trials. BMC Cancer. 2017;17(1):763. https://doi.org/10.1186/s12885-017-3757-8.
130. Breitner J, Baker L, Drye L, Evans D, Lyketsos C, Ryan L, Zandi P, Baker L, Breitner J, Saucedo HH, Anau J, Cholerton B, Kramer K, Bloomberg JH, Zandi P, Drye L, Shanklin Casper A, Meinert C, Martin B, Jenkins G, McCaffrey L, Meinert J, Vaidya V, Ahuja A, May P, Ryan L, Lyketsos CG, Steinberg M, Brandt J, Pedroso JJ, Bergey A, Gogel C, Smith L, Kraus J, Stern RA, Green RC, Gavett B, Mwicigi J, Baldwin L, McGowan T, Johnson P, Qiu W, Frederick J, Raghavan S, Rossi C, Mandell A, Dinizo D, Roth T, Porsteinsson A, Ismail M, Brand C, Richard J, Stear K, Schepp S, Cosman K, Martin K, Craft S, Baker L, Dahl D, Garrett G, Tidwell J, Thielke S, Smith L, Arbuckle M, Strong W, Ladenberg J, Callaghan M, Watson S, Skinner J, Bowton K, Sabbagh M, Belden C, Liebsack C, Davis K, Arnieri L, Malek-Ahmadi M, Nicholson L, Jacobson S, Schwartz E, Mullan M, Luis C, Parrish J, Faircloth M, Ervin T, Girard J, Burke D, Keegan A, Evans D. Results of a follow-up study to the randomized Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT). Alzheimers Dement. 2013;9(6):714–23. https://doi.org/10.1016/j.jalz.2012.11.012.
131. Hippisley-Cox J, Coupland C. Risk of myocardial infarction in patients taking cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs: population based nested case-control analysis. BMJ. 2005;330(7504):1366.
132. Horgas AL. Pain management in older adults. Nurs Clin North Am. 2017;52(4):e1–7. https://doi.org/10.1016/j.cnur.2017.08.001.
133. Graham DJ, Campen D, Hui R, Spence M, Cheetham C, Levy G, Shoor S, Ray WA. Risk of acute myocardial infarction and sudden cardiac death in patients treated with cyclo-oxygenase 2 selective and non-selective nonsteroidal anti-inflammatory drugs: nested case–control study. Lancet. 2005;365:475–81.
134. Kearney PM, Baigent C, Godwin J, Halls H, Emberson JR, Patrono C. Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomized trials. BMJ. 2006;332(7553):1302–8.
135. Bally M, Nadeau L, Brophy JM. Studying additive interaction in a healthcare database: case study of NSAIDs, cardiovascular profiles, and acute myocardial infarction. PLoS One. 2018;13(8):e0201884. https://doi.org/10.1371/journal.pone.0201884.

136. Quinn T. Review: real-world use of nonsteroidal anti-inflammatory drugs is associated with acute myocardial infarction. Ann Intern Med. 2017;167(6):JC30. https://doi.org/10.7326/ACPJC-2017-167-6-030.
137. Hernandez-Diaz S, Varas-Lorenzo C, Garcia Rodriguez LA. Non-steroidal antiinflammatory drugs and the risk of acute myocardial infarction. Basic Clin Pharmacol Toxicol. 2006;98(3):266–74.
138. Esparza-Villalpando V, Pozos-Guillén A, Masuoka-Ito D, Gaitán-Fonseca C, Chavarría-Bolaños D. Analgesic efficacy of preoperative dexketoprofen trometamol: a systematic review and meta-analysis. Drug Dev Res. 2017; https://doi.org/10.1002/ddr.21419.
139. Moore RA, Barden J. Systematic review of dexketoprofen in acute and chronic pain. BMC Clin Pharmacol. 2008;8:11. https://doi.org/10.1186/1472-6904-8-11.
140. Varrassi G, Hanna M, Macheras G, Montero A, Montes Perez A, Meissner W, Perrot S, Scarpignato C. Multimodal analgesia in moderate-to-severe pain: a role for a new fixed combination of dexketoprofen and tramadol. Curr Med Res Opin. 2017;33(6):1165–73. https://doi.org/10.1080/03007995.2017.1310092.
141. Cannon CP, Curtis SP, FitzGerald GA, Krum H, Kaur A, Bolognese JA, Reicin AS, Bombardier C, Weinblatt ME, van der Heijde D, Erdmann E, Laine L, MEDAL Steering Committee. Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomized comparison. Lancet. 2006;368 (9549):1771–81.
142. McGettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. JAMA. 2006;296 (13):1633–44.
143. Scarpignato C, Lanas A, Blandizzi C, Lems WF, Hermann M, Hunt RH, International NSAID Consensus Group. Safe prescribing of non-steroidal anti-inflammatory drugs in patients with osteoarthritis – an expert consensus addressing benefits as well as gastrointestinal and cardiovascular risks. BMC Med. 2015;13:55. https://doi.org/10.1186/s12916-015-0285-8.
144. Arellano FM, Yood MU, Wentworth CE, et al. Use of cyclooxygenase 2 inhibitors (COX-2) and prescription nonsteroidal anti-inflammatory drugs (NSAIDS) in UK and USA populations. Implications for COX-2 cardiovascular profile. Pharmacoepidemiol Drug Saf. 2006;15(12):861–72.
145. Helin-Salmivaara A, Virtanen A, Vesalainen R, Grönroos JM, Klaukka T, Idänpään-Heikkilä JE, Huupponen R. NSAID use and the risk of hospitalization for first myocardial infarction in the general population: a nationwide case-control study from Finland. Eur Heart J. 2006;27(14):1657–63.
146. Bally M, Dendukuri N, Rich B, Nadeau L, Helin-Salmivaara A, Garbe E, Brophy JM. Risk of acute myocardial infarction with NSAIDs in real world use: bayesian meta-analysis of individual patient data. BMJ. 2017;357:j1909. https://doi.org/10.1136/bmj.j1909.
147. Nissen SE, Yeomans ND, Solomon DH, Lüscher TF, Libby P, Husni ME, Graham DY, Borer JS, Wisniewski LM, Wolski KE, Wang Q, Menon V, Ruschitzka F, Gaffney M, Beckerman B, Berger MF, Bao W, Lincoff AM, PRECISION Trial Investigators. Cardiovascular safety of celecoxib, naproxen, or ibuprofen for arthritis. NEJM. 2016;375:2519–29.
148. Becker MC, Wang TH, Wisniewski L, Wolski K, Libby P, Lüscher TF, Borer JS, Mascette AM, Husni ME, Solomon DH, Graham DY, Yeomans ND, Krum H, Ruschitzka F, Lincoff AM, Nissen SE, PRECISION Investigators. Rationale, design, and governance of Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen Or Naproxen (PRECISION), a cardiovascular end point trial of nonsteroidal antiinflammatory agents in patients with arthritis. Am Heart J. 2009;157(4):606–12. https://doi.org/10.1016/j.ahj.2008.12.014.
149. Arfè A, Scotti L, Varas-Lorenzo C, Nicotra F, Zambon A, Kollhorst B, Schink T, Garbe E, Herings R, Straatman H, Schade R, Villa M, Lucchi S, Valkhoff V, Romio S, Thiessard F, Schuemie M, Pariente A, Sturkenboom M, Corrao G, On behalf of the Safety of Non-steroidal Anti-inflammatory Drugs (SOS) Project Consortium. Non-steroidal anti-inflammatory drugs and risk of heart failure in four European countries: nested case-control study. BMJ. 2016;354:i4857. https://doi.org/10.1136/bmj.i4857.
150. Andersohn F, Schade R, Suissa S, Garbe E. Cyclooxygenase-2 selective nonsteroidal anti-inflammatory drugs and the risk of ischemic stroke: a nested case-control study. Stroke. 2006;37(7):1725–30.
151. Chen LC, Ashcroft DM. Do selective COX-2 inhibitors increase the risk of cerebrovascular events? A meta-analysis of randomized controlled trials. J Clin Pharm Ther. 2006;31(6):565–76.
152. MacDonald TM, Hawkey CJ, Ford I, McMurray JJV, Scheiman JM, Hallas J, Findlay E, Grobbee DE, Hobbs FDR, Ralston SH, Reid DM, Walters MR, Webster J, Ruschitzka F, Ritchie LD, Perez-Gutthann S, Connolly E, Greenlaw N, Wilson A, Wei L, Mackenzie IS. Randomized trial of switching from prescribed non-selective non-steroidal anti-inflammatory drugs to prescribed celecoxib: the Standard care vs. Celecoxib Outcome Trial (SCOT). Eur Heart J. 2017;38(23):1843–50. https://doi.org/10.1093/eurheartj/ehw387.
153. Caughey GE, Roughead EE, Pratt N, Killer G, Gilbert AL. Stroke risk and NSAIDs: an Australian population-based study. Med J Aust. 2011;195(9):525–9.
154. Tacconelli S, Bruno A, Grande R, Ballerini P, Patrignani P. Nonsteroidal anti-inflammatory drugs and cardiovascular safety – translating pharmacological data into clinical readouts. Expert Opin Drug Saf. 2017;16(7):791–807. https://doi.org/10.1080/14740338.2017.1338272.

155. Wang T, Zhai L, Zhang H, Zhao L, Guo Y. Picroside II inhibits the MEK-ERK1/2-COX2 signal pathway to prevent cerebral ischemic injury in rats. J Mol Neurosci. 2015;57(3):335–351. https://doi.org/10.1007/s12031-015-0623-5. Epub 2015 Aug 4.
156. Zhang Y, Hoda MN, Zheng X, Li W, Luo P, Maddipati KR, Seki T, Ergul A, Wang MH. Combined therapy with COX-2 inhibitor and 20-HETE inhibitor reduces colon tumor growth and the adverse effects of ischemic stroke associated with COX-2 inhibition. Am J Physiol Regul Integr Comp Physiol. 2014;307(6):R693–R703. https://doi.org/10.1152/ajpregu.00422.2013. Epub 2014 Jul 2.
157. Ungprasert P, Matteson EL, Thongprayoon C. Non-aspirin nonsteroidal anti-inflammatory drugs and risk of hemorrhagic stroke: a systematic review and meta-analysis of observational studies. Stroke. 2016;47(2):356–64. https://doi.org/10.1161/STROKEAHA.115.011678.
158. Cheng HF, Harris RC. Cyclooxygenases, the kidney, and hypertension. Hypertension. 2004;43(3):525–30.
159. Francois H, Coffman TM. Prostanoids and blood pressure: which way is up? J Clin Invest. 2004;114(6):757–9.
160. Hsu CC, Wang H, Hsu YH, Chuang SY, Huang YW, Chang YK, Liu JS, Hsiung CA, Tsai HJ. Use of nonsteroidal anti-inflammatory drugs and risk of chronic kidney disease in subjects with hypertension: nationwide longitudinal cohort study. Hypertension. 2015;66(3):524–33. https://doi.org/10.1161/HYPERTENSIONAHA.114.05105.
161. Conlin PR, Moore TJ, Swartz SL, Barr E, Gazdick L, Fletcher C, DeLucca P, Demopoulos L. Effect of indomethacin on blood pressure lowering by captopril and losartan in hypertensive patients. Hypertension. 2000;36(3):461–5.
162. Hwang AY, Dave CV, Smith SM. Use of prescription medications that potentially interfere with blood pressure control in new-onset hypertension and treatment-resistant hypertension. Am J Hypertens. 2018; https://doi.org/10.1093/ajh/hpy118.
163. Singh G, Miller JD, Huse DM, Pettitt D, D'Agostino RB, Russell MW. Consequences of increased systolic blood pressure in patients with osteoarthritis and rheumatoid arthritis. J Rheumatol. 2003;30(4):714–9.
164. Dilger K, Herrlinger C, Peters J, Seyberth HW, Schweer H, Klotz U. Effects of celecoxib and diclofenac on blood pressure, renal function, and vasoactive prostanoids in young and elderly subjects. J Clin Pharmacol. 2002;42(9):985–94.
165. El-Gowelli HM, Ibrahim KS, El-Yazbi AF, El-Mas MM. Role of NADPHox/Rho-kinase signaling in the cyclosporine-NSAIDs interactions on blood pressure and baroreflexes in female rats. Life Sci. 2017;185:15–22. https://doi.org/10.1016/j.lfs.2017.07.019.
166. Martinez CS, Piagette JT, Escobar AG, Martín Á, Palacios R, Peçanha FM, Vassallo DV, Exley C, Alonso MJ, Miguel M, Salaices M, Wiggers GA. Aluminum exposure at human dietary levels promotes vascular dysfunction and increases blood pressure in rats: a concerted action of NAD(P)H oxidase and COX-2. Toxicology. 2017;390:10–21. https://doi.org/10.1016/j.tox.2017.08.004. Epub 2017 Aug 19.
167. Swan SK, Rudy DW, Lasseter KC, Ryan CF, Buechel KL, Lambrecht LJ, Pinto MB, Dilzer SC, Obrda O, Sundblad KJ, Gumbs CP, Ebel DL, Quan H, Larson PJ, Schwartz JI, Musliner TA, Gertz BJ, Brater DC, Yao SL. Effect of cyclooxygenase-2 inhibition on renal function in elderly persons receiving a low-salt diet. A randomized, controlled trial. Ann Intern Med. 2000;133(1):1–9.
168. Aw TJ, Haas SJ, Liew D, Krum H. Meta-analysis of cyclooxygenase-2 inhibitors and their effects on blood pressure. Arch Intern Med. 2005;165(5):490–6.
169. Ruschitzka F, Borer JS, Krum H, Flammer AJ, Yeomans ND, Libby P, Lüscher TF, Solomon DH, Husni ME, Graham DY, Davey DA, Wisniewski LM, Menon V, Fayyad R, Beckerman B, Iorga D, Lincoff AM, Nissen SE. Differential blood pressure effects of ibuprofen, naproxen, and celecoxib in patients with arthritis: the PRECISION-ABPM (Prospective Randomized Evaluation of Celecoxib Integrated Safety Versus Ibuprofen or Naproxen Ambulatory Blood Pressure Measurement) Trial. Eur Heart J. 2017;38(44):3282–92. https://doi.org/10.1093/eurheartj/ehx508.
170. Sowers JR, White WB, Pitt B, Whelton A, Simon LS, Winer N, Kivitz A, van Ingen H, Brabant T, Fort JG, Celecoxib Rofecoxib Efficacy and Safety in Comorbidities Evaluation Trial (CRESCENT) Investigators. The effects of cyclooxygenase-2 inhibitors and nonsteroidal anti-inflammatory therapy on 24-hour blood pressure in patients with hypertension, osteoarthritis, and type 2 diabetes mellitus. Arch Intern Med. 2005;165(2):161–8.
171. Whelton A, White WB, Bello AE, Puma JA, Fort JG, SUCCESS-VII Investigators. Effects of celecoxib and rofecoxib on blood pressure and edema in patients > or = 65 years of age with systemic hypertension and osteoarthritis. Am J Cardiol. 2002;90(9):959–63.
172. Pepine CJ, Gurbel PA. Cardiovascular safety of NSAIDs: additional insights after PRECISION and point of view. Clin Cardiol. 2017;40(12):1352–6. https://doi.org/10.1002/clc.22814.
173. Walker C, Biasucci LM. Cardiovascular safety of non-steroidal anti-inflammatory drugs revisited. Postgrad Med. 2018;130(1):55–71. https://doi.org/10.1080/00325481.2018.1412799.
174. Wongrakpanich S, Wongrakpanich A, Melhado K, Rangaswami J. A comprehensive review of non-steroidal antiiInflammatory drug use in the elderly. Aging Dis. 2018;9(1):143–50. https://doi.org/10.14336/AD.2017.0306.
175. Fischer LM, Schlienger RG, Matter CM, Jick H, Meier CR. Discontinuation of nonsteroidal anti-inflammatory drug therapy and risk of acute myocardial infarction. Arch Intern Med. 2004;164(22):2472–6.
176. Kurth T, Glynn RJ, Walker AM, et al. Inhibition of clinical benefits of aspirin on first myocardial

infarction by nonsteroidal antiinflammatory drugs. Circulation. 2003;108(10):1191–5.
177. Maniar KH, Jones IA, Gopalakrishna R, Vangsness CT Jr. Lowering side effects of NSAID usage in osteoarthritis: recent attempts at minimizing dosage. Expert Opin Pharmacother. 2018;19(2):93–102. https://doi.org/10.1080/14656566.2017.1414802.
178. Moore N, Scheiman JM. Gastrointestinal safety and tolerability of oral non-aspirin over-the-counter analgesics. Postgrad Med. 2018;8:1–12. https://doi.org/10.1080/00325481.2018.1429793.
179. Pathan SA, Mitra B, Cameron PA. A systematic review and meta-analysis comparing the efficacy of nonsteroidal anti-inflammatory drugs, opioids, and paracetamol in the treatment of acute renal colic. Eur Urol. 2018;73(4):583–95. pii: S0302-2838(17)30977-6. https://doi.org/10.1016/j.eururo.2017.11.001.
180. Athersuch TJ, Antoine DJ, Boobis AR, Coen M, Daly AK, Possamai L, Nicholson JK, Wilson ID. Paracetamol metabolism, hepatotoxicity, biomarkers and therapeutic interventions: a perspective. Toxicol Res (Camb). 2018;7(3):347–57. https://doi.org/10.1039/c7tx00340d.
181. da Silva DPB, Florentino IF, da Silva DM, Lino RC, Cardoso CS, Moreira LKS, Vasconcelos GA, Vinhal DC, Cardoso ACD, Villavicencio B, Verli H, Vaz BG, Lião LM, da Cunha LC, Menegatti R, Costa EA. Molecular docking and pharmacological/toxicological assessment of a new compound designed from celecoxib and paracetamol by molecular hybridization. Inflammopharmacology. 2018; https://doi.org/10.1007/s10787-018-0516-7. Epub ahead of print.
182. Bateman DN. Paracetamol poisoning: beyond the nomogram. Br J Clin Pharmacol. 2015;80(1):45–50. https://doi.org/10.1111/bcp.12604.
183. Roberts E, Delgado Nunes V, Buckner S, Latchem S, Constanti M, Miller P, Doherty M, Zhang W, Birrell F, Porcheret M, Dziedzic K, Bernstein I, Wise E, Conaghan PG. Paracetamol: not as safe as we thought? A systematic literature review of observational studies. Ann Rheum Dis. 2016;75(3):552–9. https://doi.org/10.1136/annrheumdis-2014-206914.
184. Vliegenthart AD, Shaffer JM, Clarke JI, Peeters LE, Caporali A, Bateman DN, Wood DM, Dargan PI, Craig DG, Moore JK, Thompson AI, Henderson NC, Webb DJ, Sharkey J, Antoine DJ, Park BK, Bailey MA, Lader E, Simpson KJ, Dear JW. Comprehensive microRNA profiling in acetaminophen toxicity identifies novel circulating biomarkers for human liver and kidney injury. Sci Rep. 2015;5:15501. https://doi.org/10.1038/srep15501.
185. Curhan GC, Willett WC, Rosner B, Stampfer MJ. Frequency of analgesic use and risk of hypertension in younger women. Arch Intern Med. 2002;162(19):2204–8.
186. Forman JP, Stampfer MJ, Curhan GC. Non-narcotic analgesic dose and risk of incident hypertension in US women. Hypertension. 2005;46(3):500–7.
187. White WB, Kloner RA, Angiolillo DJ, Davidson MH. Cardiorenal safety of OTC analgesics. J Cardiovasc Pharmacol Ther. 2018;23(2):103–18. https://doi.org/10.1177/1074248417751070.
188. Chan AT, Manson JE, Albert CM, Chae CU, Rexrode KM, Curhan GC, Rimm EB, Willett WC, Fuchs CS. Nonsteroidal antiinflammatory drugs, acetaminophen, and the risk of cardiovascular events. Circulation. 2006;113(12):1578–87.
189. Dedier J, Stampfer M, Hankinson S, Willett WC, Speizer FE, Curhan GC. Nonnarcotic analgesic use and the risk of hypertension in US women. Hypertension. 2002;40:604–8.
190. de Vries F, Setakis E, van Staa TP. Concomitant use of ibuprofen and paracetamol and the risk of major clinical safety outcomes. Br J Clin Pharmacol. 2010;70:429–38. https://doi.org/10.1111/j.1365-2125.2010.03705.x.
191. Beach SR, Celano CM, Noseworthy PA, Januzzi JL, Huffman JC. QTc prolongation, torsades de pointes, and psychotropic medications. Psychosomatics. 2013;54(1):1–13.
192. Beach SR, Kostis WJ, Celano CM, Januzzi JL, Ruskin JN, Noseworthy PA, Huffman JC. Meta-analysis of selective serotonin reuptake inhibitor-associated QTc prolongation. J Clin Psychiatry. 2014;75(5):e441–9.
193. Funai Y, Funao T, Ikenaga K, Takahashi R, Hase I, Nishikawa K. Use of tricyclic antidepressants as analgesic adjuvants results in nonhazardous prolongation of the QTc interval. Osaka City Med J. 2014;60(1):11–9.
194. Hasnain M, Vieweg WV. QTc interval prolongation and torsade de pointes associated with second-generation antipsychotics and antidepressants: a comprehensive review. CNS Drugs. 2014;28(10):887–920.
195. Jasiak NM, Bostwick JR. Risk of QT/QTc prolongation among newer nonSSRI antidepressants. Ann Pharmacother. 2014;48(12):1620–8.
196. Maljuric NM, Noordam R, Aarts N, Niemeijer MN, van den Berg ME, Hofman A, Kors JA, Stricker BH, Visser LE. Use of selective serotonin re-uptake inhibitors and the heart rate corrected QT interval in a real-life setting: the population-based Rotterdam Study. Br J Clin Pharmacol. 2015;80(4):698–705.
197. Sala M, Coppa F, Cappucciati C, Brambilla P, d'Allio G, Caverzasi E, Barale F, De Ferrari GM. Antidepressants: their effects on cardiac channels, QT prolongation and Torsade de Pointes. Curr Opin Investig Drugs. 2006;7(3):256–63.
198. Spindelegger CJ, Papageorgiou K, Grohmann R, Engel R, Greil W, Konstantinidis A, Agelink MW, Bleich S, Ruether E, Toto S, Kasper S. Cardiovascular adverse reactions during antidepressant treatment: a drug surveillance report of German-speaking countries between 1993 and 2010. Int J Neuropsychopharmacol. 2014;18(4). pii: pyu080. https://doi.org/10.1093/ijnp/pyu080.
199. Tisdale JE. Drug-induced QT interval prolongation and torsades de pointes: role of the pharmacist in

risk assessment, prevention and management. Can Pharm J (Ott). 2016;149(3):139–52.
200. Varney A, Womersley K, Agius M. What are the risks associated with the use of NSAIDs as an adjunct to SSRIs for treatment of depression? An evaluation of current evidence. Psychiatr Danub. 2017;29 (Suppl 3):375–82.
201. Johnson EM, Whyte E, Mulsant BH, Pollock BG, Weber E, Begley AE, Reynolds CF. Cardiovascular changes associated with venlafaxine in the treatment of late-life depression. Am J Geriatr Psychiatry. 2006;14(9):796–802.
202. Roberts RL, Joyce PR, Mulder RT, Begg EJ, Kennedy MA. A common P-glycoprotein polymorphism is associated with nortriptyline-induced postural hypotension in patients treated for major depression. Pharmacogenomics J. 2002;2(3):191–6.
203. Veith RC, Raskind MA, Caldwell JH, Barnes RF, Gumbrecht G, Ritchie JL. Cardiovascular effects of tricyclic antidepressants in depressed patients with chronic heart disease. N Engl J Med. 1982;306(16): 954–9.
204. Kim J, Phongsamran P, Park S. Use of antidepressant drugs in transplant recipients. Prog Transplant. 2004;14(2):98–104.
205. Lee YC, Lin CH, Lin MS, Lin JW, Chang CH, Lai MS. Effects of selective serotonin reuptake inhibitors versus tricyclic antidepressants on cerebrovascular events: a nationwide population-based cohort study. J Clin Psychopharmacol. 2013;33(6):782–9.
206. Thanacoody HK, Thomas SH. Tricyclic antidepressant poisoning: cardiovascular toxicity. Toxicol Rev. 2005;24(3):205–14.
207. Kahl KG, Westhoff-Bleck M, Krüger THC. Effects of psychopharmacological treatment with antidepressants on the vascular system. Vascular Pharmacol. 2017; 96–98:11–8. https://doi.org/10.1016/j.vph.2017.07.004.
208. Kremer M, Salvat E, Muller A, Yalcin I, Barrot M. Antidepressants and gabapentinoids in neuropathic pain: mechanistic insights. Neuroscience. 2016;338: 183–206. https://doi.org/10.1016/j.neuroscience.2016.06.057.
209. Patel R, Dickenson AH. Mechanisms of the gabapentinoids and α 2 δ-1 calcium channel subunit in neuropathic pain. Pharmacol Res Perspect. 2016;4(2): e00205. https://doi.org/10.1002/prp2.205.
210. Moore RA, Wiffen PJ, Derry S, McQuay HJ. Gabapentin for chronic neuropathic pain and fibromyalgia in adults. Cochrane Database Syst Rev. 2011; (3): CD007938.
211. Zaccara G, Gangemi P, Perucca P, Specchio L. The adverse event profile of pregabalin: a systematic review and metaanalysis of randomized controlled trials. Epilepsia. 2011;52:826–36.
212. Dieleman JM, Nierich AP, Rosseel PM, van der Maaten JM, Hofland J, Diephuis JC, Schepp RM, Boer C, Moons KG, van Herwerden LA, Tijssen JG, Numan SC, Kalkman CJ, van Dijk D. Intraoperative high-dose dexamethasone for cardiac surgery: a randomized controlled trial. JAMA. 2012;308: 1761–7.
213. Dieleman JM, van Paassen J, van Dijk D, Arbous MS, Kalkman CJ, Vandenbroucke JP, van der Heijden GJ, Dekkers OM. Prophylactic corticosteroids for cardiopulmonary bypass in adults. Cochrane Database Syst Rev. 2011;5:CD005566.
214. Sauerland S, Nagelschmidt M, Mallmann P, Neugebauer EA. Risks and benefits of preoperative high dose methylprednisolone in surgical patients: a systematic review. Drug Saf. 2000;23:449–61.
215. Fardet L, Fève B. Systemic glucocorticoid therapy: a review of its metabolic and cardiovascular adverse events. Drugs. 2014;74(15):1731–45. https://doi.org/10.1007/s40265-014-0282-9.
216. Langley P, Muller-Schwefe G, Nicolaou A, Liedgens H, Pergolizzi J, Varrassi G. The societal impact of pain in the European Union: health-related quality of life and healthcare resource utilization. J Med Econ. 2010;13(3):571–81.
217. Peppin JF, Cheatle MD, Kirsh KL, McCarberg BH. The complexity model: a novel approach to improve chronic pain care. Pain Med. 2015;16:653–66.
218. Callahan D. Managed care and the goals of medicine. J Am Geriatr Soc. 1998;46:385–8.

Does Chronic Pain Affect Heart Function?

41

Giovanna Goldaniga and Massimo Allegri

Contents

Abstract

Though it is well defined how acute pain affects heart function, this relationship is less understood and defined with chronic pain.

Chronic pain is not only an acute pain that lasts for several months, but it is a disease by itself with important societal and clinical burden. Chronic pain is really common (up to 20% of adult population) and it affects all people at every age even though there is a slight increase of incidence in older ones. Interestingly not only these epidemiologic data are quite similar to those of cardiovascular diseases but it is well demonstrated that there is an increased co-occurrence of chronic pain and cardiovascular disease. Finally, new studies have found that chronic pain shares common genetic variant with depression and cardiovascular diseases.

Hence, it is important to better understand both if chronic pain affects heart function and if there are shared mechanisms between these two diseases. There is growing observational evidence suggesting some correlation between chronic pain and cardiovascular disease.

The most important common pathogenetic factor is the endothelium disfunction and its inflammatory response. For example, some interesting data showed that endothelial disfunction is present in several patients with fibromyalgia, a common chronic pain syndrome.

Sympathetic Nervous System is another important pathophysiological mechanism shared by chronic pain and cardiovascular diseases. Even though this relationship is more

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*,
https://doi.org/10.1007/978-3-030-28008-6_41

understood in acute pain, also in chronic pain there are some interesting relationships, such as in complex regional pain syndrome.

Next, there are several experimental animal and clinical data that suggest not only a correlation between chronic pain and hypertension, but also chronic pain and heart rate variability suggesting new interesting insights that better explain the co-occurrence between these two disabilitating diseases. These correlations are also to be better investigated to understand how chronic pain can worsen the outcome in patients with cardiovascular disease, evaluating if the better control of pain can improve the outcome.

Keywords

Chronic pain · Heart function · Quality of life · Hypertension · Cardiovascular disease

Introduction

In order to define the relationship between chronic pain and cardiovascular diseases, it is important to well understand the difference between acute and chronic pain that have completely different pathophysiological mechanisms.

Usually, when we think to pain, we think to the common symptom that we feel when we hurt ourselves or after surgery or related to other diseases. Hence, pain is often considered "only" a symptom of other ongoing diseases. This pain is defined acute pain. Hence, acute pain is an "alarm message" that there is something is perturbing homeostasis and that has to be solved by the organism.

In this clinical setting, acute pain is a signal of a problem and it is accompanied by other several related clinical cardiovascular symptoms, such as tachycardia, hypertension, and activation of orthosympathetic system. During acute pain, there is also a psychological response as the person, who is reporting acute pain, is hyperactivated seeking to "fight" the problem cause of the pain. Hence, people with acute pain are anxious, agitated with a further activation of orthosympathetic system, which continues to being activated until when the problem has been resolved.

Acute pain treatment is addressed to find its cause and resolve the disease. If inflammation is the cause, we have to stop it with steroids or nonsteroidal antinflammatory drugs (NSAIDs); if there is a mass of tumor, we have to remove it. Hence, physician will look for a "causative" treatment using also analgesic to control pain as long as the problem has not identified and treated. It has been demonstrated that opioids are effective drugs to be used to control acute pain, meanwhile we are treating the cause of pain.

As it is a symptom we can measure it with a subjective "thermometer," a scale from 0 (no pain) to 10 (the worst pain possible) called Numeric Rate Scale (NRS). Obviously the evaluation is merely subjective, but it is widely accepted that a pain greater than three has to be always treated also to reduce orthosympathetic activation. World Health Organization has proposed several years ago a "scale" to treat acute pain accordingly its intensity: nonantinflammatory drugs if there is acute inflammation and pain is mild (step I), weak opioids if pain is moderate (step II) and strong opioids if pain is severe (step III).

It is evident that acute pain affects negatively cardiovascular system, but the relationship will end as soon as the pain disappears. As acute pain is an alarm, it is normal that cardiovascular system is being activated, but, in the meantime, the treatment has not to be addressed (unless there are severe cardiovascular symptoms) to cardiovascular symptoms but to the cause of pain, in order to stop it as soon as possible.

Chronic pain has a completely different pathophysiology. Chronic pain is not a symptom, but a disease by itself. Pain is not a sign of other disease and/or it has become independent of the former stimuli, which has generated it. As it is not anymore an "alarm signal" and it is lasting from several months/years, the relationship between chronic pain and cardiovascular system is different and better described below. Furthermore, from psychological point of view, chronic pain decreases patient's nervous system activity and mood with depression and catastrophizing symptoms, which are not related with activation of orthosympathetic

system, as acute pain does, but with a complex modulation and response of nervous system. Frequently, also peripheral nervous system is affected with peripheral neuropathic pain.

Chronic pain therapy is not anymore addressed to the cause of pain (as it does not exist anymore or it is not treatable), ***but to modulate the disease*** in order to obtain a good quality of life with the least impairment possible. Steroids or nonantinflammatory drugs (NSAIDs) are not indicated as there is not an acute inflammation to be controlled. Opioids could be used in nociceptive chronic pain, but they have several side effects when used for a prolonged period. Antidepressants and anticonvulsant drugs could be really effective, almost if there is a neuropathic component, even though they have several side effects also on the cardiovascular system. Other options are mini-invasive techniques, such as radiofrequency nerve lesions and/or spinal cord stimulation.

As it is a disease and not a symptom, it is important not to monitor only how severe the pain is, but it is needed to use different multidimensional scales in order to evaluate both the different components of pain (nociceptive vs. neuropathic, at rest vs. at movement, etc.) and how much pain affects all daily activities, such as working and social ability, mood, cognitive function.

Chronic pain, as cardiovascular diseases, is extremely frequent in adult population; in fact, between 15% and 25% of adult people suffer from some type of chronic pain syndromes. Furthermore, as cardiovascular diseases, it affects older people more than younger ones, even though is more common than cardiovascular disease in younger people.

Furthermore, chronic pain, as cardiovascular diseases, is the cause of huge societal impact not only for its direct costs but also (and mainly) for its indirect cost and societal impact, such as absenteeism, lost of productivity, higher risk to develop other diseases, socio-psychological issues. A recent article [1] has calculated that in 2010 in USA almost 100 millions of people were affected by chronic pain. It has been evaluated that it was the disease with the highest societal cost in USA (range between 560 and 635 billion of dollars in 2010), followed by cardiovascular diseases (309 billions of dollars). Interestingly the same analysis has also pointed out that pain has societal costs higher than those from cardiovascular disease, diabetes, and cancer together.

As both the prevalence of chronic pain and of cardiovascular disease are high, it has also to be considered the possibility that people may have both diseases with even bigger increases of the costs.

Finally, it is important to underline that Van Hecke et al. [2] demonstrated, in two different large cohorts (named Generation Scotland and TwinsUK), an increased co-occurrence of chronic pain, depression, and cardiovascular disease. The authors found that genetics more than environmental factors correlate these three important clinical problems (among the most important in causing disability and frailty).

In conclusion, it becomes important to understand and deepen if and which pathophysiological relationships and biological mechanisms are shared by these two diseases, evaluating their correlations. A better knowledge of these correlations will help physician not only to better treat patients with these two concomitant diseases, but also to find new insights to better understand how to prevent incidence of chronic pain and cardiovascular disease. In fact prevention will be the future not only for cardiovascular problems but also for pain.

Relationship Between Chronic Pain and Cardiovascular Diseases

There is a growing observational evidence suggesting some correlation between chronic pain and cardiovascular disease. Unfortunately, the clinical pathophysiology is still unclear as the majority of studies are mainly animal studies that indicate possible correlations.

Theoretically, chronic pain syndromes and cardiovascular diseases share common pathophysiological mechanism, such as endothelium dysfunction, sympathetic and central nervous system, psychosocial and genetic variables [2, 3].

Endothelium dysfunction could be a shared pathogenetic factor between chronic pain and inflammatory cardiovascular disease. In fact, we know that vascular endothelium is important in regulating not only vascular homeostasis, through several aspects of coagulation cascade and vascular tone [3], but also inflammation determining the onset of chronic inflammatory diseases, such as bladder pain syndrome [4]. Endothelial dysfunction is associated with enhanced local expression of matrix metalloproteinases, causing both inflammation and development and atherosclerotic plaques instability with increased risk of cardiovascular disease. An endothelial nitric oxide synthase mutation was found to be associated with coronary spasms and cardiac morbidity [3, 5]. Furthermore, chronic pain, as important and long lasting stress factor, enhances catecholamine release, possibly leading to a catecholamine-induced multifactorial endothelial damage (persistent activation of calcium channels, membrane damage, and microvascular spasms) [6]. Microvascular endothelial dysfunction can, then, sensitize the coronary circulation to the vasoconstrictor effects of catecholamines [7]. In Fibromyalgia an endothelial dysfunction was detected as reflected by an impaired brachial artery flow-mediated dilatation (FMD) response [6]. In fact, in these patients both endothelial-dependent and endothelial-independent vasodilatation are impaired. FMD is endothelium-dependent and it is mainly controlled by the release of endothelial nitric oxide (NO) [6, 8]. Hence, the impairment of endothelium-dependent FMD suggests a decreased endothelial NO activity that directly regulates artery stiffness in vivo. Considering this common pathogenetic link, there are interesting clinical correlations among some chronic pain syndromes and cardiovascular disease [6, 9]. High brachial artery pulse wave velocity was significantly higher in Fibromyalgia patients with a clear direct correlation not only with age, but also with specific determinants of chronic pain, such as pain intensity (measured by Visual Analogue), FIQ (Fibromyalgia impact questionnaire) score, depression, anxiety, and fatigue [6]. The correlation between increased arterial stiffness/vascular endothelial dysfunction has been found also in men with chronic prostatitis/chronic pelvic pain. Ho-Mei Chen et al. [9], in a retrospective matched-cohort study, found an epidemiological association between Bladder Pain Syndrome/Interstitial Cystitis and a subsequent Coronary Heart Disease diagnosis [3].

Obviously, all these clinical studies provide only preliminary data with important methodological bias. This possible association needs to be studied in larger prospective clinical trials.

Sympathetic Nervous System is another important physiopathological mechanism shared by chronic pain and cardiovascular diseases. For long time, it has been thought that abnormal activity of the Sympathetic Nervous System may be involved in the pathogenesis of chronic pain syndromes, such as complex regional pain syndrome [10, 11]. Pain is often correlated with signs of autonomic dysfunction and in some cases, blocking efferent sympathetic supply to the affected region relieves pain [12]. A common dysfunction of sympathetic nervous system can be found also through the clinical observation of correlation between chronic pain and hypertension [13]. Nevertheless this correlation is not mediated only by Sympathetic Nervous System [14].

The correlation between acute pain, sympathetic nervous system, and blood pressure is more clear. In fact, perception of acute pain plays an adaptive role creating a homeostasis disturbance, trying to prevent the tissue damage. The consequence of ascending nociception is the recruitment of segmental spinal reflexes through the physiological neuronal connections. In proportion to the magnitude and duration of the stimulus, these spinal reflexes can activate sympathetic nervous system activation, increasing peripheral resistances, heart rate, and stroke volume. The response also involves the neuroendocrine system, with hormones release (e.g., ACTH, beta-endorphin, prolactin) from the anterior pituitary, glucocorticoids from the adrenal cortex, epinephrine from the adrenal medulla, and norepinephrine from the sympathetic nerves. Pain increases also norepinephrine and corticotropin release through activation of locus coeruleus [15]. Then, with the reduction of painful stimuli's

arousal levels, there is a progressive reduction in sensitivity to acute pain and in autonomic activation, with a consensual tendency to restore of blood pressure. On the other hand, in chronic pain syndrome, in which the "alarm meaning" of pain is lost, the relationship between pain and blood pressure is not linear as in acute pain. In fact, chronic pain can induce hypertension, but in some case patient is completely anergic, due to the stress related to chronic pain, and also the cardiovascular system does not succeed in replying to pain with hypertension. Hence, the response is really patient dependent.

Interestingly, there are also some experimental animal models that suggest a Hypertension-Associated Hypoalgesia [16, 17]. Pinho et al. [16] used different rat models (spontaneously hypertensive rats, induced by infusion of angiotensin II or 1,3-dipropyl-8-sulfophenylxanthine, and renal artery ligatio) to demonstrate that hypertensive rats developed lesser hyperalgesia and allodynia compared to controls when monoarthritis is caused. Ghione et al. [17] compared spinal nociceptive transmission in two different animals: Wistar-Kyoto normotensive rats and spontaneous hypertensive rats. They showed a different response to noxious heating of the hind foot of varying intensity (temperature) at dorsal horn neurons in two types of cells involved in nociceptive transmission: the wide-dynamic-range neurons, which respond both to nociceptive and non-nociceptive stimuli, and the high-threshold (HT) neurons, which respond only to nociceptive stimuli. The responses of both types of neurons have been demonstrated more delayed and less intense in hypertensive rats than normotensive rats.

The question remains if the hypoalgesia is secondary to hypertension or does it contribute to hypertension [18]. In some experiments, hypoalgesia in hypertensive rats is present even before they develop hypertension, but hypoalgesia is not observed in all rats that have been clipped the renal artery; furthermore, the administration of antihypertensive drugs has never demonstrated a reduction of hypoalgesia [19].

Evaluating results from human experiments, Bruehl [20] demonstrated in healthy volunteer that opioids are not able to reduce hypertension induced by an acute nociceptive stimulus. In the meantime he also found that chronic pain patients have lower pain threshold compared to healthy volunteers, suggesting a dysfunction in pain regulatory system in patients with chronic pain.

It is well demonstrated that reduced perception of peripheral nociceptive with the central increase in pain threshold is mediated by increased activity in the inhibitory descending pathways mediated by norepinephrine and serotonin, related also with increased vascular activity. Hence, this central activity could then be associated with the development of arterial hypertension [18]. This mechanism can be one of the causes of the increased risk of hypertension in patients with chronic pain [21]. In fact, a retrospective review, conducted on randomly selected records of 300 patients with chronic pain, showed that cardiovascular/pain regulatory system interactions appear altered: elevated blood pressure is associated with increased acute and chronic pain responsiveness [21]. The Tromsø Study [13] is a prospective epidemiologic study that confirmed the hypothesis that increased hypertension risk in the chronic pain population might be linked to chronic pain-related dysfunction in interacting cardiovascular-pain modulatory systems. Furthermore, recently it has been demonstrated also an altered vagal activity in patients with chronic pain and descending inhibitory pathways disfunction [22].

Several clinical trials confirmed that pain regulatory system pathways are altered in chronic pain conditions [23]. In patients with chronic low back or orofacial pain, elevate blood pressure levels at rest were associated with an increased sensitivity to acute pain and a higher intensity of chronic pain [23]. This dysfunction may be related to decreased sensitivity of baroreceptors in chronic pain and to an impairment of the descending inhibitory pain pathways normally activated by an increase in the stimulation of baroreceptors. In fact, Maixner et al. [23] compared patients affected by temporo-mandibular disorders (TMDs), more sensitive to noxious stimuli, compared to those without TMD pain. They found a both peripheral and central sensitization sustained by sensitization of peripheral nociceptors and baroreceptor and by impairment

of descending pathways with concomitant increase of arterial blood pression. These results have been confirmed also in a cohort of chronic low back pain patients where a positive relationship between higher resting blood pressure and increased chronic pain intensity pain has been found [20].

Chronic pain could also be the cause of reversible secondary hypertension determined by stimulation of sympathetic nerve fibers in pathologically degenerative cervical disc with consequent cervical vertigo and hypertension. Recently, Peng [24] publishes two cases of patients with cervical spondylosis with also vertigo and hypertension who recovered completely after anterior cervical discectomy and fusion. Hence, they postulated that a treatment of the cause of pain could reduce also the cardiovascular risk in patients with cervical osteoarthritis or spondylosis.

Also the noradrenergic system of the locus coeruleus is involved in central cardiovascular control and pain regulating processes [25–28], but actually there are not any clear pathophysiological correlations or clinical evidence between pain and cardiovascular disease at this level.

As discussed above, also vagus nerve influences the modulation of pain. Jin et al. [29] investigated daily change in cardiovascular parameters and plasma norepinephrine in free moving rats after chronic constriction injury (CCI) of the sciatic nerve. Authors have found three different stages after this lesion. Firstly, there is an increase of blood pressure and heart rate that can be maintained up to 3 days but not associated with an increase of norepinephrine. Then animals have showed hyperalgesia with increased cardiovascular activity for 2 weeks after CCI. Finally, there is a predominance of parasympathetic tone measured by increased high-frequency (0.8–3.0 Hz) power in pulse interval variability.

In effect, heart rate variability (HRV) is a proxy measure for vagal activity reflecting also dysfunction of the descendent inhibitory pathway, associated with chronic pain [29, 30]. Koenig et al. [30] investigated the association between HRV and pain in individuals with and without chronic pain revealing a negative correlation between these two variables only in individuals without chronic pain. On the other hand analgesic intake has been proven to mediate the association between HRV and pain [31]: an effective analgesic treatment leads to a restoration in HRV [31].

Also psychosocial variables have common pathophysiological mechanisms shared by both chronic pain states and cardiovascular disease.

A history of cardiovascular disease is reported more often in those with severe pain than would be expected by chance, even when adjusting for shared risk factors [32]. Furthermore, psychosocial variables associated with the pain experience may have an impact on cardiovascular health [33]. In individuals with chronic pain, the risk was found to vary accordingly to factors common also for cardiovascular disease, such as healthy behavior, exercise, lower levels of cholesterol, and smoking. The risk factors were more prevalent in individuals with chronic pain, and even more common with the increasing of pain severity [34]. A recent study has also demonstrated that older people with chronic pain (spinal pain) has an increased risk to die for cardiovascular-specific mortality [35]. This study is important as it demonstrates that chronic pain is not only a disease by itself associated with poor health and quality of life. In fact, the correlations between chronic pain and heart can explain also why chronic pain patients have an increased risk of mortality. Hence, these data suggest that treating chronic pain has the endpoint to modulate the disease and to improve patients' outcome.

Finally, it is interesting to underline that there are also some genetic correlation between chronic pain, cardiovascular disease, and depression, as demonstrated in a twins' study [2].

Pain and cardiovascular system have some common genetic determined biological pathways, such as endocannabinoid system, hypothalamic-pituitary-adrenal axis, and inflammation. Endocannabinoid system genetic variations can lead to an age-related ventricular dysfunction [36], while genetic variants in cannabinoid and/or adrenergic pathway components have been implicated in chronic pain conditions [37].

Another important common mediator is guanosine triphosphate cyclohydrolase 1 (GCH1),

which is the first enzyme in the tetrahydrobiopterin (BH4) biosynthesis, an important co-factor for the formation of nitric oxide, biogenic amines, and serotonin [38]. Its expression and/or activity are upregulated during inflammation, following ischemic stroke or peripheral nerve injury, increasing BH4 production. Excess BH4 in peripheral sensory neurons contributes to the onset of neuropathic. On the other hand the inhibition of GCH1 activity or reduced GCH1 upregulation reduces pain in various animal models. This enzyme is important also in cardiovascular disease as in blood vessels BH4 is required to produce nitric oxide by endothelial NOS (eNOS). Relative BH4 deficiency leads to an increased production of reactive oxygen species, instead of nitric oxide, contributing to endothelial dysfunction. Clinical significant GCH1 have been recognized in several coding and noncoding regions of the gene leading to an increased risk of cardiovascular disease [39, 40] and reduce risk to develop chronic pain [39].

Another interesting target is the P2X receptor, a gateway of communication among the nervous, immune, and cardiovascular systems [41–43]. P2X receptors are ATP-gated cation channels that mediate fast excitatory transmission in several regions of the brain and spinal cord. Furthermore, P2X mediates the influx of cations and the release of proinflammatory cytokines affecting neuronal cell death through regulation of interleukin-1-beta, a key mediator in neurodegeneration, chronic inflammation, and chronic pain. P2X receptor-deficient mice have substantially attenuated inflammatory responses, including models of neuropathic and chronic inflammatory pain [43, 44].

Finally, there also some epigenetic evidence, especially studies on micro-RNA, of some common markers shared by cardiovascular and chronic pain diseases. Unfortunately, at this time there is no evidence that could suggest their use in clinical practice but in the future they could be promising not only in finding valuable biomarkers but also in giving new insights of the common pathophysiology between chronic pain and cardiovascular disease [45, 46].

Conclusion

Chronic pain and cardiovascular diseases share several common pathophysiological mechanisms that have to be better investigated. Chronic pain could be a trigger of hypertension and other cardiovascular diseases. Finally, several drugs commonly used in acute and chronic pain could have a severe impact on cardiovascular system and we have to consider it before choosing them.

Hence, it is really important to better manage these two problems as possible interconnected in order to improve the patients' quality of life and life expectancy.

Cross-References

- ▶ Depression and Cardiovascular Diseases
- ▶ Immune System and Mind-Body Medicine: An Overview
- ▶ When the Heart Hurts

References

1. Gaskin DJ, Richard P. The economic costs of pain in United States. J Pain. 2012;13(8):715–24.
2. Van Hecke O, Hocking LJ, Torrance N, Campbell A, Padmanabhan S, Porteous DJ, McIntosh AM, Burri AV, Tanaka H, Williams FM, Smith BH. Chronic pain, depression and cardiovascular disease linked through a shared genetic predisposition: analysis of a family-based cohort and twin study. PLoS One. 2017;12(2):e0170653.
3. Quyyumi AA. Endothelial function in health and disease: new insights into the genesis of cardiovascular disease. Am J Med. 1998;105:32S–9S.
4. Chen HM, Lin CC, Kang CS, Lee CT, Lin HC, Chung SD. Bladder pain syndrome/interstitial cystitis increase the risk of coronary heart disease. Neurourol Urodyn. 2014;33:511–5.
5. Abe K, Yamamuro M, Nagayoshi Y, Kojima S, Kaikita K, Sugiyama S, Yasue H, Ogawa H. A novel genetic marker for coronary spasm in women from a genome-wide single nucleotide polymorphism analysis. Pharmacogenet Genomics. 2007;17:919–30.
6. Ji HL, Kyoung IC, Seong MK, Hyeon GL, Tae IK. Arterial stiffness in female patients with fibromyalgia and its relationship to chronic emotional and physical stress. Korean Circ J. 2011;41:596–602.
7. Vita JA, Treasure CB, Yeung AC, Vekshtein VI, Fantasia GM, Fish RD, Ganz P, Selwyn AP. Patients

with evidence of coronary endothelial dysfunction as assessed by acetylcholine infusion demonstrate marked increase in sensitivity to constrictor effects of catecholamines. Circulation. 1992;85:1390–7.
8. Joannides R, Haefeli WE, Linder L, Richard V, Bakkali EH, Thuillez C, Lüscher TF. Nitric oxide is responsible for flow-dependent dilatation of human peripheral conduit arteries in vivo. Circulation. 1995;91:1314–9.
9. Shoskes DA, Prots D, Karns J, Horhn J, Shoskes AC. Greater endothelial dysfunction and arterial stiffness in men with chronic prostatitis/chronic pelvic pain syndrome – a possible link to cardiovascular disease. J Urol. 2011;186(3):907–10.
10. Borchers AT, Gershwin ME. Complex regional pain syndrome: a comprehensive and critical review. Autoimmun Rev. 2014;13(3):242–65.
11. Rockett M. Diagnosis, mechanisms and treatment of complex regional pain syndrome. Curr Opin Anaesthesiol. 2014;27(5):494–500.
12. Baron R, Levine JD, Fields HL. Causalgia and reflex sympathetic dystrophy: does the sympathetic nervous system contribute to the generation of pain? Muscle Nerve. 1999;22:678–95.
13. Olsen RB, Bruehl S, Nielsen CS, Rosseland LA, Eggen AE, Stubhaug A. Hypertension prevalence and diminished blood pressure-related hypoalgesia in individuals reporting chronic pain in a general population: the Tromsø study. Pain. 2013;154(2):257–62.
14. Al'Absi M, Petersen KL, Wittmers LE. Blood pressure but not parental history for hypertension predicts pain perception in women. Pain. 2000;88(1):61–8.
15. Zamir N, Maixner W. The relationship between cardiovascular and pain regulatory systems. Ann N Y Acad Sci. 1986;467:371–84.
16. Pinho D, Morato M, Couto MR, Marques-Lopes J, Tavares I, Albino-Teixeira A. Does chronic pain alter the normal interaction between cardiovascular and pain regulatory systems? Pain modulation in the hypertensive-monoarthritic rat. J Pain. 2011;12(2):194–204.
17. Ghione S. Hypertension-associated hypalgesia. Evidence in experimental animals and humans, pathophysiological mechanisms, and potential clinical consequences. Hypertension. 1996;28:494–504.
18. Saccò M, Meschi M, Regolisti G, Detrenis S, Bianchi L, Bertorelli M, Pioli S, Magnano A, Spagnoli F, Giuri PG, Fiaccadori E, Caiazza A. The relationship between blood pressure and pain. J Clin Hypertens. 2013;15(8):600–5.
19. Sitsen JM, de Jong W. Observations on pain perception and hypertension in spontaneously hypertensive rats. Clin Exp Hypertens. 1984;6:1345–56.
20. Bruehl S, Chung OY, Ward P, et al. The relationship between resting blood pressure and acute pain sensitivity in healthy normotensives and chronic back pain sufferers: the effects of opioid blockade. Pain. 2002;100:191–201.
21. Bruehl S, Chung OY, Jirjis JN, Biridepalli S. Prevalence of clinical hypertension in patients with chronic pain compared to nonpain general medical patients. Clin J Pain. 2005;21(2):147–53.
22. Rodrigues P, Correa L, Ribeiro M, Silva B, Reis F, Nogueira L. Patients with impaired descending nociceptive inhibitory system present altered cardiac vagal control at rest. Pain Physician. 2018;21(4):E409–18.
23. Maixner W, Fillingim R, Kincaid S, Sigurdsson A, Harris MB. Relationship between pain sensitivity and resting arterial blood pressure in patients with painful temporo-mandibular disorders. Psychosom Med. 1997;59:503–11.
24. Peng B, Pang X, Li D, Yang H. Cervical spondylosis and hypertension: a clinical study of 2 cases. Medicine. 2015;94(10):e618.
25. Kaehler ST, Sinner C, Philippu A. Release of catecholamines in the locus coeruleus of freely moving and anaesthetized normotensive and spontaneously hypertensive rats: effects of cardiovascular changes and tail pinch. Naunyn Schmiedeberg's Arch Pharmacol. 2000;361(4):433–9.
26. Koulu M, Saavedra JM, Niwa M, Linnoila M. Increased catecholamine metabolism in the locus coeruleus of young spontaneously hypertensive rats. Brain Res. 1986;369:361–4.
27. Murase S, Inui K, Nosaka S. Baroreceptor inhibition of the locus coeruleus noradrenergic neurons. Neuroscience. 1994;61:635–43.
28. Schneider C, Singewald N, Philippu A. Inhibition of catecholamines (noradrenaline, dopamine) release in the locus coeruleus and the hypothalamus by baroreceptor activation: identification of the involved baroreceptors. Naunyn Schmiedeberg's Arch Pharmacol. 1995;352(3):291–6.
29. Jin Y, Sato J, Yamazaki M, Omura S, Funakubo M, Senoo S, Aoyama M, Mizumura K. Changes in cardiovascular parameters and plasma norepinephrine level in rats after chronic constriction injury on the sciatic nerve. Pain. 2008;135(3):221–31.
30. Koenig J, Loerbroks A, Jarczok MN, Fischer JE, Thayer JF. Chronic pain and heart rate variability in a cross-sectional occupational sample: evidence for impaired vagal control. Clin J Pain. 2016;32:218–25.
31. Koenig J, Jarczok MN, Fischer JE, Thayer JF. The association of (effective and ineffective) analgesic intake, pain interference and heart rate variability in a cross-sectional occupational sample. Pain Med. 2015;16:2261–70.
32. Parsons S, McBeth J, Macfarlane GJ, Hannaford PC, Symmons DP. Self-reported pain severity is associated with a history of coronary heart disease. Eur J Pain. 2015;19(2):167–75.
33. Leonard MT, Chatkoff DK, Gallaway M. Association between pain catastrophizing, spouse responses to pain, and blood pressure in chronic pain patients: a pathway to potential comorbidity. Int J Behav Med. 2013;20(4):590–8.
34. Sibille KT, Steingrímsdóttir ÓA, Fillingim RB, Stubhaug A, Schirmer H, Chen H, McEwen BS,

Nielsen CS. Investigating the burden of chronic pain: an inflammatory and metabolic composite. Pain Res Manag. 2016;2016:7657329.
35. Fernandez M, Boyle E, Hartvigsen J, Ferreira ML, Refshauge KM, Maher CG, Christensen K, Hopper JL, Ferreira PH. Is this back pain killing me? All-cause and cardiovascular-specific mortality in older Danish twins with spinal pain. Eur J Pain. 2017;21(5):938–48.
36. Walsh SK, Hector EE, Andreasson AC, Jonsson-Rylander AC, Wainwright CL. GPR55 deletion in mice leads to age-related ventricular dysfunction and impaired adrenoceptor-mediated inotropic responses. PLoS One. 2014;9(9):e108999.
37. Hocking LJ, Smith BH, Jones GT, Reid DM, Strachan DP, Macfarlane GJ. Genetic variation in the beta2-adrenergic receptor but not catecholamine-*O*-methyltransferase predisposes to chronic pain: results from the 1958 British Birth Cohort Study. Pain. 2010;149(1):143–51.
38. Thony B, Auerbach G, Blau N. Tetrahydrobiopterin biosynthesis, regeneration and functions. Biochem J. 2000;347:11–6.
39. Antoniades C, Channon KM, Tegeder I, Lötsch J. Clinical genetics of functionally mild non-coding GTP cyclohydrolase 1 (GCH1) polymorphisms modulating pain and cardiovascular risk. Mutat Res. 2008;659(3):195–201.
40. Zhang L, Rao F, Zhang K, Khandrika S, Das M, Vaingankar SM, Bao X, Rana BK, Smith DW, Wessel J, Salem RM, Rodriguez-Flores JL, Mahata SK, Schork NJ, Ziegler MG, O'Connor DT. Discovery of common human genetic variants of GTP cyclohydrolase 1 (GCH1) governing nitric oxide, autonomic activity, and cardiovascular risk. J Clin Invest. 2007;117(9):2658–71.
41. Skaper SD, Debetto P, Giusti P. P2X(7) receptors in neurological and cardiovascular disorders. Cardiovasc Psychiatry Neurol. 2009;2009:861324.
42. Skaper SD, Debetto P, Giusti P. The P2X7 purinergic receptor: from physiology to neurological disorders. FASEB J. 2010;24(2):337–45.
43. Benatti C, Blom JM, Rigillo G, Alboni S, Zizzi F, Torta R, Brunello N, Tascedda F. Disease-induced neuroinflammation and depression. CNS Neurol Disord Drug Targets. 2016;15(4):414–33.
44. Badoer E. Microglia: activation in acute and chronic inflammatory states and in response to cardiovascular dysfunction. Int J Biochem Cell Biol. 2010;42(10):1580–5.
45. Andersen HH, Duroux M, Gazerani P. MicroRNAs as modulators and biomarkers of inflammatory and neuropathic pain conditions. Neurobiol Dis. 2014;71:159–68.
46. Hagiwara S, Kantharidis P, Cooper ME. MicroRNA as biomarkers and regulator of cardiovascular development and disease. Curr Pharm Des. 2014;20(14):2347–70.

Osteopathic Pain Management and Cardiovascular Diseases

42

Liria Papa

Contents

Abstract

Increasing age, obesity, smoking, and depression have been common overlapped risk factors between cardiovascular diseases (CVD) and chronic musculoskeletal pain (CMP) conditions, in the last decade. CMP prevalence is estimated from 19% to 30%. Percentage increases with increasing age after >65 years old. It is associated with the development of CVD.

Literature shows an association between CMP and the increased risk of mortality. This is secondary to cardiovascular (CV) damages.

Osteopathic manipulative treatment (OMT) is an approach focused on the management of CMP which emphasizes the role of musculoskeletal system (MSs) both in health and sickness. OMT improves quality of life and functional status in patients suffering from chronic pain but also suffering from physiological parameters as heart rate variability or respiratory volumes.

This chapter aims at illustrating the osteopathic management of pain with specific focus

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*,
https://doi.org/10.1007/978-3-030-28008-6_40

on implications of CVD on mechanism of pain and how it can be helpful as a multidisciplinary approach in CVD patients.

Keywords

Osteopathic treatment · Osteopathic management · Chronic pain · Cardiovascular disease · Pain management

Abbreviations

ACC	Anterior cingulate cortex
Ang-II	Angiotensin-II
CABG	Coronary artery bypass graft
CMP	Chronic musculoskeletal pain
CNS	Central nervous system
CP	Chronic pain
CV	Cardiovascular
CVD	Cardiovascular disease
DH	Dorsal horn
DRG	Dorsal root ganglion
ECM	Extracellular matrix
EMG	Electromyography
FNE	Free nerve ending
GC	Glucocorticoids
HRV	Heart rate variability
IC	Insular cortex
LBP	Low back pain
MS	Musculoskeletal
MSNA	Muscle sympathetic nervous activity
MSs	Musculoskeletal system
NHS	National health systems
NMDA	N-methyl-D-aspartate
NTS	Nucleus tractus solitarius
OMT	Osteopathic manipulative treatment
PAG	Periaqueductal gray matter
PFC	Prefrontal cortex
PGE	Prostaglandine
PM	Pain matrix
QoL	Quality of life
SBP	Sub-acute pain
SD	Somatic dysfunction
SMA	Supplementary motor area
SNS	Sympathetic nervous system
SP	Substantia P
TH	Thalamus
TRL	Toll-like receptor

Introduction

Cardiovascular diseases (CVD) are one of the leading conditions which influence the National Health Systems (NHS) in terms of risk assessment, prevention, and social costs.

In the last decade, CVD prevalence has increased due to ageing and population growth from high- to lower-income countries. One-third of all deaths, all over the world, are related to CVD. Moreover, short- and long-duration CVD sequelae boost 15% and 25%, respectively, needing the development of new prevention and rehabilitation policy [1–7].

Increasing age, obesity, smoking, and depression are the common overlapped risk factors between CVD and the broad-spectrum of chronic pain (CP) conditions. CP represents another leading expenditure for disability and social costs in the NHS, related to various diseases such as cancer, osteoarthritis, fibromyalgia, and neuropathy.

Chronic musculoskeletal pain (CMP) prevalence is ranged from 19% to 30% in adult population, increasing with age >65 years old with a progressive impairment in quality of life (QoL) and physical function [8–13].

Some interesting studies have found out an association between CP and CVD in terms of morbidity and mortality. In Swedish adult population, the relationship between chronic pain and all the potential causes of mortality showed an increased risk associated with CP, firstly related to CVD and secondly to cancer conditions.

Furthermore, the extension of pain and the number of locations contributed to increase the risk [14]. Similar findings were obtained by Ryan et al. [15] in a secondary analysis on 5054 middle-aged and elderly adults in the Health Survey for England (2008). The prevalence and risk factors of CVD were associated with CMP population. Additionally, the reduction of physical activity or increased sedentary lifestyle contributed to cardiovascular (CV) conditions risks. A similar trend, not so significant, was observed in middle-aged adults.

Finally, a recent systematic review of 25 studies has statistically demonstrated a significant association between CP and CVD mortality and

cardiac and cerebrovascular diseases (OR ranged 1.21–1.81). The analysis showed a larger effect size between chronic pain phenotypes and cardiovascular outcomes, supporting the model in which chronic pain predisposes CVD through chronic stress model [16].

Management of CP involves a wide range of approaches, including drugs, acupunctures, exercises, manual therapies, and others.

Literature supports the model of multidisciplinary approach to prevent, reduce, and support patients with chronic pain, requiring an improvement of basic culture in the populations' lifestyle. It is also helpful to decrease CV risky factors [17].

As far as manual therapies are concerned, the osteopathic manipulative treatment (OMT) is an approach focused on the management of CMP, which emphasizes the role of musculoskeletal system (MSs) in health and sickness. Osteopathic treatment improves the function of tissues and the related body system, throughout a palpatory assessment of movements and postures and using a variety of manual techniques [18].

The OMT showed relevant effects in reducing pain and improving functional status (i.e., chronic low back pain, neck pain, tension-type headache) and also in balancing functional measures such as heart rate variability, respiratory parameters, and pro-inflammatory cytokines [19].

This chapter aims at illustrating the osteopathic management of pain with particular focus on the implications of CVD on pain mechanism and health status. Exploring the benefits of osteopathic treatment assures CVD patients of multidisciplinary approaches.

Osteopathic Principles and Pain Analysis

According to the International Association for the Study of Pain (IASP), the definition of pain considers two important aspects: unpleasant sensation and perception as an emotional experience [20].

Literature offers a wide discussion on pain definition; however, it has to be complained at least once in a lifetime, and it is related to many body conditions such as illnesses and injuries or to nonspecific disorders and emotional circumstances [21]. Regardless of the damage, pain is characterized by complex pathways in the central nervous system (CNS), involving processes of memory by means of sensitization and neuroplasticity. These mechanisms support the awareness of experiencing danger, and they involve CNS at all levels, emotional and cognitive areas included [22].

The experience of pain results unique for each patient, and it is considered as a nonstop challenge for all health-care providers.

Clinical classification of pain is based on its pathophysiologic mechanisms, its characteristics, and its developments in time. As far as mechanisms are concerned, pain depends on the interested injured tissues, classifying neuropathic pain (nerve's injury) versus inflammatory pain. Both pains are triggered by spontaneous exacerbation due to an inflammatory process in tissues, while the neuropathic pain is detected as a paroxysmal sensation due to the neuronal conduction injury. Non-specific (or aspecific) pain, as well known as transient pain, is elicited by the presence of nociception in the absence of injured tissues [23].

Clinic characteristics are a miscellaneous field associated with type of injury diseases and/or mood. Hyperalgesia and allodynia are a mismatched response to non- and less-painful stimuli. Intensity is recognized to be mild ($\leq$4/10), moderate (5/10 or 6/10), and severe ($\geq$7/10) [24]. 6 weeks is the recovery time for an acute pain state, and 3 months or more are necessary in case of chronic pain state [23].

Neurophysiology of Pain

The central nervous system has the leading role in experiencing pain as a signal of danger and injury. Repeated physical and chemical stimuli are able to excite C and Aδ fibers transducing the sensation of tissue injury. Therefore, pain is processed by CNS, and it is modulated as perception [22].

Considering chronic pain as dominant condition, peripheral and central sensitization processes are taken into consideration for analyzing the pain.

According to Woolf, sensitization is an activity-dependent synaptic plasticity related to inflammatory communication among tissues, afferent fibers, and spinal interneurons [25].

Several studies in tissue injury found out an increasing number of open receptor sites on synaptic membranes of free nerve ending (FNE) receptors due to the interaction of inflammatory cytokines such as prostaglandin (PGE), substantia P (SP), nitric oxide, histamine, necrosis factors, and interleukins [26].

Current investigations have also linked this synaptic adjustment to the mechanotransduction of altered physical force from tissues to receptors by integrins [27]. Zhang et al. [28] investigated the integrin-dependent pathway sustained pain after mechanical stretch, showing of an upregulation of subunit β1 after 7 days, which contributed SP-mediated nociception.

In order to define the characteristic and the intensity of noxious stimuli, peripheral sensitization decreases the discharge threshold of fibers and sustains a continuous transmission of nociception. The effect of increased excitability in afferent fibers induces a transcriptional activity in dorsal root ganglion (DRG), which corresponds to a production, to an allocation of receptor sites, and to neurotransmitter vesicles in both neural endings.

This transcriptional activity modifies the spinal cord dorsal horn communication [29]. Reihnold et al. [30] discriminated the reaction among DRG cells directly involved in detecting gene expression changes linked to neuropathic pain in all neurons.

Based on the *spinal gate control theory* by Melzack and Wall, in 1965, the central sensitization involves interneuron plasticity changes and the inhibitory control on nociception.

Two aspects were principally investigated: the inflammatory communication among dorsal horn (DH) neurons (decreasing threshold excitability) and the roles of N-methyl-D-aspartate (NMDA) receptors which sustain the phenomena [25].

Several authors studied the variation in excitatory interneurons. This message was reinforced by releasing inflammatory co-transmitters, such as PGE, to react nociceptive transduction from afferent fibers. As observed on FNE receptors, this change is due to modified transcriptional cell functions involving receptor site structures, too [31].

Recent researches focused their attention on facilitated receptor membranes, not only in neural cells but also in DH's glial cells, emphasizing the role of the immune system in central sensitization [32]. Konig et al. [33] demonstrated TNF-α as a pain molecule, and this is considered the key of communication between microglia and DH neurons.

Chronicization mechanism recognizes the role of NMDA receptors in the memory process linked to long-term DH neurons potential as in the suprathalamic nucleus and in cortex. Woolf's studies proved the upregulation of these receptors from persistent pain conditions allowing a transmission of ascending nociceptive signals [25].

Actually, scientific knowledge updates NMDA receptor roles related to chronic stress molecules (i.e., catecholamines and glucocorticoids) accountable for DH neuroplasticity interplaying with glial interleukins [34]. Basso et al. explored the role of granulocytes on the development of sensitization to visceral pain, showing how spinal microglia increased the excitability and triggered the hypersensitivity pain due to CRH interaction [35].

Indeed, the role of chronic stress theory, in CP conditions, has been recognized as a retaining ascending signal, promoting adaptive memory in both limbic nucleus and influencing the inhibitory descending pathway.

Growing evidence underlined the role of the increased activity of ON-cells in periaqueductal gray matter (PAG) to retain the hyperalgesia condition, supporting by stress-induced neuroplasticity of descending regulators [36].

Mapping the activity of brain structure with functional magnetic resonance in response to painful stimuli or chronic pain, it became clear that most of the activated areas of what has been called pain matrix were not specific for pain, but were involved in physiological control of the body and emotional response (i.e., insular cortex (IC), anterior cingulate cortex (ACC), and prefrontal cortex (PFC)) [37].

Human brain imaging studies showed that IC known as interoceptive cortex, processed visceral and somatic nociception, as well as all other sensorial information, and elicited emotion sensation of pain, playing a pivotal role in processing and learning pain experience. Its connectivity interested ACC, generating motivational components of pain. These areas are interested by mnemonic processes due to an increase of IC and ACC long-term potential in neuropathic pain studies [38].

PFC has a crucial role in executive function. Its wide connection with the neocortex, hippocampus, PAG, amygdala, thalamus, and basal nuclei is related to one another. Several authors investigated the connectivity changes in CP, showing a different modulation in PAG activation, an increase of connectivity in dopamine pathways as emotional response (i.e., ventral tegmental area) and motor response (i.e., basal ganglia). Finally, PFC influenced the autonomic response of cardiovascular system and the respiratory system throughout amygdala connectivity [39].

Cortico-limbic areas are also influenced by chronic stress response, specifically involving the neuroplasticity of hippocampal neurons in CP conditions due to cortico-releasing hormones [40]. A critical aspect of pain, before being perceived, is the signal of danger, and it requests an adaptive strategy to preserve the life of the tissue. The organization of PM involves sublimbic effector nucleus driving CNS output to tissue [41].

First of all, the neurogenic inflammation is a FNE response to tissue injury, and it is sustained by peripheral sensitization. Antidromic stimulus allows the release of inflammatory mediators in FNE [42]. Inflammatory molecules drive the signals to repair injuries of the tissue, which engage vascular endothelial cells, myofibroblast cells, and fibroblast cells for supporting extracellular matrix (ECM) remodeling [43]. Simultaneously, CNS integration pathways create a multilevel and modal adaptive response involving autonomic outflow and neuroendocrine axis in order to comply the physiologic variables in a pain status (i.e., cardiac and respiratory frequency, thermal regulation, and energy expenditures) [44].

Osteopathic Pain Management

The osteopathic manipulative treatment is based on "a concept of health care supported by expanding scientific knowledge which embraces the concept of unity of living organism's structure (anatomy) and function (physiology). Osteopathic philosophy emphasizes the following principles: the human being is a dynamic unit function. The body possesses self-regulatory mechanisms which are self-healing in nature. Structures and functions are interrelated at all levels" [18].

During an osteopathic visit and during a treatment, the philosophy previously mentioned is applied to investigate pain conditions, to identify related somatic dysfunctions (SD) [45], and to arrange the rational and the sequence of osteopathic techniques.

Non-specific CMP conditions are the major targets for osteopathic intervention. While the history of pain is being investigated, the osteopath has to take into consideration (see Table 1):

- Homeostatic issue, such as peripheral sensitization and tissue remodeling
- The previous history, involving adaptive relations between structure and function
- Perception of well-being, as a link between intensity and disability [46–48]

Concerning homeostatic issue, the analysis of pain should answer two main fields, what exacerbates pain and what evocates pain?

Both questions are related to sensitization mechanism established in the tissue and spinal cord. Hyperalgesia is a spontaneous phenomenon, and it can be linked to the local and global movement of a stressed painful tissue. Miyagi et al. [49] found several numbers of afferent fibers and inflammatory cytokine expressions in degenerating intervertebral disk compared to the healthy ones. The results agreed with other studies to support the influence of inflammation and of FNE sensitizations to tissue remodeling. Mechanosensitivity changes seem to sustain the exacerbation of pain during physical stress, as demonstrated by Zhang in joint capsules [28].

Table 1 Osteopathic management of pain

Osteopathic principles			
	Homeostatic	Previous	Perception
Taking history	Issue	History	Well-being
Who?	Sensitization	Illness	Social relationship
Chronic pain	Process	Mood disorder	
	Tissue remodeling	Surgery	Functional disability
		Functional disorder	
How?	Neurophysiology	Pathophysiology (inflammation and repair processes)	Pain matrix
Knowledge	Functional anatomy		Chronic stress model
What?	*Exacerbate*	*Arrange*	*Contribute*
Happen to pain	*Evoke*	*Sustain*	

An interesting review, focused on immune-tissue communication, linked the regulation of toll-like receptor (TLR) family to all involved cells (tissue, immune, and neuronal cells) from inflammatory stages to healing stages. Unbalancing in TLR functions contributes to the chronicization of inflammatory responses, and it moves the tissues over fibrosis [50]. This has been found in osteoarthritic joints, whose disability was often described, by patients, as a pain in the early stages of this pathology [51].

The biomechanical investigation of current pain begins from a localized point in the whole body. Central sensitization mechanism supports the expansion and the projection of pain in adjacent regions or nonadjacent ones, involving several spinal cord levels, convergent areas in DH, the thalamus, and the cortex [25].

Indeed, it is necessary to recognize a previous influence on the pain pathways. Past history of the patient permits to investigate events (i.e., injuries and surgeries), diseases, or functional disorders (dyspepsia, dysmenorrhea, irritable bowel syndrome, etc.) which facilitate central sensitization and stress response. A wide literature explored the concept of allostasis and allostatic load as physiological regulatory processes required for well-being and survival [52]. CNS networks coordinate patterns of processing (cognition, awareness, memory, etc.), movement, and emotional state (with autonomic outflow), regulating the whole physiology. These networks were influenced by chronic stress mediators and were associated with pain and pathological states [53]. Recent studies have shown stress hormone hypersecretion (alone or associated with distinct disorders) such as anxiety, obesity, autoimmune disorders, type 2 diabetes mellitus, and polycystic ovary syndrome. It has been associated with psychological and somatic manifestations, increased fat mass, osteosarcopenia/frailty, cellular dehydration, and chronic systemic inflammation [54].

The analysis of perception is an important step in the management of pain, and it must be done considering "human being as a dynamic unit" body-mind function [46].

As far as the investigation of pain perception is concerned, an interesting study of Hashmi et al. [55] sustained the shift of brain activity toward a predominantly emotional involvement in CP states. The perception of back pain was observed to engage different brain activations across different groups of back pain. Recovering subacute pain (SBP) group, no prior back pain history and experienced less than 2 months, showed an activity in IC, ACC, and thalamus (TH) regions which decrease at the remission of the pain state. These areas were active, and they involved PFC and the amygdala in persistent SBP (pain lasted at least 3 months) and CP group (at least 6 months) and PFC. These areas had a predominant activity in chronic conditions. The nonoverlapping regions (involved in CP) supported the concept of emotional-related circuits as prior adaptive network characterizing the chronicization of pain.

PFC is involved in sensorial (i.e., smell), physiological (i.e., thirst), or hedonistic (i.e., money) pleasures throughout dopaminergic signals. It also

elaborates the control of cardiorespiratory variables related to pleasure perceptions. Therefore, PFC and dopamine are recognized as an emotional state leading to reach pleasure across dopaminergic reward system, as showed in studies on drug addiction [56].

Quality of life is related to the ability to have a good life, and it is influenced by economical, cultural, and spiritual factors, physiological status included. Symptoms are sensations. Physical symptoms are "a perception, a feeling or a belief about the state of one's own body," and emotional involvements such as worry, frustration, and fear must be considered. The functional status depends on symptoms, personalities, and motivations in terms of socio physical function [57]. In general, the well-being in adults with physical disabilities is associated with social relationships. Negative social interactions, lack of social support, and family functioning were found out to be associated with anxiety and depressive indexes [58].

Concerning CP, there are evidences of a significant relationship between an increased pain intensity and a decreased quality of life, in adults over 40 years old, with different pain conditions associated with osteoarthritis, rheumatoid arthritis, and neuropathy [59].

Furthermore, pain intensity, disability, information, and employment are associated with the development of mood disorder in CMP [60]. Finally, as demonstrated by Coppierters et al. [61], CP patients showed a low QoL, and their cognitive impairment was inversely correlated with QoL supporting the link among chronic conditions, perceptions, and cognitive performances.

Restoring pain conditions is one of the main goals of therapists, and it remains a challenge, too. In fact, health-care providers could differently perceive the patient's QoL, as showed in a study on assessment of QoL in multiple sclerosis. Investigation based on a comparison between domains of a 36 questionnaire format was considered important by both patients and neurologists. The results showed two different points of view, in which patients evaluate vitality, general health, and body pain as a relevant aspect (in consider by neurologists); instead, doctors focused their attentions on physical functions and physical role of limitations [62].

Indeed, collecting a center-patient history is essential in determining the impact of pain on physical, mental, and emotional functions. It is necessary to take into consideration the patient's priority [46].

The second step in the osteopathic management of pain is the palpatory assessment. Its goal is the recognization of the functional demands of adaptive responses.

Osteopathic objective examination is focused on (see Table 2):

- Identifying the somatic dysfunctions (SDs) and their relationships with complained conditions
- Analyzing SDs relations throughout the body and their perturbations on functional systems [18, 46]

Table 2 Osteopathic management of pain assessment

Osteopathic principles			
	Homeostatic	Previous	Perception
Body exam	Issue	History	Well-being
Who?	Somatic dysfunction	Illness	Social relationship
Chronic pain	Tenderness	Mood disorder	
	Range of motion	Surgery	Functional disability
	Texture remodeling	Functional disorder	
How?	Tissue changes	Movement adjustment	Emotional behaviors
Palpatory skill	Tissue memory	Postural adaptation	Motor behaviors
	Experience		
What?	*Exacerbate*	*Arrange*	*Contribute*
Happen to pain	*Evoke*	*Sustain*	

Somatic dysfunction is defined as a perturbation in movement capability and a positional adjustment expressed by vertebral column joints [18]. The concept could be extended to all joints including any tissue plan sliding. SD is supposed to be related to a remodeling connective tissue, mediated by peripheral sensitization and to stress mediators, locally and globally [63]. Palpatory findings of SD are postulated to be tissue tenderness of involved joint, asymmetry in the range of movements, and different tissue texture (recognized as "restricted barrier") in comparison to other joints [18]. Even if the reliability of detecting SD has been questioned, its concept of tissue and body movements are the basic knowledge in a palpatory ability [64].

The very first characteristic of SD is tenderness, inducing pain by palpation in superficial and deeper musculoskeletal (MS) tissues. Provoked pain is related to a nociceptive peripheral and central sensitization mechanism, and the measure of pain pressure has been demonstrated to be lower in many CMP conditions [65–67].

In 1940, Korr and Denslow's facilitated segment theory ascribed the establishment of somatic dysfunction as a lowering mechanoceptors by stressful movements: an altered transmission involving nociception, sustaining tenderness, having adaptive changes of muscular tone and vasomotion in MS tissues. Actually, this view integrates concepts as well as tissue movements. These are detected from receptors as interoception [68].

During palpatory SD tests, osteopath induces movement in tissue with forces and directions, stressing the physiological limits of movement. In response to these stimuli, FNE could transduce movements in tissue as danger stressor, provoking a pain sensation. In capsular inflamed joints, this event is characterized by DRG transcription activity, sustaining transmission and neurogenic inflammation [28]. Furthermore, several studies demonstrated fibroblast as a different based on type response, consisting in different directions and in frequent physical movements. In particular, repeated nonrhythmic strains caused a production of inflammatory cytokines, supporting the nociceptive message in tissue [69].

Pain history analysis and related factors permit the osteopath to recognize the main body regions involved in the presentation, and he/she can examine them to detect the somatic dysfunctions by tenderness. While examining hyperalgesia and tenderness, it is possible to relate SD to pain status, confirmed by relief to application of inhibition test on tissue.

Inducted movements in osteopathic palpation (from pressure to multi-direction forces), allow the osteopath to detail density, elastic response, and spontaneously adaptation of the tissues which characterizes the texture definition. This decision-making process is supported by neuroplasticity. The process depends on each operator [64].

The connective tissue remodels itself in response to the inflammatory state as soon as it is recognized, and it has been investigated in connection with the influence of physical force [71].

Fibrosis, as consequence of inflammation, was mediated by macrophages' polarization in pro- and anti-inflammatory type [72]. Macrophage polarization was related to muscle repair process [73], fascia [74], and peritoneal fibrosis [75]. An interesting study of Lagrota-Candido et al. [76] showed the relationship among inflammation, MS remodeling, and genetic backgrounds, supporting the concept that each body is unique in self-healing.

Reorientation of fibrillary components in the ECM (in persistent and repetitive stress) was studied in different conditions, like hypertrophic scar and tendon remodeling.

In vitro studies showed an organization of fibrillary matrix, parallel to strain, and share a mediated stress by fibroblast orientation (upright to stress) [77]. In physiological length, range of tendons and different elongations were related to several levels of matrix genes. The activation of growth factors increased the mechanical strain [78]. Legerlotz et al. [79] investigated the link between fatigue loading and collagen expression in tendons (sustained by expression of IL-6), which had different degrees of fatigue injury. Finally, conversion of skin fibroblasts into hypertrophic scar fibroblasts was related to the magnitude of applied stretching, and it produced an

increased synthesis of collagen types I and III (supporting the influence of mechanical stress on fiber density in connective tissue) [80].

In vivo investigation of fascia, ECM showed complex pathways in distribution of movement whose fibrillary architecture distributes intrinsic and extrinsic forces among tissues (i.e., blood vessel, tendon, epithelium) [81].

In musculoskeletal connective tissue remodeling, inflammatory and mechanical interactions agree with the osteopathic concept of "restricted barrier" in SD; density and elastic response identify changes in tissues limiting expression of movement.

In addition, MS fascia has been considered as a sensory organ thanks to the high presence of FNE and mechanoceptors, which map the myotome and dermatome distribution. MS fascia has been recognized as involved in nociception and as a mechanism of sensitization [68].

Osteopathic palpation methods propose an assessment aimed at identifying the intrinsic movements expressed by tissue along fascial connections with and without imposed movements. Assessment without applied forces – indirect method – is based on the development of palpatory skills which are able to perceive intrinsic tissue movements [18].

It has been supposed that intrinsic movements are due to fascial properties of contractility, viscoelasticity, and fluidic dynamics, which organized the fascial system as a "semiconductive system exhibiting coherent vibration throughout the organism" [68].

Biomechanical models of osteopathic examination support the identification of SD relation across the whole body. Observation and assessment of postural adjustments are helpful to recognize primary and secondary influences among SDs, distinguishing posture and movements in affected patients' CP [70].

Functional imaging in CP has demonstrated changes in connectivity of the motor cortex, cerebellum, and basal ganglia (BG) characterizing the structure of PM [82]. Supplementary motor areas (SMA) were involved in motor control and pain processing. In particular, an increased activity was detected in the middle cingulate cortex and SMA as motor process, and pain occurred simultaneously [83]. Oertel et al. [84] showed how IC involved SMA in processing the relationship between intensity and perception of noxious stimuli.

Planning and execution of movements are properties of cerebellum pathways, which were discovered to be implicated in processing pain by means of increased connectivity with SMA [85]. Finally, emotional procedure memory in BG was associated with pain status; the caudate nucleus and the putamen were engaged in response to acute sensation, while nucleus accumbens changed its connectivity in CP [86].

Therefore, postural adjustment and movement patterns in CP could be related to changes in behavioral motor pathways arranged to support pain status by CNS. These also mediate changes in tissues throughout amygdala homeostatic control and brainstem nucleus. Hashimi et al. [55] showed an increased connectivity between the amygdala and pain cortex (IC, ACC, PFC) directly associated to chronicization. Cortico-releasing factor neurons of these regions were found related to impaired descending control in CP, as another contributing factor to chronicization [87]. In addition, the amygdala has a crucial role in controlling inflammatory response to stress, as showed by Muscatell et al [88].

The motor cortex, ACC, and hypothalamus connectivity were related to muscle sympathetic nervous activity (MSNA) in response to pain stimuli with different pathways. Increased MSNA group and decreased MSNA group connectivity diverged in control of brainstem nuclei, suggesting the emotional pathways of pain related to increased sympathetic activity to muscle [89].

CNS response to pain supports the concept of adaptations of tissue texture not only organized by local inflammatory factors but also by neuronal activity, coordinating hormonal and autonomic homeostasis in relation to motor control patterns. Texture changes throughout fascial systems sustain a bodily and subjective (depending on history) ability restructuring to coordinate loading on MSs. The aim is preserving as much as possible the ability of the movement to conduct social

interactions. Analyzing these organized changes, osteopaths should be able to collect rational bases to plan OMTs.

Osteopathic Management in Cardiac and Cardiovascular Diseases

The high prevalence of cardiovascular diseases is documented in osteopathic practice.

Cross-sectional survey studies, conducted in the United Kingdom and in Australia, showed some patients' profiles – including complained subacute and chronic musculoskeletal pain – both genders between 30 and 50 years old and other patients' profiles aged over 65 years old. Thirty-seven percent of patients had comorbidities, and a first diagnosis was related to the presence of CVD (10–17%) [90, 91].

Osteopath must consider two main aspects as far as the management of overlapped CV conditions in CMP is concerned (see Table 3):

- Disease involvement in pain chronicization
- Bodily involvement MS adjustments in sustaining CV system dysregulation [18]

Cardiac Pain Management

Pain pathways are involved in cardiac diseases. Angina pectoris represents the main symptom associated with imbalance in myocardial oxygen supply, and it refers to upper regions of the body, including the chest, left shoulder, upper limb, and neck. The upper thoracic spinal cord levels involve cardiac pains; they are characterized by the convergent on DH of afferents, from musculoskeletal and gastroenteric chest structures. This map explains the distribution of cardiac pain [92].

The presence of previous episodes of angina pectoris and/or coronary artery disease should be evaluated as a contribution of sensitization mechanisms in the neck, shoulder, and chest CMP, or headache. Biomechanics of thorax should be taken into consideration during cardiac pain. These biomechanics coordinate the breathing and support the cardiac oxygen demand influenced by anxiety perception. PM organization and the influences of stressing factors on memory processes could sustain this breathing strategy. It involves overload in lumbar pelvic muscle and contributes to sustain CMP in lower body regions.

By mapping the spinal cord, primary afferent fibers and cardiac neurons in DRG showed a wide distribution area which involves middle and lower thorax levels (from ventricular chambers and ascending axon projections to cervical DRG from eighth to fifth level) [93]. Myocardial afferent neurons conduct nociception in response to ischemic stimulus [94] and have a related increased activity in transcription of TNF α, supporting sensitization changes during heart infraction [95].

Cardiac pain modulation was also found to be related to the activation of reflex circuits in ventral lamina of thoracic DH, and it is supposed to

Table 3 Osteopathic management of cardiovascular disease

Osteopathic principles			
	Homeostatic	Previous	Perception
Osteopathic treatment	Issue	History	Well-being
Who?	Cardiac pain sensitization	Movement adjustment	Fear
			Social relationship
Chronic pain	Breathing biomechanics	Postural adaptation	Functional disability
	Muscle oxygenation		
How?	Heart rate variability	Allostatic overload	Emotional behaviors
Body involvement	Blood pressure		Motor behaviors
	Tissue drainage		
What?	*Exacerbate*	*Arrange*	*Contribute*
Happen to pain	*Evoke*	*Sustain*	

sustain the secondary hyperalgesia complained after a cardiac ischemia [96]. An ischemic model of reflex response by Liu et al. [97] explained the spinal involvement in visceral somatic cardiac reflexes. Reflex activities were reflected by an increased paraspinal electromyography (EMG) subsequent to hypossic and inflammatory stimuli in myocardial tissue. EMG detected a higher activity in response to ischemic signals rather than irritant chemicals. A concomitant divergent response in blood pressure (increased in ischemia and decreased in inflammation), suggesting a brainstem modulation – as another mechanism related to secondary muscle hyperalgesia – was detected, too.

Brainstem region is known as a pain modulator thanks to the dichotomous activity of PAG. In this context, the role of vagus nerve and its sensory nucleus (nucleus tractus solitarius (NTS)) have been demonstrated to be implicated in both inhibitory and excitatory influences on the modulation of the pain across its projections to cervical DH [92]. Furthermore, NTS showed an excitatory activity on paraspinal EMG when cardiac-evoked nociception induce an increasing glutaminergic-NMDA receptor activity. The involvement of NMDA receptors in sensitization mechanism supports the hypothesis of brainstem region involvement in secondary hyperalgesia [98].

These findings support the investigation of somatic dysfunctions in cervical and thoracic regions related to the pain status referred by patients (extended to all trunk regions). In fact, diaphragmatic and lumbar pelvic muscles are involved in respiratory biomechanics as an active participation and tonic control of movement. The diaphragm muscle is responsible for the respiratory movements of lower rib cage. An interesting study of Bastir et al. [99] showed wider movements and a strong positive correlation between the shape and the lower rib cage diameters – compared to upper rib cage when diaphragmatic respiration is involved. A contribution to the change in lower thorax is carried out by abdominal muscles, lumbar spine muscles in the posterior wall included. In bronchopneumopathy, a deformation of the thorax has been recognized as a consequence of the alterations in breathing [100], which corresponded to a reduction in rib cage volumes and abdominal volume increasing [101]. In addition, an interesting study of Hirjakova et al. [102] showed the relationship between breathing and balance, during visual tasks, which was found as associated with the recruitment strategy for stability and for emotional response, supporting the involvement of lower regions of the body as a contribution to dissipation of respiratory forces.

An emotional environment should be considered in breathing biomechanics in patients experiencing cardiac pain.

The prevalence of mood disorder, after myocardial infraction, has been assessed in 13% for general anxiety and 19% for depression [103, 104]. Mood disorder has been investigated by CNS functional imaging studies, showing an altered connectivity among ACC, PFC, and the amygdala related to the acquisition and the extinction of both emotional stimuli and fear [105]. As described in the previous section, the same areas are involved in PM organization and are implicated in emotional and motor experienced pain.

In syndrome X, the experience of angina pectoris was found to be associated with increased connectivity among IC, PFC, and the cerebellum [106]. The same areas are involved in several interoceptive and nociceptive processes, such as the interoceptive perception of heartbeat. In healthy subjects, Pollatos et al. detected the interoceptive awareness of heartbeat to be related to increased connectivity on the insular cortex – with the putamen and thalamus in attention tasks and with the parietal lobe and thalamus in physical tasks [107].

Connectivity among IC, the cerebellum, and brainstem was also found to be increased in breathing in chemoceptive stressor stimuli, as an adaptive physiological strategy in hypercapnia [108, 109]. In addition, von Leupoldt et al. studies [110] investigated the affective dimension of dyspneic condition, finding an involvement of IC and amygdala connectivity along with an unpleasant sensation in resistive load inducing dyspnea.

Finally, PFC connectivity with the amygdala was positively correlated with heart rate in emotional tasks [111], associated with PAG activity to

control heart rate in negative and positive emotions [112]. PFC role has been linked to the rewarding memory circuits in both unpleasant and pleasant affections [56].

The implication of negative affection and rewarding memory circuits in many unpleasant conditions – which covered cardiac symptoms, signs, and their relationship with motor control area – supports the necessity to check respiratory biomechanics and its role in maintaining postural and motor behaviors altered in cardiac diseases.

Reflections in Cardiovascular Dysfunctions

Cardiovascular diseases are a widespread range of pathologies in which altered functions involve the CV system in all levels. Pathophysiology deals with intrinsic regulation (neuronal and paracrine), autonomic control, and hormonal environments, which dysregulate heart frequency, blood pressure, and drainage circles.

Osteopathic management of CVD analyzes how the body adaptive adjustments contribute to the CV system dysfunction and if the OMT has the wherewithal to influence it positively [18].

Respiratory biomechanics in cardiac pain should be analyzed for several reasons, such as pain sensitization, cardiac reflexes, and functional relation of the heart and lung. Breathing movement strategies supply oxygenation tissue throughout different ways: blood gas exchanges and drainage mechanisms. While breathing, muscular work modifies the volume of the trunk, supports venous circulation, and supports cardiac load [113].

An interesting study of Miller et al. [114] revealed a breathing modulation of femoral venous pressure depending on abdominal pressure (dynamic at rest) and decreasing during muscle recruitment. Venous pressure does not respond to different strategies of breathing, but it supports the ability to coherently dissipate the breath across abdominal volume plasticity, mediated by MSs.

In CVD, heart failure (HF) is the main condition involving respiratory system and breathing biomechanics as shown in a study by Balzan comparing stroke volume and cardiac output in healthy and HF subjects. In this chapter, HF patients did not show a variation in stroke volume and cardiac output at rest as in healthy subjects, while during light exercise, increased findings were detected. It was supposed to be related to a lack of ability to involve abdominal pump in respiratory strategy to support cardiac load in supine position. The recruitment of limb muscle pump during standing position and exercise allows them to improve the support to the heart [115].

The osteopathic approach investigates the relationship among muscle chains (in terms of fascial sliding plan remodeling), and it studies joint expressions of movements and related changes in tissue texture. The osteopathic approach aims at helping the expression of moments and its influence on homeostatic system. OMT could influence the recruitment strategy in breathing and muscle pump supporting venous blood flow, cardiac load, and tissue oxygenation. O-Yurvati et al. [116] found significant changes in cardiac function and blood perfusion due to OMT in patients recovering after coronary artery bypass graft surgery. OMT was applied on rib cage dysfunction to improve respiratory function. Results indicate a positive short-term influence on cardiovascular functions at least.

Two main fields should be considered as linked to the functional status expression in CVD: the increased sympathetic nervous system (SNS) activity and the chronic stress. These expressions are recognized to be as a contribution to generate and sustain disease conditions.

The increase of the sympathetic outflow (to peripheral arteriolar resistance) and myocardium is related to autonomic dysregulation in CVD. Blood pressure and inotropic cardiac function are both influenced. Cardiac neuraxis concerns plastic capabilities in a responsive attempt to maintain an adequate inotropic function. Functional and structural neuroplasticity have been shown at all levels of neural hierarchy, from intrinsic organization to cortical-limbic regions [117].

The sensory and sympathetic fiber remodeling were related to an upregulation of inflammatory signals and to a dysregulation of

mechanotransduction signals in both arrhythmic [118] and ischemic cardiac diseases [119].

Changes in heart network are supported by inflammatory and chronic stress-mediating sensitization in brainstem CV nuclei, which sustain bodily blood pressure (increasing SNS activity) and involving neurohumoral pathway of the hypothalamus. In blood hypertensive conditions, CV nuclei in the brainstem have been related to be sensitivity mechanisms – involving Angiotensin-II (Ang II) pathways – from the hypothalamus. This contributes to dysregulate baroreflex activity (on long-term blood pressure control) [120], hormonal control (of adrenal axis) [121], and blood pressure (in heart failure) [122].

Blood pressure control also involves the mechanoreflexes (from peripheral resistances), specifically from muscular vessels, and supports the blood demand associated with physical activity. FNE muscular receptors, which are a firm responsiveness to mechanical and chemical stimuli of muscle load, are linked to excitability of SNS and are involved in blood hypertension sustenance by sensitization of nitric oxide central pathway in rostral-ventral-lateral medulla and NTS [123].

The SNS is also involved in musculoskeletal tissue remodeling as well as in CVD. Sympathetic sprouting has been found as part of wound healing [124] and in fracture callus [125] as mediator in the beginning phases of repairing process. It has been associated with inflammatory process in tendinopathy [126], rheumatoid arthritis [127], and osteoarthritis in early stages [128].

SNS has been recognized to participate in defense response of the organism, influenced by fight-flight CNS reaction and adrenal axis activation for regulating inflammation, blood supply, and immune cells [129]. Furthermore, the response to pain stimulus involved an increased SNS activity in muscles sustaining the development of CMP conditions [130].

Osteopathic management placates pain conditions and improves movements and health status, too. Sympathetic activity increase, in CVD patients, could influence musculoskeletal remodeling in supporting postural and movement strategies, worsening CMP conditions. Perturbation in movement involves tissue remodeling of MMs and sustains a possible dysregulation of the CV system. CMP and its adaptive MS strategies could contribute to maintain mechanoreflex sensitivity in CVD and to overload blood pressure control.

Zegarra-Parodi et al. [131] detected a significant and persistent skin vasodilatation in bilateral superior limb (after spinal mobilization of cervico-dorsal region) proposing a pressure-dependent involvement of spinal somatic mechanoceptors. In a sit-to-stand test, mechanoreflex regulation of blood pressure was studied in healthy patients as related to postural muscle requirements. EMG activity of inferior limb muscles was found as associated with variation in blood pressure and in balance. Results indicated how inferior limb muscles were directly involved in supporting blood pressure (in a changing position), while its strategy of balance maintenance was linked to blood pressure (in a standing position) [132]. After similar conditions (i.e., tilt test), OMT on cervical region showed significant changes in heart rate variability (HRV) confirming the influence on blood pressure control [133]. Another contribution to tissue remodeling and CVD derives from central and peripheral interactions with chronic stress mediators. In association with SNS activities, glucocorticoids (GC) have been found to be as a fundamental feature in pathophysiology of CVD supporting endothelial dysfunctions, sensitization Ang II circuits of blood pressure control, and memory adaptive processes in cortico-limbic circuits to CV regulation [134].

It should be considered that patients refer chronic stress conditions during his/her osteopathic visit. She/he sustains pain and comorbidities and differently reacts to pain. Some studies suggest a bidirectional communication between pain and stress hormones, establishing chronicization mechanisms, behavioral strategy [135], and mood disorder [136] while facing an inflammatory state [137].

Several stress mediators (i.e., GC and Ang II) on localized vessels showed an association with

an increased expression of integrins and ECM proteins, supporting connective tissue remodeling in blood hypertension [134, 138]. GC-induced neuroplasticity was found to be associated with chronic unpredictable mild stress in the amygdala [139]. In a CVD population, Tawakol et al. [140] demonstrated a positive correlation between amygdala connectivity and inflammatory index related to atherosclerosis. Chronic stress was sustained as a CV risk factor. Inflammatory environments are the main mediators of EMC remodeling, which have influenced endothelial function, lymphatic drainage [141], fascial composition, and elasticity expression (i.e., stiffness) [142], in CV and MS systems, respectively.

In addition, chronic stress has been investigated as involved in body mass composition, expenditure of energies, and related health status. Humoral and inflammatory stress mediator contributes to water controlling, fat composition, muscle mass, and bone mass, supplying healthy or unhealthy status and its own perception [54].

The effect of OMT suggests a possible beneficial interaction on reducing inflammatory mediators both in vivo [143] and in vitro [144] studies. Beneficial interaction in enhancing lymphatic system is probably due to the improvement of the ability to control postural/movement demands [145] as a reduction of chronic stress condition.

A last consideration should be done on the prevalence of CVD in elderly people. Frailty is the characteristic of ageing population, defined as "cumulative decline that erodes homeostatic reserve until relatively minor stressor events trigger disproportionate changes in health status, typically a fall or delirium" [146].

In this context, osteopathic management should respect both the energetic availability and the functional ability expressed by tissue ageing. A wide range of manual techniques in osteopathic treatment allow to plan a tailored approach to improve balance rather than amplitude in movements [18].

Some studies showed as OMT can be useful to decrease postural ways [147] and increase quality of life in adults [148], supporting a positive influence on perception and balance control in osteopathic management.

Osteopathic Treatment and Health Status

Supporting the efficacy on middle-term osteopathic manipulative treatment (on several pain and functional conditions) is recognized as a main difficulty [63].

In CMP field, some osteopathic trials are present in literature. The OSTEOPATHIC trial included 455 chronic low back pain (LBP) subjects and showed a significant improvement in pain and disability scales after OMT, with a large effect size in patients with high severity of LBP [149]. In the trial, somatic dysfunctions and inflammatory indexes were detected to support results. SD presence, in lumbar spine, was positively correlated with LBP severity and back-specific disability and inversely associated with quality of life [150]. Furthermore, high number of SD were recorded as depressed [151]. As far as inflammatory indexes are concerned, measures of IL-1β and IL-6, correlated with SD and the OMT, are associated with a decrease in TNF-α [144]. The results support the concept that the osteopathic assessment could be useful to evaluate CMP. OMT is helpful to improve clinical status and reducing pain signals.

Interesting reviews showed how musculoskeletal disorder OMT had a moderate-quality evidence to relieve pain and improve functional status (i.e., LBP, LBP in pregnancy, headache) [152–155]. In pediatric field, OMT was associated with a reduction of length of stay – in pre-terms infant [156] – and it showed controversy evidence in other pediatric disorders, such as otitis media, respiratory conditions, and scoliosis [157]. Concerning functional disorder (i.e., enteric and urinary), few studies investigate the efficacy of OMT and suggest a benefit from the osteopathic management, presenting a favorable result on symptoms and QoL [158, 159].

Several hypotheses have been proposed, in the last 20 years of osteopathic researches, to support clinical trial results.

The "interoceptive paradigm" proposed by D'Alessandro et al. [63] induces a reflection on how OMT influences health status:

- Improvement of the movement expressed by joints and fascial sliding plan represents a new organization of the MS behaviors due to interoceptive information generated by OMT.
- Tissue mechanotransduction transforms the induced forces of OMT in a new tissue communication in which functional remodeling of ECM supports the new strategic demand of movements.
- The new strategy acquired by means of OMT improves perception and descending body regulations, balancing SNS firing and inflammatory status related to chronic stress conditions.

Interoception, defined by Craig as "the sense of the physiological condition of entire body," is mapped and integrated by the insular cortex, which collects information from all tissues and from the sensorial system. It processes them in emotional and cognitive integration. Posterior IC has been recognized to collect and process visceral sensitivity and interoception from somatic structures (i.e., MS tissue and the skin) which also covered proprioception sensitivity. IC processes interoception with other sensorial information and collaborates with the cingulate cortex and PFC to elaborate emotional and cognitive adaptive responses, supporting internal physiology and its allostasis.

The anterior IC plays a crucial role in coordinating amygdala homeostatic nuclei, involving hormonal and autonomic regulations [160].

The role of IC and its connectivity in pain and in CV condition has been described in the previous section. The influence of OMT as "interoceptive reintegration" is supported by changes in IC connectivity depending on the type of touch, as showed by Cerritelli et al [161]. Furthermore, it can be hypothesized that the effect of OMT is associated with this interoceptive rehabilitation.

Heart rate variability is considered an index which expresses a physiological control of the autonomic nervous system onto the heart. CVD and CMP have been associated with an impairment of HRV; in particular these conditions demonstrate an increased SNS activity on the heart supporting its pathophysiologic involvement [162].

Osteopathic treatment was found having influence on HRV in different conditions as investigated by Heley et al. A recent study confirms previous results showing an increased parasympathetic and decreased sympathetic activities to modulate cardiac rhythms after OMT [163]. Functional magnetic resonance study showed a correlation among IC, ACC, and PFC connectivity and the response of HRV to painful stimuli, supporting the involvement of descending cortical control in heart frequency and in blood pressure [164]. The osteopathic treatment could induce a balance in cardiac indexes informing cortical pathways across interoceptive stimuli.

O-Yurvati's findings, [116] after coronary artery bypass graft (CABG) surgery, in which a single manual treatment mediated the improvement of oxygenation and cardiac indexes, were supported by another study which investigated the effect of daily osteopathic treatment on bowel function during recovery from CABG surgery.

Visceral function was improved as well as functional assessment score, resulting as a reduction of length of staying in OMT group [165]. If the visceral function is regulated on the base of interoception, it is reasonable to conceive that osteopathic techniques, applied after a rational and palpatory analysis of patients, supporting an interoceptive integration and influencing CV homeostasis.

Supporting this hypothesis, another osteopathic trials' contribution on balance disorders was carried out. OMT showed short- and middle-terms efficacy on dizziness conditions [166, 167]. Disability index of imbalance improved, and it was correlated to the reduction of postural way, in particular, in physical and functional scale, after OMT in vestibular benign disorder [168]. The IC is involved in dizziness integration as demonstrated by Riccelli et al. [169] sustaining the possible interaction of OMT stimuli in interoceptive and proprioceptive integration.

The osteopathic techniques influence the interoception. Another challenge in osteopathic research is finding out how osteopathic spinal manipulation of lumbar region and OMT demonstrated an influence on cortical motor excitability [170] and corticospinal descending motor

pathways [171]. These results could denote the CNS response tissue-inducted forces transduced by MS interoceptors.

The influence of osteopathic techniques on tissues is unclear; in vitro experiment, a model of osteopathic-induced forces suggests a response in fibroblast cells. The reduction of IL-6 production from 24-h repeated strained fibroblast to 24-h indirect OMT supports the hypothesis of a direct interaction with tissue (communication) [145], implicating possible effect on ECM production and remodeling, rather than on cytokine secretion [172].

The biological effects in OMT are the key to understand how CNS integrates a treatment. CNS connectivity reorganization should be considered as an influence at different levels. It should be considered as an affective touch related to care-ness as an interoceptive sensitivity associated with a tissue change and as a proprioceptive integration linked to postural movement strategies.

Conclusion

The prevalence of cardiovascular disease and chronic musculoskeletal pain is increasing in general population over 50 years old. Prevention and emergency policy in NHS improve the rating of mortality in CVD, although disability grew requiring an improvement policy for rehabilitation and support services [3]. The comorbidity between CMP and CVD is sustained by mutual mechanisms such as sensitization, neuroplasticity, and chronic stress [16].

Osteopathic manipulative treatment could be helpful in multidisciplinary approaches to CVD patients, improving musculoskeletal tissues and functions, autonomic balance, and oxygenation supply. OMT reduces pain conditions and improves quality of life.

In 2016, it has been proposed a clinical trial asking for osteopathic intervention. It has been done to permit osteopaths to cooperate with cardiac rehabilitation in CABG surgery, whose aim will be evaluating OMT usefulness in supporting rehabilitation programs [173].

The OMT sustain joints capability and fascial properties. Muscle load expression could be helpful to support functionality of CV system throughout the improvement of mechanoreflex modulation and lymphatic circulation in hypertension and heart failure conditions.

Considering the involvement in some CVD of nociception and coexistent status of sensitization to pain, osteopathic management has the potential to improve perception, evocation, and related functional disability of pain. This is possible due to interoceptive influences rather than nociceptive influences on PM. Furthermore, the improvement in postural stability and in perception of balance could be useful in supporting the rehabilitation of physical sequelae in CVD.

Cross-References

- ▶ Physical Activity and Cardiovascular Health
- ▶ When the Heart Hurts

References

1. Roth GA, Johnson C, Abajobir A, Abd-Allah F, Abera SF, Abyu G, et al. Global, regional, and national burden of cardiovascular diseases for 10 causes, 1990 to 2015. J Am Coll Cardiol. 2017; 70(1):1–25. https://doi.org/10.1016/j.jacc.2017.04.052. Epub 2017 May 17
2. www.who.int/nmh/publications/ncd_report2010/en/
3. Vos T, Allen C, Arora M, Barber RM, Bhutta ZA, Brown A, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the global burden of disease study 2015. Lancet. 2016;388(10053):1545–602. https://doi.org/10.1016/S0140-6736(16)31678-6.
4. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney MT, et al. European guidelines on cardiovascular disease prevention in clinical practice. Rev Esp Cardiol (Engl Ed). 2016;69(10): 939. https://doi.org/10.1016/j.rec.2016.09.009.
5. Piepoli MF, Corrà U, Adamopoulos S, Benzer W, Bjarnason-Wehrens B, Cupples M, et al. Secondary prevention in the clinical management of patients with cardiovascular diseases. Core components, standards and outcome measures for referral and delivery: a policy statement from the cardiac rehabilitation section of the European Association for Cardiovascular Prevention & Rehabilitation. Endorsed by

the Committee for Practice Guidelines of the European Society of Cardiology. Eur J Prev Cardiol. 2014;21(6):664–81. https://doi.org/10.1177/2047487312449597.
6. Shields GE, Wells A, Doherty P, Heagerty A, Buck D, Davies LM. Cost-effectiveness of cardiac rehabilitation: a systematic review. Heart. 2018.;pii: heartjnl-2017-312809; https://doi.org/10.1136/heartjnl-2017-312809.
7. Mansfield KE, Sim J, Jordan JL, Jordan KP. A systematic review and meta-analysis of the prevalence of chronic widespread pain in the general population. Pain. 2016;157(1):55–64. https://doi.org/10.1097/j.pain.0000000000000314.
8. Elzahaf RA, Tashani OA, Unsworth BA, Johnson MI. The prevalence of chronic pain with an analysis of countries with a human development index less than 0.9: a systematic review without meta-analysis. Curr Med Res Opin. 2012;28(7):1221–9. https://doi.org/10.1185/03007995.2012.703132.
9. Leadley RM, Armstrong N, Lee YC, Allen A, Kleijnen J. Chronic diseases in the European Union: the prevalence and health cost implications of chronic pain. J Pain Palliat Care Pharmacother. 2012;26(4):310–25. https://doi.org/10.3109/15360288.2012.736933.
10. Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. Eur J Pain. 2006;10(4):287–333.
11. Docking RE, Fleming J, Brayne C, Zhao J, Macfarlane GJ, Jones GT. Epidemiology of back pain in older adults: prevalence and risk factors for back pain onset. Rheumatology (Oxford). 2011;50(9):1645–53. https://doi.org/10.1093/rheumatology/ker175.
12. Andrews P, Steultjens M, Riskowski J. Chronic widespread pain prevalence in the general population: a systematic review. Eur J Pain. 2018;22(1):5–18. https://doi.org/10.1002/ejp.1090.
13. Manchikanti L, Singh V, Falco FJ, Benyamin RM, Hirsch JA. Epidemiology of low back pain in adults. Neuromodulation. 2014;17(Suppl 2):3–10. https://doi.org/10.1111/ner.12018.
14. Andersson HI. Increased mortality among individuals with chronic widespread pain relates to lifestyle factors: a prospective population-based study. Disabil Rehabil. 2009;31(24):1980–7. https://doi.org/10.3109/09638280902874154.
15. Ryan CG, McDonough S, Kirwan JP, Leveille S, Martin DJ. An investigation of association between chronic musculoskeletal pain and cardiovascular disease in the Health Survey for England (2008). Eur J Pain. 2014;18(5):740–50. https://doi.org/10.1002/j.1532-2149.2013.00405.x.
16. Fayaz A, Ayis S, Panesar SS, Langford RM, Donaldson LJ. Assessing the relationship between chronic pain and cardiovascular disease: a systematic review and meta-analysis. Scand J Pain. 2016;13:76–90. https://doi.org/10.1016/j.sjpain.2016.06.005.
17. Tick H, Nielsen A, Pelletier KR, Bonakdar R, Simmons S, Glick R, et al. Evidence-based nonpharmacologic strategies for comprehensive pain care: the consortium pain task force white paper. Pain task force of the academic consortium for integrative medicine and health. Explore (NY). 2018;14(3):177–211. https://doi.org/10.1016/j.explore.2018.02.001.
18. Chila A. Foundations of osteopathic medicine. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2010.
19. Slattengren AH, Nissly T, Blustin J, Bader A, Westfall E. Best uses of osteopathic manipulation. J Fam Pract. 2017;66(12):743–7.
20. IASP. Pain terms: a list with definitions and notes on usage: recommended by the IASP Subcommittee on taxonomy. Pain. 1979;6:249.
21. Cohen M, Quintner J, van Rysewyk S. Reconsidering the International Association for the Study of Pain definition of pain. Pain Rep. 2018;3(2):e634. https://doi.org/10.1097/PR9.0000000000000634.
22. Khalid S, Tubbs RS. Neuroanatomy and neuropsychology of pain. Cureus. 2017;9(10):e1754. https://doi.org/10.7759/cureus.1754.
23. Loeser JD, Melzack R. Pain: an overview. Lancet. 1999;353(9164):1607–9.
24. Collins SL, Moore RA, McQuay HJ. The visual analogue pain intensity scale: what is moderate pain in millimetres? Pain. 1997;72(1–2):95–7.
25. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. Pain. 2011;152(3 Suppl):S2–15. https://doi.org/10.1016/j.pain.2010.09.030.
26. Reichling DB, Levine JD. Critical role of nociceptor plasticity in chronic pain. Trends Neurosci. 2009;32(12):611–8. https://doi.org/10.1016/j.tins.2009.07.007.
27. Brierley SM. Molecular basis of mechanosensitivity. Auton Neurosci. 2010;153(1–2):58–68. https://doi.org/10.1016/j.autneu.2009.07.017.
28. Zhang S, Zhao E, Winkelstein BA. A nociceptive role for integrin signaling in pain after mechanical injury to the spinal facet capsular ligament. Ann Biomed Eng. 2017;45(12):2813–25. https://doi.org/10.1007/s10439-017-1917-2.
29. Kim DS, Figueroa KW, Li KW, Boroujerdi A, Yolo T, Luo ZD. Profiling of dynamically changed gene expression in dorsal root ganglia post peripheral nerve injury and a critical role of injury-induced glial fibrillary acidic protein in maintenance of pain behaviors [corrected]. Pain. 2009;143(1–2):114–22. https://doi.org/10.1016/j.pain.2009.02.006.
30. Reinhold AK, Batti L, Bilbao D, Buness A, Rittner HL, Heppenstall PA. Differential transcriptional profiling of damaged and intact adjacent dorsal root ganglia neurons in neuropathic pain. PLoS One. 2015;10(4):e0123342. https://doi.org/10.1371/journal.pone.0123342.
31. Pace MC, Passavanti MB, De Nardis L, Bosco F, Sansone P, Pota V, et al. Nociceptor plasticity: a closer

look. J Cell Physiol. 2018;233(4):2824–38. https://doi.org/10.1002/jcp.25993.
32. Bradesi S. Role of spinal cord glia in the central processing of peripheral pain perception. Neurogastroenterol Motil. 2010;22(5):499–511. https://doi.org/10.1111/j.1365-2982.2010.01491.x.
33. König C, Morch E, Eitner A, Möller C, Turnquist B, Schaible HG, Ebersberger A. Involvement of spinal IL-6 trans-signaling in the induction of hyperexcitability of deep dorsal horn neurons by spinal tumor necrosis factor-alpha. J Neurosci. 2016;36(38):9782–91. https://doi.org/10.1523/JNEUROSCI.4159-15.2016.
34. Alexander JK, DeVries AC, Kigerl KA, Dahlman JM, Popovich PG. Stress exacerbates neuropathic pain via glucocorticoid and NMDA receptor activation. Brain Behav Immun. 2009;23(6):851–60. https://doi.org/10.1016/j.bbi.2009.04.001.
35. Basso L, Lapointe TK, Iftinca M, Marsters C, Hollenberg MD, Kurrasch DM, Altier C. Granulocyte-colony-stimulating factor (G-CSF) signaling in spinal microglia drives visceral sensitization following colitis. Proc Natl Acad Sci USA. 2017;114(42):11235–40. https://doi.org/10.1073/pnas.1706053114.
36. Heinricher MM, Tavares I, Leith JL, Lumb BM. Descending control of nociception: specificity, recruitment and plasticity. Brain Res Rev. 2009;60(1):214–25. https://doi.org/10.1016/j.brainresrev.2008.12.009.
37. Garcia-Larrea L, Peyron R. Pain matrices and neuropathic pain matrices: a review. Pain. 2013;154(Suppl 1):S29–43. https://doi.org/10.1016/j.pain.2013.09.001.
38. Zhuo M. Contribution of synaptic plasticity in the insular cortex to chronic pain. Neuroscience. 2016;338:220–9. https://doi.org/10.1016/j.neuroscience.2016.08.014.
39. Ong WY, Stohler CS, Herr DR. Role of the prefrontal cortex in pain processing. Mol Neurobiol. 2018; https://doi.org/10.1007/s12035-018-1130-9.
40. Vachon-Presseau E. Effects of stress on the corticolimbic system: implications for chronic pain. Prog Neuro-Psychopharmacol Biol Psychiatry. 2017. pii: S0278-5846;(17):30598-5. https://doi.org/10.1016/j.pnpbp.2017.10.014.
41. Boadas-Vaello P, Homs J, Reina F, Carrera A, Verdú E. Neuroplasticity of supraspinal structures associated with pathological pain. Anat Rec (Hoboken). 2017;300(8):1481–501. https://doi.org/10.1002/ar.23587.
42. Sousa-Valente J, Brain SD. A historical perspective on the role of sensory nerves in neurogenic inflammation. Semin Immunopathol. 2018;40(3):229–36. https://doi.org/10.1007/s00281-018-0673-1.
43. Akaishi S, Ogawa R. Hyakusoku H keloid and hypertrophic scar: neurogenic inflammation hypotheses. Med Hypotheses. 2008;71(1):32–8. https://doi.org/10.1016/j.mehy.2008.01.032.
44. Goldstein DS, McEwen B. Allostasis, homeostats, and the nature of stress. Stress. 2002;5(1):55–8.
45. http://apps.who.int/classifications/icd10/browse/2010/en#/M95-M99.
46. Kuchera ML. Osteopathic manipulative medicine considerations in patients with chronic pain. J Am Osteopath Assoc. 2005;105(9 Suppl 4):S29–36.
47. Cavalieri TA. Management of pain in older adults. J Am Osteopath Assoc. 2005;105(3 Suppl 1):S12–7.
48. Leleszi JP, Lewandowski JG. Pain management in end-of-life care. J Am Osteopath Assoc. 2005;105(3 Suppl 1):S6–11.
49. Miyagi M, Millecamps M, Danco AT, Ohtori S, Takahashi K, Stone LS. ISSLS prize winner: increased innervation and sensory nervous system plasticity in a mouse model of low back pain due to intervertebral disc degeneration. Spine (Phila Pa 1976). 2014;39(17):1345–54. https://doi.org/10.1097/BRS.0000000000000334.
50. Micera A, Balzamino BO, Di Zazzo A, Biamonte F, Sica G, Bonini S. Toll-like receptors and tissue remodeling: the pro/cons recent findings. J Cell Physiol. 2016;231(3):531–44. https://doi.org/10.1002/jcp.25124.
51. Eitner A, Hofmann GO, Schaible HG. Mechanisms of osteoarthritic pain. Studies in humans and experimental models. Front Mol Neurosci. 2017;10:349. https://doi.org/10.3389/fnmol.2017.00349.
52. McEwen BS, Bowles NP, Gray JD, Hill MN, Hunter RG, Karatsoreos IN, Nasca C. Mechanisms of stress in the brain. Nat Neurosci. 2015;18(10):1353–63. https://doi.org/10.1038/nn.4086.
53. Goldstein DS, Kopin IJ. Homeostatic systems, biocybernetics, and autonomic neuroscience. Auton Neurosci. 2017;208:15–28. https://doi.org/10.1016/j.autneu.2017.09.001.
54. Stefanaki C, Pervanidou P, Boschiero D, Chrousos GP. Chronic stress and body composition disorders: implications for health and disease. Hormones (Athens). 2018;17(1):33–43. https://doi.org/10.1007/s42000-018-0023-7.
55. Hashmi JA, Baliki MN, Huang L, Baria AT, Torbey S, Hermann KM, et al. Shape shifting pain: chronification of back pain shifts brain representation from nociceptive to emotional circuits. Brain. 2013;136(Pt 9):2751–68. https://doi.org/10.1093/brain/awt211.
56. Berridge KC, Kringelbach ML. Pleasure systems in the brain. Neuron. 2015;86(3):646–64. https://doi.org/10.1016/j.neuron.2015.02.018.
57. Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. JAMA. 1995;273(1):59–65.
58. Tough H, Siegrist J, Fekete C. Social relationships, mental health and wellbeing in physical disability: a systematic review. BMC Public Health. 2017;17(1):414. https://doi.org/10.1186/s12889-017-4308-6.
59. Leadley RM, Armstrong N, Reid KJ, Allen A, Misso KV, Kleijnen J. Healthy aging in relation to chronic

pain and quality of life in Europe. Pain Pract. 2014;14 (6):547–58. https://doi.org/10.1111/papr.12125.
60. Strøm J, Bjerrum MB, Nielsen CV, Thisted CN, Nielsen TL, Laursen M, Jørgensen LB. Anxiety and depression in spine surgery-a systematic integrative review. Spine J. 2018;18(7):1272–85. https://doi.org/10.1016/j.spinee.2018.03.017.
61. Coppieters I, Ickmans K, Cagnie B, Nijs J, De Pauw R, Noten S, Meeus M. Cognitive performance is related to central sensitization and health-related quality of life in patients with chronic whiplash-associated disorders and fibromyalgia. Pain Physician. 2015;18 (3):E389–401.
62. Ysrraelit MC, Fiol MP, Gaitán MI, Correale J. Quality of life assessment in multiple sclerosis: different perception between patients and neurologists. Front Neurol. 2018;8:729. https://doi.org/10.3389/fneur.2017.00729.
63. D'Alessandro G, Cerritelli F, Cortelli P. Sensitization and interoception as key neurological concepts in osteopathy and other manual medicines. Front Neurosci. 2016;10:100. https://doi.org/10.3389/fnins.2016.00100.
64. Esteves JE, Spence C. Developing competence in diagnostic palpation: perspectives from neuroscience and education. Int J Osteopath Med. 2014;17(1): 52–60. https://doi.org/10.1016/j.ijosm.2013.07.001.
65. Fingleton C, Smart K, Moloney N, Fullen BM, Doody C. Pain sensitization in people with knee osteoarthritis: a systematic review and meta-analysis. Osteoarthr Cartil. 2015;23(7):1043–56. https://doi.org/10.1016/j.joca.2015.02.163.
66. Corrêa JB, Costa LO, de Oliveira NT, Sluka KA, Liebano RE. Central sensitization and changes in conditioned pain modulation in people with chronic nonspecific low back pain: a case-control study. Exp Brain Res. 2015;233(8):2391–9. https://doi.org/10.1007/s00221-015-4309-6.
67. Castien RF, van der Wouden JC, De Hertogh W. Pressure pain thresholds over the cranio-cervical region in headache: a systematic review and meta-analysis. J Headache Pain. 2018;19(1):9. https://doi.org/10.1186/s10194-018-0833-7.
68. Tozzi P. A unifying neuro-fasciagenic model of somatic dysfunction – underlying mechanisms and treatment – Part I. J Bodyw Mov Ther. 2015;19(2): 310–26. https://doi.org/10.1016/j.jbmt.2015.01.001.
69. Yagmur C, Akaishi S, Ogawa R, Guneren E. Mechanical receptor-related mechanisms in scar management: a review and hypothesis. Plast Reconstr Surg. 2010;126(2):426–34. https://doi.org/10.1097/PRS.0b013e3181df715d.
70. Lunghi C, Tozzi P, Fusco G. The biomechanical model in manual therapy: is there an ongoing crisis or just the need to revise the underlying concept and application? J Bodyw Mov Ther. 2016;20(4):784–99. https://doi.org/10.1016/j.jbmt.2016.01.004.
71. Eming SA, Wynn TA, Martin P. Inflammation and metabolism in tissue repair and regeneration. Science. 2017;356(6342):1026–30. https://doi.org/10.1126/science.aam7928.
72. Kharraz Y, Guerra J, Mann CJ, Serrano AL, Muñoz-Cánoves P. Macrophage plasticity and the role of inflammation in skeletal muscle repair. Mediat Inflamm. 2013;2013:491497. https://doi.org/10.1155/2013/491497.
73. Arnold L, Henry A, Poron F, Baba-Amer Y, van Rooijen N, Plonquet A, et al. Inflammatory monocytes recruited after skeletal muscle injury switch into antiinflammatory macrophages to support myogenesis. J Exp Med. 2007;204(5):1057–69.
74. Karkampouna S, Kreulen M, Obdeijn MC, Kloen P, Dorjée AL, Rivellese F, et al. Connective tissue degeneration: mechanisms of palmar fascia degeneration (Dupuytren's disease). Curr Mol Biol Rep. 2016;2(3):133–40.
75. Shi J, Li Q, Sheng M, Zheng M, Yu M, Zhang L. The role of TLR4 in M1 macrophage-induced epithelial-mesenchymal transition of peritoneal mesothelial cells. Cell Physiol Biochem. 2016;40(6):1538–48. https://doi.org/10.1159/000453204.
76. Lagrota-Candido J, Canella I, Pinheiro DF, Santos-Silva LP, Ferreira RS, Guimarães-Joca FJ, et al. Characteristic pattern of skeletal muscle remodelling in different mouse strains. Int J Exp Pathol. 2010;91(6):522–9. https://doi.org/10.1111/j.1365-2613.2010.00737.x.
77. Steward RL Jr, Cheng CM, Wang DL, LeDuc PR. Probing cell structure responses through a shear and stretching mechanical stimulation technique. Cell Biochem Biophys. 2010;56(2–3):115–24. https://doi.org/10.1007/s12013-009-9075-2.
78. Jones ER, Jones GC, Legerlotz K, Riley GP. Cyclical strain modulates metalloprotease and matrix gene expression in human tenocytes via activation of TGFβ. Biochim Biophys Acta. 2013;1833(12): 2596–607. https://doi.org/10.1016/j.bbamcr.2013.06.019.
79. Legerlotz K, Jones GC, Screen HR, Riley GP. Cyclic loading of tendon fascicles using a novel fatigue loading system increases interleukin-6 expression by tenocytes. Scand J Med Sci Sports. 2013;23(1):31–7. https://doi.org/10.1111/j.1600-0838.2011.01410.x.
80. Kuang R, Wang Z, Xu Q, Cai X, Liu T. Exposure to varying strain magnitudes influences the conversion of normal skin fibroblasts into hypertrophic scar cells. Ann Plast Surg. 2016;76(4):388–93. https://doi.org/10.1097/SAP.0000000000000654.
81. Guimberteau JC, Armstrong C. Architecture of human living Fascia. The extracellular matrix and cells revealed through endoscopy. Edinburgh: Handspring Publishing; 2015.
82. Zambreanu L, Wise RG, Brooks JC, Iannetti GD, Tracey I. A role for the brainstem in central sensitisation in humans. Evidence from functional magnetic resonance imaging. Pain. 2005;114(3):397–407.
83. Misra G, Coombes SA. Neuroimaging evidence of motor control and pain processing in the human

midcingulate cortex. Cereb Cortex. 2015;25 (7):1906–19. https://doi.org/10.1093/cercor/bhu001.
84. Oertel BG, Preibisch C, Martin T, Walter C, Gamer M, Deichmann R, Lötsch J. Separating brain processing of pain from that of stimulus intensity. Hum Brain Mapp. 2012;33(4):883–94. https://doi.org/10.1002/hbm.21256.
85. Coombes SA, Misra G. Pain and motor processing in the human cerebellum. Pain. 2016;157(1):117–27. https://doi.org/10.1097/j.pain.0000000000000337.
86. Borsook D, Upadhyay J, Chudler EH, Becerra L. A key role of the basal ganglia in pain and analgesia – insights gained through human functional imaging. Mol Pain. 2010;6:27. https://doi.org/10.1186/1744-8069-6-27.
87. Andreoli M, Marketkar T, Dimitrov E. Contribution of amygdala CRF neurons to chronic pain. Exp Neurol. 2017;298(Pt A):1–12. https://doi.org/10.1016/j.expneurol.2017.08.010.
88. Muscatell KA, Dedovic K, Slavich GM, Jarcho MR, Breen EC, Bower JE, et al. Greater amygdala activity and dorsomedial prefrontal-amygdala coupling are associated with enhanced inflammatory responses to stress. Brain Behav Immun. 2015;43:46–53. https://doi.org/10.1016/j.bbi.2014.06.201.
89. Kobuch S, Fazalbhoy A, Brown R, Henderson LA, Macefield VG. Central circuitry responsible for the divergent sympathetic responses to tonic muscle pain in humans. Hum Brain Mapp. 2017;38(2):869–81. https://doi.org/10.1002/hbm.23424.
90. Burke SR, Myers R, Zhang AL. A profile of osteopathic practice in Australia 2010–2011: a cross sectional survey. BMC Musculoskelet Disord. 2013;14:227. https://doi.org/10.1186/1471-2474-14-227.
91. Fawkes CA, Leach CM, Mathias S, Moore AP. A profile of osteopathic care in private practices in the United Kingdom: a national pilot using standardised data collection. Man Ther. 2014;19(2):125–30. https://doi.org/10.1016/j.math.2013.09.001.
92. Foreman RD, Garrett KM, Blair RW. Mechanisms of cardiac pain. Compr Physiol. 2015;5(2):929–60. https://doi.org/10.1002/cphy.c140032.
93. Guić MM, Kosta V, Aljinović J, Sapunar D, Grković I. Characterization of spinal afferent neurons projecting to different chambers of the rat heart. Neurosci Lett. 2010;469(3):314–8. https://doi.org/10.1016/j.neulet.2009.12.016.
94. Fu LW, Longhurst JC. Bradykinin and thromboxane A2 reciprocally interact to synergistically stimulate cardiac spinal afferents during myocardial ischemia. Am J Physiol Heart Circ Physiol. 2010;298(1):H235–44. https://doi.org/10.1152/ajpheart.00782.2009.
95. Niu YL, Guo Z, Zhou RH. Up-regulation of TNF-alpha in neurons of dorsal root ganglia and spinal cord during coronary artery occlusion in rats. Cytokine. 2009;47(1):23–9. https://doi.org/10.1016/j.cyto.2009.04.003.
96. Jou CJ, Farber JP, Qin C, Foreman RD. Afferent pathways for cardiac-somatic motor reflexes in rats. Am J Physiol Regul Integr Comp Physiol. 2001;281 (6):R2096–102.
97. Liu Y, Zhou LJ, Wang J, Li D, Ren WJ, Peng J, et al. TNF-α differentially regulates synaptic plasticity in the hippocampus and spinal cord by microglia-dependent mechanisms after peripheral nerve injury. J Neurosci. 2017;37(4):871–81. https://doi.org/10.1523/JNEUROSCI.2235-16.2016.
98. Liu XH, Sun N, Du JQ, Tang JS, Han M, Zhu JX, Huo FQ. Chemical lesioning and glutamate administration reveal a major role for the nucleus tractus solitarius in the cardiac-somatic reflex in rats. Neuroscience. 2012;207:326–32. https://doi.org/10.1016/j.neuroscience.2012.01.042.
99. Bastir M, García-Martínez D, Torres-Tamayo N, Sanchis-Gimeno JA, O'Higgins P, Utrilla C, et al. In vivo 3D analysis of thoracic kinematics: changes in size and shape during breathing and their implications for respiratory function in recent humans and fossil hominins. Anat Rec (Hoboken). 2017;300(2): 255–64. https://doi.org/10.1002/ar.23503.
100. Sverzellati N, Colombi D, Randi G, Pavarani A, Silva M, Walsh SL, et al. Computed tomography measurement of rib cage morphometry in emphysema. PLoS One. 2013;8(7):e68546. https://doi.org/10.1371/journal.pone.0068546.
101. Priori R, Aliverti A, Albuquerque AL, Quaranta M, Albert P, Calverley PM. The effect of posture on asynchronous chest wall movement in COPD. J Appl Physiol. 1985;114(8):1066–75. 2013. https://doi.org/10.1152/japplphysiol.00414.2012.
102. Hirjaková Z, Neumannová K, Kimijanová J, Šuttová K, Janura M, Hlavačka F. Breathing changes accompanying balance improvement during biofeedback. Neurosci Lett. 2017;651:30–5. https://doi.org/10.1016/j.neulet.2017.04.051.
103. Tully PJ, Cosh SM. Generalized anxiety disorder prevalence and comorbidity with depression in coronary heart disease: a meta-analysis. J Health Psychol. 2013;18(12):1601–16. https://doi.org/10.1177/1359105312467390.
104. Thombs BD, Bass EB, Ford DE, Stewart KJ, Tsilidis KK, Patel U, et al. Prevalence of depression in survivors of acute myocardial infarction. J Gen Intern Med. 2006;21(1):30–8.
105. Bishop SJ. Neurocognitive mechanisms of anxiety: an integrative account. Trends Cogn Sci. 2007;11(7): 307–16.
106. Rosen SD, Paulesu E, Wise RJ, Camici PG. Central neural contribution to the perception of chest pain in cardiac syndrome X. Heart. 2002;87(6): 513–9.
107. Pollatos O, Schandry R, Auer DP, Kaufmann C. Brain structures mediating cardiovascular arousal and interoceptive awareness. Brain Res. 2007;1141:178–87.
108. McKay LC, Critchley HD, Murphy K, Frackowiak RS, Corfield DR. Sub-cortical and brainstem sites

associated with chemo-stimulated increases in ventilation in humans. NeuroImage. 2010;49(3):2526–35. https://doi.org/10.1016/j.neuroimage.2009.11.007.
109. Pattinson KT, Mitsis GD, Harvey AK, Jbabdi S, Dirckx S, Mayhew SD, et al. Determination of the human brainstem respiratory control network and its cortical connections in vivo using functional and structural imaging. NeuroImage. 2009;44(2):295–305. https://doi.org/10.1016/j.neuroimage.2008.09.007.
110. von Leupoldt A, Sommer T, Kegat S, Baumann HJ, Klose H, Dahme B, Büchel C. The unpleasantness of perceived dyspnea is processed in the anterior insula and amygdala. Am J Respir Crit Care Med. 2008;177(9):1026–32. https://doi.org/10.1164/rccm.200712-1821OC.
111. Sakaki M, Yoo HJ, Nga L, Lee TH, Thayer JF, Mather M. Heart rate variability is associated with amygdala functional connectivity with MPFC across younger and older adults. NeuroImage. 2016;139:44–52. https://doi.org/10.1016/j.neuroimage.2016.05.076.
112. Gray MA, Beacher FD, Minati L, Nagai Y, Kemp AH, Harrison NA, Critchley HD. Emotional appraisal is influenced by cardiac afferent information. Emotion. 2012;12(1):180–91. https://doi.org/10.1037/a0025083.
113. Pinsky MR. Cardiopulmonary interactions: physiologic basis and clinical applications. Ann Am Thorac Soc. 2018;15(Supplement_1):S45–8. https://doi.org/10.1513/AnnalsATS.201704-339FR.
114. Miller JD, Pegelow DF, Jacques AJ, Dempsey JA. Skeletal muscle pump versus respiratory muscle pump: modulation of venous return from the locomotor limb in humans. J Physiol. 2005;563(Pt 3):925–43.
115. Balzan FM, da Silva RC, da Silva DP, Sanches PR, Tavares AM, Ribeiro JP, et al. Effects of diaphragmatic contraction on lower limb venous return and central hemodynamic parameters contrasting healthy subjects versus heart failure patients at rest and during exercise. Physiol Rep. 2014;2(12):e12216. https://doi.org/10.14814/phy2.12216.
116. O-Yurvati AH, Carnes MS, Clearfield MB, Stoll ST, McConathy WJ. Hemodynamic effects of osteopathic manipulative treatment immediately after coronary artery bypass graft surgery. J Am Osteopath Assoc. 2005;105(10):475–81.
117. Ardell JL, Armour JA. Neurocardiology: structure-based function. Compr Physiol. 2016;6(4):1635–53. https://doi.org/10.1002/cphy.c150046.
118. Nakano Y, Chayama K, Ochi H, Toshishige M, Hayashida Y, Miki D, et al. A nonsynonymous polymorphism in semaphorin 3A as a risk factor for human unexplained cardiac arrest with documented ventricular fibrillation. PLoS Genet. 2013;9(4):e1003364. https://doi.org/10.1371/journal.pgen.1003364.
119. Zhou S, Chen LS, Miyauchi Y, Miyauchi M, Kar S, Kangavari S, et al. Mechanisms of cardiac nerve sprouting after myocardial infarction in dogs. Circ Res. 2004;95(1):76–83.
120. Johnson AK, Zhang Z, Clayton SC, Beltz TG, Hurley SW, Thunhorst RL, Xue B. The roles of sensitization and neuroplasticity in the long-term regulation of blood pressure and hypertension. Am J Physiol Regul Integr Comp Physiol. 2015;309(11):R1309–25. https://doi.org/10.1152/ajpregu.00037.2015.
121. Leenen FHH, Blaustein MP, Hamlyn JM. Update on angiotensin II: new endocrine connections between the brain, adrenal glands and the cardiovascular system. Endocr Connect. 2017;6(7):R131–45. https://doi.org/10.1530/EC-17-0161.
122. Zucker IH, Xiao L, Haack KK. The central renin-angiotensin system and sympathetic nerve activity in chronic heart failure. Clin Sci (Lond). 2014;126(10):695–706. https://doi.org/10.1042/CS20130294.
123. Smith SA, Leal AK, Murphy MN, Downey RM, Mizuno M. Muscle mechanoreflex overactivity in hypertension: a role for centrally-derived nitric oxide. Auton Neurosci. 2015;188:58–63. https://doi.org/10.1016/j.autneu.2014.12.004.
124. Reinke JM, Sorg H. Wound repair and regeneration. Eur Surg Res. 2012;49(1):35–43. https://doi.org/10.1159/000339613.
125. García-Castellano JM, Díaz-Herrera P, Morcuende JA. Is bone a target-tissue for the nervous system? New advances on the understanding of their interactions. Iowa Orthop J. 2000;20:49–58.
126. Jewson JL, Lambert GW, Storr M, Gaida JE. The sympathetic nervous system and tendinopathy: a systematic review. Sports Med. 2015;45(5):727–43. https://doi.org/10.1007/s40279-014-0300-9.
127. Dirmeier M, Capellino S, Schubert T, Angele P, Anders S, Straub RH. Lower density of synovial nerve fibres positive for calcitonin gene-related peptide relative to substance P in rheumatoid arthritis but not in osteoarthritis. Rheumatology (Oxford). 2008;47(1):36–40.
128. Grässel SG. The role of peripheral nerve fibers and their neurotransmitters in cartilage and bone physiology and pathophysiology. Arthritis Res Ther. 2014;16(6):485.
129. Jänig W. Sympathetic nervous system and inflammation: a conceptual view. Auton Neurosci. 2014;182:4–14. https://doi.org/10.1016/j.autneu.2014.01.004.
130. Burton AR, Fazalbhoy A, Macefield VG. Sympathetic responses to noxious stimulation of muscle and skin. Front Neurol. 2016;7:109. https://doi.org/10.3389/fneur.2016.00109.
131. Zegarra-Parodi R, Pazdernik VK, Roustit M, Park PY, Degenhardt BF. Effects of pressure applied during standardized spinal mobilizations on peripheral skin blood flow: a randomised cross-over study. Man Ther. 2016;21:220–6. https://doi.org/10.1016/j.math.2015.08.008.
132. Garg A, Xu D, Laurin A, Blaber AP. Physiological interdependence of the cardiovascular and postural

control systems under orthostatic stress. Am J Physiol Heart Circ Physiol. 2014;307(2):H259–64. https://doi.org/10.1152/ajpheart.00171.2014.
133. Henley CE, Ivins D, Mills M, Wen FK, Benjamin BA. Osteopathic manipulative treatment and its relationship to autonomic nervous system activity as demonstrated by heart rate variability: a repeated measures study. Osteopath Med Prim Care. 2008;2:7. https://doi.org/10.1186/1750-4732-2-7.
134. Golbidi S, Frisbee JC, Laher I. Chronic stress impacts the cardiovascular system: animal models and clinical outcomes. Am J Physiol Heart Circ Physiol. 2015;308(12):H1476–98. https://doi.org/10.1152/ajpheart.00859.2014.
135. Fu Y, Neugebauer V. Differential mechanisms of CRF1 and CRF2 receptor functions in the amygdala in pain-related synaptic facilitation and behavior. J Neurosci. 2008;28(15):3861–76. https://doi.org/10.1523/JNEUROSCI.0227-08.2008.
136. Tran L, Schulkin J, Greenwood-Van Meerveld B. Importance of CRF receptor-mediated mechanisms of the bed nucleus of the stria terminalis in the processing of anxiety and pain. Neuropsychopharmacology. 2014;39(11):2633–45. https://doi.org/10.1038/npp.2014.117.
137. Im E. Multi-facets of corticotropin-releasing factor in modulating inflammation and angiogenesis. J Neurogastroenterol Motil. 2015;21(1):25–32. https://doi.org/10.5056/jnm14076.
138. Chao JT, Davis MJ. The roles of integrins in mediating the effects of mechanical force and growth factors on blood vessels in hypertension. Curr Hypertens Rep. 2011;13(6):421–9. https://doi.org/10.1007/s11906-011-0227-6.
139. Wang SS, Yan XB, Hofman MA, Swaab DF, Zhou JN. Increased expression level of corticotropin-releasing hormone in the amygdala and in the hypothalamus in rats exposed to chronic unpredictable mild stress. Neurosci Bull. 2010;26(4):297–303. https://doi.org/10.1007/s12264-010-0329-1.
140. Tawakol A, Ishai A, Takx RA, Figueroa AL, Ali A, Kaiser Y, et al. Relation between resting amygdalar activity and cardiovascular events: a longitudinal and cohort study. Lancet. 2017;389(10071):834–45. https://doi.org/10.1016/S0140-6736(16)31714-7.
141. Negrini D, Moriondo A. Lymphatic anatomy and biomechanics. J Physiol. 2011;589(Pt 12):2927–34. https://doi.org/10.1113/jphysiol.2011.206672.
142. Klingler W, Velders M, Hoppe K, Pedro M, Schleip R. Clinical relevance of fascial tissue and dysfunctions. Curr Pain Headache Rep. 2014;18(8):439. https://doi.org/10.1007/s11916-014-0439-y.
143. Licciardone JC, Kearns CM, Hodge LM, Bergamini MV. Associations of cytokine concentrations with key osteopathic lesions and clinical outcomes in patients with nonspecific chronic low back pain: results from the OSTEOPATHIC trial. J Am Osteopath Assoc. 2012;112(9):596–605.
144. Meltzer KR, Standley PR. Modeled repetitive motion strain and indirect osteopathic manipulative techniques in regulation of human fibroblast proliferation and interleukin secretion. J Am Osteopath Assoc. 2007;107(12):527–36.
145. Schander A, Padro D, King HH, Downey HF, Hodge LM. Lymphatic pump treatment repeatedly enhances the lymphatic and immune systems. Lymphat Res Biol. 2013;11(4):219–26. https://doi.org/10.1089/lrb.2012.0021.
146. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet. 2013;381(9868):752–62. https://doi.org/10.1016/S0140-6736(12)62167-9.
147. Lopez C, Blanke O. The thalamocortical vestibular system in animals and humans. Brain Res Rev. 2011;67(1–2):119–46. https://doi.org/10.1016/j.brainresrev.2010.12.002.
148. Papa L, Mandara A, Bottali M, Gulisano V, Orfei S. A randomized control trial on the effectiveness of osteopathic manipulative treatment in reducing pain and improving the quality of life in elderly patients affected by osteoporosis. Clin Cases Miner Bone Metab. 2012;9(3):179–83.
149. Licciardone JC, Kearns CM, Minotti DE. Outcomes of osteopathic manual treatment for chronic low back pain according to baseline pain severity: results from the OSTEOPATHIC trial. Man Ther. 2013;18(6):533–40. https://doi.org/10.1016/j.math.2013.05.006.
150. Licciardone JC, Kearns CM. Somatic dysfunction and its association with chronic low back pain, back-specific functioning, and general health: results from the OSTEOPATHIC trial. J Am Osteopath Assoc. 2012;112(7):420–8.
151. Licciardone JC, Gatchel RJ, Kearns CM, Minotti DE. Depression, somatization, and somatic dysfunction in patients with nonspecific chronic low back pain: results from the OSTEOPATHIC trial. J Am Osteopath Assoc. 2012;112(12):783–91.
152. Orrock PJ, Myers SP. Osteopathic intervention in chronic non-specific low back pain: a systematic review. BMC Musculoskelet Disord. 2013;14:129. https://doi.org/10.1186/1471-2474-14-129.
153. Franke H, Franke JD, Fryer G. Osteopathic manipulative treatment for nonspecific low back pain: a systematic review and meta-analysis. BMC Musculoskelet Disord. 2014;15:286. https://doi.org/10.1186/1471-2474-15-286.
154. Franke H, Franke JD, Belz S, Fryer G. Osteopathic manipulative treatment for low back and pelvic girdle pain during and after pregnancy: a systematic review and meta-analysis. J Bodyw Mov Ther. 2017;21(4):752–62. https://doi.org/10.1016/j.jbmt.2017.05.014.
155. Cerritelli F, Lacorte E, Ruffini N, Vanacore N. Osteopathy for primary headache patients: a systematic review. J Pain Res. 2017;10:601–11. https://doi.org/10.2147/JPR.S130501.

156. Lanaro D, Ruffini N, Manzotti A, Lista G. Osteopathic manipulative treatment showed reduction of length of stay and costs in preterm infants: a systematic review and meta-analysis. Medicine (Baltimore). 2017;96(12):e6408. https://doi.org/10.1097/MD.0000000000006408.
157. Posadzki P, Lee MS, Ernst E. Osteopathic manipulative treatment for pediatric conditions: a systematic review. Pediatrics. 2013;132(1):140–52. https://doi.org/10.1542/peds.2012-3959.
158. Müller A, Franke H, Resch KL, Fryer G. Effectiveness of osteopathic manipulative therapy for managing symptoms of irritable bowel syndrome: a systematic review. J Am Osteopath Assoc. 2014;114(6):470–9. https://doi.org/10.7556/jaoa.2014.098.
159. Franke H, Hoesele K. Osteopathic manipulative treatment (OMT) for lower urinary tract symptoms (LUTS) in women. J Bodyw Mov Ther. 2013;17(1):11–8. https://doi.org/10.1016/j.jbmt.2012.05.001.
160. Craig A. How do you fell? An interoceptive moment with your neurobiological self. Princeton: Princeton University Press; 2015.
161. Cerritelli F, Chiacchiaretta P, Gambi F, Ferretti A. Effect of continuous touch on brain functional connectivity is modified by the operator's tactile attention. Front Hum Neurosci. 2017;11:368. https://doi.org/10.3389/fnhum.2017.00368.
162. Singh SK, Roy A. Assessment of heart rate variability in the patients suffering with chronic pain of musculoskeletal origin. Natl J Physiol Pharm Pharmacol. 2017;7(7):712–8. https://doi.org/10.5455/njppp.2017.7.0204803032017.
163. Ruffini N, D'Alessandro G, Mariani N, Pollastrelli A, Cardinali L, Cerritelli F. Variations of high frequency parameter of heart rate variability following osteopathic manipulative treatment in healthy subjects compared to control group and sham therapy: randomized controlled trial. Front Neurosci. 2015;9:272. https://doi.org/10.3389/fnins.2015.00272.
164. Perlaki G, Orsi G, Schwarcz A, Bodi P, Plozer E, Biczo K, et al. Pain-related autonomic response is modulated by the medial prefrontal cortex: an ECG-fMRI study in men. J Neurol Sci. 2015;349(1–2):202–8. https://doi.org/10.1016/j.jns.2015.01.019.
165. Wieting JM, Beal C, Roth GL, Gorbis S, Dillard L, Gilliland D, Rowan J. The effect of osteopathic manipulative treatment on postoperative medical and functional recovery of coronary artery bypass graft patients. J Am Osteopath Assoc. 2013;113(5):384–93.
166. Fraix M. Osteopathic manipulative treatment and vertigo: a pilot study. PM R. 2010;2(7):612–8. https://doi.org/10.1016/j.pmrj.2010.04.001.
167. Fraix M, Gordon A, Graham V, Hurwitz E, Seffinger MA. Use of the SMART balance master to quantify the effects of osteopathic manipulative treatment in patients with dizziness. J Am Osteopath Assoc. 2013;113(5):394–403.
168. Papa L, Amodio A, Biffi F, Mandara A. Impact of osteopathic therapy on proprioceptive balance and quality of life in patients with dizziness. J Bodyw Mov Ther. 2017;21(4):866–72. https://doi.org/10.1016/j.jbmt.2017.03.001.
169. Riccelli R, Passamonti L, Toschi N, Nigro S, Chiarella G, Petrolo C, et al. Altered insular and occipital responses to simulated vertical self-motion in patients with persistent postural-perceptual dizziness. Front Neurol. 2017;8:529. https://doi.org/10.3389/fneur.2017.00529.
170. Ponzo V, Cinnera AM, Mommo F, Caltagirone C, Koch G, Tramontano M. Osteopathic manipulative therapy potentiates motor cortical plasticity. J Am Osteopath Assoc. 2018;118(6):396–402. https://doi.org/10.7556/jaoa.2018.084.
171. Fryer G, Pearce AJ. The effect of lumbosacral manipulation on corticospinal and spinal reflex excitability on asymptomatic participants. J Manip Physiol Ther. 2012;35(2):86–93. https://doi.org/10.1016/j.jmpt.2011.09.010.
172. Zein-Hammoud M, Standley PR. Modeled osteopathic manipulative treatments: a review of their in vitro effects on fibroblast tissue preparations. J Am Osteopath Assoc. 2015;115(8):490–502. https://doi.org/10.7556/jaoa.2015.103.
173. Roncada G. Effects of osteopathic treatment on pulmonary function and chronic thoracic pain after coronary artery bypass graft surgery (OstinCaRe): study protocol for a randomised controlled trial. BMC Complement Altern Med. 2016;16(1):482.

Part VIII

Drugs Used in Psychiatry and Neurology Affecting Cardiovascular Activity and Cardiovascular Drugs Producing Neuropsychiatric Alterations

Cardiovascular Adverse Effects of Psychotropic Drugs

43

Anna Maria Pugliese, Elisabetta Coppi, Federica Cherchi, and Giancarlo Pepeu

Contents

Abstract

The cardiovascular adverse effects that may occur during treatment with the different categories of psychotropic drugs and the differences between single drugs within each category are reviewed. The main adverse reactions reported during psychotropic drug treatments are, in order of prevalence, (1) arrhythmias, since antidepressants and neuroleptics affect several ion channels involved in the control of cardiac action potentials and thus exert a proarrhythmic activity; (2) changes in blood pressure; (3) impairment of ventricular function; and (4) thromboembolism. Benign arrhythmias and orthostatic hypotension are the most common and most manageable adverse effects. Arrhythmias, including

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*, https://doi.org/10.1007/978-3-030-28008-6_45

torsades de pointes, and impairment of ventricular function may lead to sudden death whose odds ratio for the antipsychotics ranges between 1.72 for quetiapine and 3.67 for clozapine. The risk of cardiovascular adverse effects is higher for the typical antipsychotics than for the atypical. Among the latter, clozapine prescription requires particular attention. Tricyclic antidepressants and lithium are frequently accompanied by dysrhythmias, including QT interval prolongation, but sudden death is a rare event. A marginal risk of myocardial infarction during antidepressant therapy exists, but the risk of cardiovascular adverse effects with non-tricyclic antidepressants is remarkably low and practically nonexistent for the mood modifiers, except lithium and anxiolytics.

Keywords

Antidepressants · Antipsychotics · Anxiolytics · Lithium · Dysrhythmias · Orthostatic hypotension · Torsade des pointes · QT interval · Sudden cardiac death · Ventricular dysfunction

Abbreviations

ANS	Autonomic nervous system
CI	Confidence interval
CL	Confidence limits
CVD	Cardiovascular disease
ECG	Electrocardiography
EEG	Electroencephalography
HDL	High-density lipoprotein
LDL	Low-density lipoproteins
NASSA	Noradrenergic and specific serotonergic antidepressant
OR	Odds ratio
QTc	QT interval corrected for heart rate according to Bazzett procedure
SD	Standard deviations
SE	Standard error
SMD	Severe mental disorders
SNRI	Selective noradrenaline reuptake inhibitors
SSRI	Selective serotonin reuptake inhibitors
TCA	Tricyclic antidepressants
TdP	Torsades de pointes

Introduction

The aim of this chapter is to review the possible adverse cardiovascular effects of psychoactive medications, their features, incidence, and the risk that they may represent for the users. Psychoactive medications are among the most widely used drugs. In Italy, they represent the sixth therapeutic category with the highest public expenditure, about 1.8 billion euros per year (AIFA – National Report on Medicines use in Italy 2016 [1]). Historically, chlorpromazine, a phenothiazine derivative, is considered the first true psychotropic drug. It was introduced in the early 1950s of the twentieth century for the treatment of schizophrenia first in France and within a few years throughout the world [2]. Few years after the introduction, sudden deaths during treatment with chlorpromazine and its analogues were reported [3, 4] suggesting that antipsychotic drugs may exert a direct cardiac toxicity in addition to other unwanted effects, namely, obesity, dyslipidemia, and type 2 diabetes, that in turn increase the cardiovascular risk of the patients with severe mental disorders (SMD). SMD are by themselves a risk factor for cardiovascular disease (CVD). Schizophrenic patients are more likely to have a first diagnosis of CVD at younger age. Nearly half of men with schizophrenia had a CVD diagnosed under the age of 55 [5]. Moreover, patients with SMD die, on average, 15–20 years earlier than people without SMD [6]. Their mortality rate is more than two times higher than in the general population [7], and CVD is the principal cause of death accounting for up to 50% cases of early mortality in schizophrenia. Since most patients with SMD are treated with psychotropic drugs, the question arises to which extent psychotropic drugs contribute to the increase of CVD risk. The issue is not fully defined [8], but adverse drug effects may contribute to the early and frequent development of cardiovascular disease in this population, together with the genetic vulnerability [9] and the poor physical health [10] that characterize SMD patients.

Much information on the cardiovascular effects of psychotropic drugs, including sudden death, can be found in a few reviews [11–14].

The main cardiovascular adverse reactions that may occur during psychotropic drug treatments are, in order of prevalence, (1) arrhythmias, since antidepressants and neuroleptics can affect several ion channels involved in the control of cardiac action potentials and thus exert a proarrhythmic activity; (2) changes in blood pressure; (3) impairment of ventricular function; and (4) thromboembolism. Arrhythmias and impairment of ventricular function may lead to sudden death. Psychotropic drugs may also increase CVD risk by causing the already mentioned dysmetabolic alterations such as obesity and type 2 diabetes. For instance, it is recognized that antipsychotics increase total and low-density lipoproteins (LDL), cholesterol, and triglycerides, while they decrease high-density lipoprotein (HDL) cholesterol [15]. Moreover, patients affected by CVD may develop psychiatric pathologies and need a treatment with psychotropic drugs. These patients require a careful selection of the therapy and a deep knowledge of its possible adverse effects.

In the following pages, the cardiovascular adverse effects that may occur during treatments with different categories of psychotropic drugs and the differences among single drugs within each category will be reviewed.

Antipsychotic Drugs

The antipsychotic drugs, also called neuroleptics, are usually classified in typical and atypical or first generation and second generation. The two classifications usually overlap. Minor cardiovascular adverse effects from antipsychotic drugs are extremely common. They include postural hypotension and tachycardia [16]. The severe adverse effects are described below.

Sudden Deaths

Unexpected or sudden deaths are the most dramatic adverse effect related to antipsychotic therapy. Their risk has been investigated by Salvo et al. [17] in a large population of psychiatric patients treated with different antipsychotic drugs. The odds ratio (OR) ranges from 1.72 (95% CI: 1.33–2.23) for quetiapine to 3.67 for clozapine (CI: 1.94–6.94). The risk was roughly in the same range according to a cohort study conducted between 2005 and 2011, using the German Pharmacoepidemiological Research database [18], in which haloperidol was associated with an increased risk of death (adjusted OR 1.45; 95% CI: 1.35–1.55). An overrepresentation of phenothiazines, in particular thioridazine, in cases of sudden death was reported in a Finnish study [19]. A high adjusted OR (5.3; 95% CL: 1.7–16.2, $P = 0.004$) for thioridazine was also found by Reilly et al. [20], and the statistical analysis demonstrated that thioridazine only was associated with sudden unexplained deaths, the most likely mechanism being drug-induced arrhythmia. Actually, two main causes underlie the increased risk of death related to antipsychotics: (1) heart muscle disorders, including myocarditis and cardiomyopathy, and (2) dysrhythmias, with large differences in the incidence between the different drugs.

Heart Muscle Disorders

A search [21] of the WHO international database on adverse drug reactions revealed that myocarditis and cardiomyopathy are rarely reported as suspected adverse drug reactions, accounting for less than 0.1% (2121) of almost 2.5 million reports. However, they may be responsible of fatal outcomes. Clozapine is the antipsychotic for which the largest number of heart muscle disorders was registered with a total of 231 cases, followed by risperidone with 16, chlorpromazine 14, and haloperidol 11. The numbers decrease progressively for the other antipsychotics. The high prevalence of clozapine-related cardiac unwanted effects prompted a number of studies on this drug [11, 22–24]. In a study [22] on 8000 patients, treated with therapeutic doses of clozapine, 23 cases of myocarditis and cardiomyopathy (absolute risk 0.29%), with 6 deaths, were described. In a recent extensive review [23], an incidence of up to 3% of myocarditis in clozapine-treated patients was reported. It is

believed that sudden deaths occurring during clozapine use may be caused by an unrecognized, fulminant myocarditis [25]. The onset of clozapine myocarditis is dose-independent and tends to occur early, days, and weeks, after the beginning of therapy. The clinical picture may be variable and begins with flu-like symptoms followed by cardiovascular symptoms including tachycardia, chest pain, syncope, arrhythmias, and hypotension [23]. High blood levels of troponin I are always present, and their measure can be used as a diagnostic marker [25] and for monitoring patients taking clozapine [26]. When it was possible to perform necropsy, an acute myocarditis with an eosinophilic infiltrate was found. Peripheral-blood eosinophilia was also detected, and the overall picture is consistent with an acute drug reaction [22]. Clozapine-associated pericarditis was also reported [26, 27]. Dilated cardiomyopathy is a rare, severe adverse effect of clozapine with an incidence of 0.02–0.1% and a mortality rate of up to 17% [28]. It has been the object of a systematic review [29]. Like myocarditis, it is dose-independent, but its onset is delayed, and the symptoms tend to develop one or more years after clozapine initiation. The clinical picture is consistent with heart failure and includes a persistent tachycardia at rest, dyspnea, and palpitations, and the echocardiography examination shows heart dilatation [22, 23, 29]. Both myocarditis [30] and dilated cardiomyopathy [31] are reversible upon clozapine discontinuation, and a switch to a different antipsychotic drug, such as olanzapine, is possible [32]. However, it must be mentioned that, in spite of the severe adverse effects, including agranulocytosis and embolism, a study including over 67,000 users in the years 1993–1997 demonstrates that clozapine reduces overall mortality in severe schizophrenic, mostly by decreasing suicide rates [33].

According to an extensive epidemiological study carried out by Coulter et al. [21] on the WHO database, the entire group of antipsychotic drugs is significantly associated with myocarditis and cardiomyopathy together, but the association is much weaker for the other drugs than for clozapine. There are differences between drugs: chlorpromazine is significantly associated with myocarditis and cardiomyopathy, separately; fluphenazine and risperidone are significantly associated with cardiomyopathy but not myocarditis. Haloperidol is associated with myocarditis but not cardiomyopathy. The clinical pictures do not differ from those described for clozapine [29]. Direct depression of heart contractility associated with rare cases of sudden death was reported with almost all typical and atypical antipsychotics [11]. Animal experiments confirm that antipsychotic drugs have a cardiac toxicity. Necrotic lesions and endocardial fibrosis lesions were observed in rabbits after 3-month treatment with haloperidol, amisulpride, olanzapine, and levomepromazine [34].

Dysrhythmias

The search for the etiology of sudden death in patients treated with antipsychotic drugs prompted extensive investigations on the electrocardiographic changes caused by these drugs. As reviewed by Feinstein [11], tachycardia occurs frequently during treatment with clotiapine, olanzapine, and haloperidol, and alteration of the cardiac rhythm has been occasionally reported with all antipsychotic drugs. An increased prevalence of dose-dependent prolonged QTc (QT interval corrected for heart rate according to the Bazzett procedure) was found in a group of 111 schizophrenic patients receiving antipsychotic drugs [35]. The relationship between QTc lengthening and increasing doses of antipsychotics was confirmed by a logistic regression analysis of a group of 495 psychiatric patients. This large number also allowed the comparison among individual antipsychotic drugs [36]. It was shown that droperidol and thioridazine treatments were strong predictors of QTc lengthening, whereas the risk associated with other antipsychotic drugs, including clozapine, was much lower. In a study in which blood concentrations of different antipsychotic drugs upon hospital admission were correlated with QT prolongation, it was shown that therapeutic or toxic blood concentrations of phenothiazine antipsychotic drugs are independent risk factors for QTc prolongation [37]. It should be mentioned, however, that the development of EEG abnormality does not

impose the interruption of the therapy. In a study on 53 psychiatric patients without baseline ECG abnormalities, 13 developed abnormalities after using clozapine but in most of them ECGs normalized during treatment continuation [38].

QT prolongation, especially in patients with medical illnesses, can predispose to torsades de pointes (TdP) [39], a polymorphic ventricular tachycardia that may lead to sudden death. A large Italian study based on 2366 patients demonstrated that, in general, typical antipsychotics prolong QTc by a direct effect [40]. Atypical antipsychotic drugs, at therapeutic doses, may also increase the QTc interval, but prolongation does not result in TdP [41]. According to a meta-analyses study of randomized controlled trial, aripiprazole, brexpiprazole, and olanzapine do not increase QT interval, whereas risperidone and quetiapine are associated with QT prolongation that, in cases of drug overdose, may lead to TdP [42]. Similar results were obtained in a large study [43] that demonstrated that haloperidol and chlorpromazine had a less favorable cardiac profile than olanzapine. Statistical analysis [44] carried out over a group of 2411 patients exposed to antipsychotic and antidepressant drugs demonstrated that the prevalence of QTc prolongation ranged from 14.7% in men to 18.6% in females for the cutoff of 450 ms, dropping to 1.26% and 1.01%, respectively, for a cutoff of 500 ms. Many factors significantly concur to QTc prolongation including female sex, age, heart rate, alcohol, drug overdose, and particularly antipsychotic polypharmacy. Taken together, these findings demonstrate the relatively low number of patients presenting a QTc prolongation and support the current guidelines that recommend avoiding the concurrent use of two or more antipsychotic drugs. They confirm a previous study [45] on 456 patients in which abnormal QTc values were found in 2% of the subjects. Finally, the overall cardiac risk of antipsychotics drugs was calculated by Leonard et al. [43] in 35.1 ventricular arrhythmia and 3.4 sudden deaths per 1000 person-years.

Dysrhythmias and their most serious consequence, sudden death, are most likely to be caused primarily by blockade of cardiac potassium channels such as hERG [16]. Thioridazine has been shown to be one of the most potent hERG potassium channel binding at a high affinity site in the hERG channel pore [46].

Effect of Antipsychotic Drugs on the Autonomic Nervous System, Orthostatic Hypotension

An alteration of the autonomic function is frequently present in schizophrenic patients [47], resulting in a lower heart rate variability and indicating a dysregulation of the sympathetic-parasympathetic regulation [48]. In acute psychosis, the treatment with antipsychotics may correct the dysregulation [49]. Conversely, in general, antipsychotic treatment is followed by various autonomic nervous system (ANS) alterations. A decrease in the low frequency and high frequency components of heart rate variability was observed in a group of 211 schizophrenic patients under treatment with different antipsychotics [50]. Long-term treatment with antipsychotic drugs is usually associated with a shift toward increased sympathetic and decreased vagal tone, affecting heart rate. When we come to individual drugs, clozapine induces a higher pulse rate variability than olanzapine, presumably due to a higher affinity of clozapine for alpha-1 adrenergic receptors [51]. The rate variability results in a benign, sustained tachycardia in up to 25% of clozapine-treated patients [24]. Conversely, a dose-dependent bradycardia was observed in patients treated with amisulpride [52]. In a study comparing the effect of risperidone, olanzapine, aripiprazole, and quetiapine monotherapy in 241 schizophrenic patients on ANS activity, quetiapine decreased sympathetic and parasympathetic activity more than the other drugs [53]. The dysregulation of ANS activity is responsible of the most frequent vascular adverse effect of antipsychotic drugs, the transient orthostatic hypotension, following change in posture, that may affect from 10% to up 75% of the subjects treated [12, 54]. Orthostatic hypotension is particularly dangerous in elderly patients since it leads to falls and bone fractures. Orthostatic hypotension is attributed mainly to the antagonism toward alpha-1 adrenergic receptors that is a feature of

both typical and atypical antipsychotics, with different degrees of potency as shown by the Schild analysis of the effects of antipsychotic drugs on norepinephrine, epinephrine, and phenylephrine concentration-response curves in isolated vascular tissues. Chlorpromazine and sertindole show a very high affinity for alpha1 receptors [55]. "In vivo" studies in the rat demonstrated that chlorpromazine, thioridazine, haloperidol, and clozapine inhibit the pressor responses induced by alpha-1 receptor agonists [56, 57]. These are the antipsychotics more likely to cause significant hypotension [12]. Dizziness may accompany hypotension, but subjective reports of dizziness do not correlate well with orthostatic blood pressure changes. In a small number of cases, namely, in elderly and in patients with pre-existing cardiac diseases, orthostatic hypotension may lead to neurogenic syncope due to a failure of the vasoconstrictor mechanisms. The incidence of syncope varies from around 0.2% in olanzapine and risperidone-treated patients [58, 59], 1% in patients treated with quetiapine [60], to 6% following exposure to clozapine [61].

Finally, it must be mentioned that all five dopamine receptor subtypes (i.e., D1, D2, D3, D4, and D5), which are targets of the antipsychotic drugs, regulate sodium excretion and blood pressure. The D1, D3, and D4 receptors interact with the renin-angiotensin-aldosterone system, whereas D2 and D5 receptors directly interact with the sympathetic nervous system to regulate blood pressure [62]. For this reason, an increase in blood pressure may also occur during treatment with antipsychotics, particularly with clozapine [63, 64]. An increased risk of essential hypertension in a large population of subject treated with atypical antipsychotics was indeed reported by Correll et al. [65].

Vascular Adverse Effects of Antipsychotic Drugs

Patients treated with antipsychotic drugs have an increased risk of developing deep venous pulmonary thromboembolism [65–68] and stroke [69–70]. According to a meta-analysis of several case-control studies [66], the increased risk of venous thromboembolism in antipsychotics user versus nonusers raises from 1.5- (95% CL: 1.28–2.37) to 2.4-fold (95% CL: 1.7–3.4) with no clear indication whether the risk is higher with typical than atypical antipsychotics. However, according to a previous meta-analysis [67], a higher risk of venous thromboembolism was observed in patients taking clozapine, olanzapine, and low-potency atypical antipsychotics. According to a large case-control study carried out in Taiwan [68], the adjusted OR for venous thromboembolism was modest but not significant among continuous users of antipsychotics; however, OR was 3.26 (95% CL: 2.06–5.17) among new antipsychotic drug users.

In a nationwide New Zealand case-control study, a 13.3-fold increase in fatal pulmonary embolism was observed in antipsychotics users in comparison of nonusers. The risk was higher among the users of low-potency first-generation antipsychotic. Conversely, no difference in occurrence rate of venous thromboembolism between high- and low-potency antipsychotics was found by Letmaier et al. [69] in a continuous drug surveillance program in Germany involving 264,422 patients receiving antipsychotics between 1993 and 2011. The overall occurrence rate in the latter study was 43 cases for 10,000 person-years. Haloperidol and analogues were responsible for the highest occurrence rate. A modest but statistically significant 1.2-fold increase risk of pulmonary embolism was detected in a US cohort study [70] involving 450,000 users of antipsychotic compared to nonusers. The risk was the same with the use of typical and atypical antipsychotics.

An increased risk of stroke has been observed in schizophrenic patients treated with antipsychotics, but the occurrence rate and the type of antipsychotic drug involved varies according to the age and conditions of the drug users. In a study of 3853 elderly community-dwelling subjects with cerebrovascular events, a duration-dependent association was found only with typical antipsychotics with an odd risk of 2.4 (95% CI: 1.08–5.5). Interestingly, the patients receiving simultaneously antipsychotics and a cholinesterase inhibitor had a lower risk of cardiovascular

events [71]. Similar results were obtained through the meta-analysis of 10 studies carried out between 1970 and 2016. It was found that first-generation antipsychotics significantly increase the risk of cerebrovascular accidents, but the risk is lower when the antipsychotics are used in patients with dementia [72] who, presumably, are treated with cholinesterase inhibitors. In a study of 802 new-onset cases of stroke over a population of 31,976 schizophrenic patients, it was found that the use of the atypical, second-generation antipsychotics was associated with an increased risk of ischemic stroke but not of hemorrhagic stroke (adjusted risk ratio 1.45, $P = 0.0009$). The risk was higher when the binding profile of the prescribed antipsychotic shows a high affinity for the histamine H1 receptor [73]. However, using the Taiwan National Health Insurance Research database, an association emerged between stroke risk and the affinity for M1 muscarinic and alpha 2 adrenergic receptors of the antipsychotics prescribed [74]. Using the same large database, it was found that the overall use of psychotropic drugs by patients with bipolar disorders was associated with an increased risk of stroke (adjusted odds ratio 1.82; 95% CI: 1.56–2.13). The adjusted odds ratio rose to 1.98 (95% CI: 1.53–2.56) when patients treated with antipsychotics only were considered [75].

Many pathogenetic factors seem to predispose to thromboembolic adverse effects in psychiatric patients treated with antipsychotics, as reviewed by Oglodek et al. [76] and Jonsson et al. [66]. Clozapine increases platelet aggregation; risperidone and ziprasidone interact with platelet membrane phospholipids. Moreover, increased levels of antiphospholipid antibodies, hyperhomocysteinaemia, C-reactive protein, and other prothrombotic factors have been invoked.

Antidepressant Drugs

The antidepressants are a large group of drugs roughly classified, according to their chemical structure or the putative mechanism of action, in TCA (tricyclic antidepressants), SSRI (selective serotonin reuptake inhibitors), SNRI (selective noradrenaline reuptake inhibitors), NASSA (noradrenergic and specific serotonergic antidepressant), plus a group called “others” antidepressants because they don’t fit in the previous groups. Reports of cardiovascular complications appeared shortly after the introduction of TCA. However, all antidepressant types may exert cardiovascular adverse effects with different incidence and severity [14]. On the other hand, depression is a risk factor for cardiovascular diseases, and patients with cardiovascular diseases frequently tend to develop depression [11, 77]. For this reason, there is a bidirectional relationship between antidepressant drugs and cardiovascular diseases since by improving depression, they may reduce the risk of cardiovascular diseases [78]. Conversely, they may exert cardiac toxicity at therapeutic doses and even more in cases of overdose.

Sudden Deaths

Thirteen sudden, unexpected deaths occurring in a group of 684 patients receiving conventional doses of the tricyclic amitriptyline with an incidence rate of 1.5% were reported by Moir et al. [79]. However, a much lower incidence of 0.0029% resulted from a “Drug Surveillance Report of German-Speaking Countries Between 1993 and 2010” involving 169,278 psychiatric inpatients treated with all types of antidepressants drugs [80]. Sudden death may result by the unmasking of a Brugada syndrome by TCA [81, 82] and rarely by SSRI. The Brugada syndrome is an inherited genetic disorder of the cardiac electrical activity with characteristic electrocardiographic patterns and a prevalence ranging between 1 in 5000 and 1 in 2000 [83]. Concerning the molecular mechanism underlining the syndrome, it has been shown [84] that amitriptyline-induced inhibition of sodium channel current I(Na) unmasks the Brugada ECG phenotype and facilitates development of an arrhythmogenic substrate, in the setting of a genetic predisposition, by creating repolarization heterogeneities and alterations of ventricular conduction. In five sudden deaths of patients treated

with SSRI described by forensic doctors [85], various degrees of interstitial and perivascular fibrosis were detected in their myocardium indicating an inflammatory pathogenesis.

Myocardial Infarction

The possibility that the use of antidepressants may increase the risk of myocardial infarction has been a matter of debate [86]. In a large study of a cohort of 2247 subjects treated with antidepressants compared with a 52,750 controls, it was found that the relative risk of myocardial infarction was 2.2 (95% CI: 1.2–3.8) in TCA users and 0.8 (95% CI: 0.2–3.5) in SSRI users, as compared with subjects who did not use antidepressants [87]. This finding confirms an excess risk of myocardial infarction in patients treated with TCA. With regard to SSRI, instead, epidemiological studies [78, 88] indicate that their use by depressed patients is associated with a decreased risk of hospitalization for myocardial infarction attributable to improvement of the depression and attenuation of serotonin-mediated platelet activation.

Dysrhythmias

Dysrhythmias in patients receiving antidepressants are frequent. The Arizona Center for Education and Research on Therapeutics (the Critical Path Institute, Tucson, Arizona, and Rockville, MD, USA) presented a list including all TCAs, many SSRI, and some of the other antidepressants, which in some studies were weakly associated with QT interval prolongation and/or TdP [13]. In a report, involving 169,278 psychiatric inpatients [80], the incidence rate of arrhythmias imputed to antidepressants, prescribed as monotherapy, was 0.02%. Treatment with TCAs was connected with a higher risk for arrhythmia (0.08%, all cases, $p = 0.02$). Especially, maprotiline (0.1%, $p = 0.024$, imputed alone) had the highest risk for arrhythmias among all TCAs. The OR of developing an abnormal QTc, defined as more than 456 ms, in patients treated with TCA was 4.4 (95% CL: 1.6–12.1) according to Reilly et al. [20]. A similar OR was reported [37] investigating the effect of TCA toxic concentrations on QTc interval abnormalities. In a study involving 38,397 subjects, a dose-response association with QTc prolongation was identified for citalopram, escitalopram, and amitriptyline but not for the other antidepressants examined, including fluoxetine, paroxetine, and venlafaxine [89]. According to a ECG investigation on a population of 8,222 patients of both sexes, TCAs seem to prolong the QTc interval as a class effect [90]. A recent, extensive review [91] emphasizes that cardiovascular adverse effects during treatment with SSRI are usually mild. Arrhythmia occurs in about 4% of the patients treated with SSRI; therefore ECG monitoring is recommended. Arrhythmias, prolonged QTc interval, and orthostatic hypotension usually only occur at higher than recommended dosages. Most cases of SSRI-induced QTc interval prolongation were observed in patients over 60 years of age, with low blood potassium levels or taking high doses of citalopram and escitalopram. In patients with pre-existing conduction delay, there is a risk of heart block [92]. However, the risk of cardiovascular adverse effects with the latter drug is quite low, as confirmed by the lack of difference in the incidence of cardiovascular adverse effects of escitalopram versus placebo in a group of patients affected by recent acute coronary syndrome, followed over a period of 1 year [93]. Trazodone at therapeutic doses has less effect on cardiac function than amitriptyline [94], and significant QT prolongation without arrhythmia or other adverse consequences was only observed after a trazodone overdose [95].

The mechanism of the proarrhythmic action of antidepressants depends on the direct, concentration-dependent, blockade of hERG potassium channels, as shown for fluoxetine by voltage clamp analyses [96].

Other Cardiovascular Adverse Effects

Orthostatic hypotension is a common adverse effect of antidepressant drugs. According to the extensive review of Manolis et al. [14], all types

of antidepressants may cause orthostatic hypotension, but the risk is higher with TCA administration, presumably because of their antagonism for the α-adrenergic receptors. The risk is lower with some SSRI such as fluoxetine or escitalopram. Patients treated with TCA are also at risk of syncopal events [97]. According to Briggs et al. [98], the overall prevalence of orthostatic hypertension among antidepressant users of more than 50 years of age is 31%; the figure doubles in the older patients. Patients with congestive heart failure receiving cardiac medications are at greatly increased risk for orthostatic hypotension [92].

Lithium and Other Mood-Stabilizing Drugs

Lithium is the drug of choice for the treatment of the bipolar disturbances, but it is known to cause cardiac adverse effects including conduction disturbance, bradycardia, and repolarization abnormalities which increase with age and the unmasking of a Brugada syndrome, particularly over 60 years [99]. According to Manolis et al. [14], lithium at therapeutic doses causes ECG alterations, characterized by T-wave flattening or inversion and rarely sinus node dysfunction without other important cardiovascular effects. The ECG alterations are usually benign and do not require the interruption of the therapy. Long-term therapy, with lithium levels within therapeutic range, is associated with atrial and ventricular electrical instability [100]. Rare cases of sudden death in patients treated with therapeutic doses of lithium have been reported [101, 102]. Lithium at toxic levels can cause severe ECG abnormality including sinoatrial block, intraventricular and atrioventricular conduction delay, and QT prolongation leading to cardiac arrhythmias and sudden death [99].

Carbamazepine, valproic acid, and lamotrigine, the most commonly used alternatives to lithium as mood stabilizers, have limited or no cardiac adverse effects at therapeutic doses. Carbamazepine only may rarely cause a complete atrioventricular block and severe bradyarrhythmias, as observed in single cases, usually in elderly subjects [103, 104]. Carbamazepine overdoses may induce sinus tachycardia and various ECG abnormalities [105]. Lamotrigine causes cardiac adverse effects, including QTc interval and QRS complex prolongation, albeit only when an overdose was assumed [106].

In a large study on bipolar patients who developed a stroke, it was found that the use of carbamazepine and valproic acid was associated with an increased risk of stroke, while the use of lithium and lamotrigine was not. The adjusted OR was 1.52 (SD 1.24–1.88) for valproic acid and 2.29 (1.49–3.51) for carbamazepine [75].

Anxiolytics

Anxiolytics are largely used psychotropic drugs, and among them the benzodiazepines lorazepam, alprazolam, and lormetazepam are the most commonly prescribed compounds in Italy (the Medicine Utilization 2018). Anxiolytics may be used as hypnotics, but some benzodiazepines and benzodiazepine analogues, such as triazolam and zolpidem, exert a pronounced hypnotic effect.

At variance with the psychotropic drugs described in the previous paragraphs, benzodiazepines and their analogues cause no cardiovascular adverse effects and are mentioned here for completeness. Diazepam only may induce arrhythmias occurring when it was used as a sedative in cardioversion [107]. A 4-week administration of a therapeutic dose of diazepam to healthy young subject caused a modest increase in heart rate and a slight blood pressure decrease in the morning hours [108]. Conversely, in elderly subjects the assumption of diazepam as hypnotic agent for 4 weeks produced an increase in blood pressure, in particular systolic blood pressure, during nighttime and in heart rate during nighttime and morning hours [109].

Conclusions

As described in the previous pages, psychotropic drug administration, even at therapeutic doses, may be accompanied by cardiovascular adverse effects, summarized in Table 1, that may hamper a successful therapy.

Table 1 Summary of cardiac adverse effects related to psychotropic drugs. The drugs with the highest risk to cause the adverse effect are listed

Adverse effects	Antipsychotics	Antidepressants	Lithium and other mood stabilizers	Anxiolytics
Sudden death	Clozapine [17] Quetiapine [17], haloperidol [18], thioridazine [19, 20]	Amitriptyline [79] SSRI [81, 82]	–	–
Hearth muscle disorders (myocarditis, cardiomyopathy, myocardial infraction)	Clozapine [11, 22–25, 29], risperidone [21] Chlorpromazine [21], haloperidol [21, 34], fluphenazine [21] Amisulpride [34] Olanzapine [34] Levomepromazine [34]	TCA [87] SSRI [78, 87, 88]	Carbamazepine [75] Valproic acid [75]	–
Dysrhythmias (ECG alterations)	Clozapine [38], olanzapine [11], haloperidol [11, 43], clotiapine [11], droperidol [36] Thioridazine [36] Risperidone [42], quetiapine [42] Chlorpromazine [43]	TCA [13] Amitriptyline [37, 89, 94] Maprotiline [80] SSRI [13, 91] Citalopram [37, 89], fluoxetine [96] Escitalopram [37, 89]	Lithium [14, 99, 100] Carbamazepine [103–105] Lamotrigine [106]	Diazepam [107]
Autonomic nervous system, orthostatic hypotension	Clozapine [24, 51, 56, 57, 61, 63, 64], thioridazine [56, 57], quetiapine [53, 60] Chlorpromazine [56, 57] Haloperidol [56, 57] Amisulpride [52] Olanzapine [58] Risperidone [59]	TCA [14, 97]	–	Diazepam [108]
Vascular adverse effects (venous pulmonary thromboembolism and stroke)	Haloperidol [70], clozapine [66, 67, 76], olanzapine [67] Risperidone [66, 76], ziprasidone [66, 76]	TCA [97]	–	–

However, also for the psychotropic drugs, considering their extensive usage, we may quote the well-known paper "Drugs – Remarkably nontoxic" [110]. The fear of cardiovascular adverse effects should not prevent the prescription of a psychotropic drug but compel the doctor to be cautious.

Orthostatic hypotension and benign arrhythmias can be easily tolerated by the patients if they are informed and instructed, their mental conditions permitting. The risk of most serious cardiovascular adverse effects can be reduced by following some rules, namely, to collect an accurate anamnesis, to perform regular ECG and clinical controls, to keep the number of drugs as low as possible and their dosage within the therapeutic range, and by an accurate and a well-informed choice of the drugs.

References

1. AIFA – National Report on Medicines use in Italy 2016. n.d.
2. Shen WW. A history of antipsychotic drug development. Compr Psychiatry. 1999;40:407–14. https://doi.org/10.1016/S0010-440X(99)90082-2.
3. Kelly HG, Fay JE, Laverty SG. Thioridazine hydrochloride (Mellaril): its effect on the electrocardiogram

and a report of two fatalities with electrocardiographic abnormalities. JAMA J Am Med Assoc. 1963;186:221. https://doi.org/10.1001/jama.1963.03710030141099.
4. Hollister LE, Kosek JC. Sudden death during treatment with phenothiazine derivatives. JAMA J Am Med Assoc. 1965;192:1035–8. https://doi.org/10.1001/jama.1965.03080250013003.
5. McLean G, Martin JL, Martin DJ, Guthrie B, Mercer SW, Smith DJ. Standard cardiovascular disease risk algorithms underestimate the risk of cardiovascular disease in schizophrenia: evidence from a national primary care database. Schizophr Res. 2014;159:176–81. https://doi.org/10.1016/j.schres.2014.07.022.
6. Walker ER, McGee RE, Druss BG. Mortality in mental disorders and global disease burden implications. JAMA Psychiatry. 2015;72:334. https://doi.org/10.1001/jamapsychiatry.2014.2502.
7. Cuijpers P, Vogelzangs N, Twisk J, Kleiboer A, Li J, Penninx BW. Differential mortality rates in major and subthreshold depression: meta-analysis of studies that measured both. Br J Psychiatry. 2013;202:22–7. https://doi.org/10.1192/bjp.bp.112.112169.
8. Chung K-H, Chen P-H, Kuo C-J, Tsai S-Y, Huang S-H, Wu W-C. Risk factors for early circulatory mortality in patients with schizophrenia. Psychiatry Res. 2018;267:7–11. https://doi.org/10.1016/j.psychres.2018.05.044.
9. Andreassen OA, Djurovic S, Thompson WK, Schork AJ, Kendler KS, O'Donovan MC, et al. Improved detection of common variants associated with schizophrenia by leveraging pleiotropy with cardiovascular-disease risk factors. Am J Hum Genet. 2013;92:197–209. https://doi.org/10.1016/j.ajhg.2013.01.001.
10. Lawrence D, Kisely S. Review: inequalities in healthcare provision for people with severe mental illness. J Psychopharmacol. 2010;24:61–8. https://doi.org/10.1177/1359786810382058.
11. Feinstein RE. Cardiovascular effects of novel antipsychotic medications. Heart Dis. 2002;4:184–90.
12. Mackin P. Cardiac side effects of psychiatric drugs. Hum Psychopharmacol Clin Exp. 2008;23:S3–14. https://doi.org/10.1002/hup.915.
13. Timour Q, Frassati D, Descotes J, Chevalier P, Christé G, Chahine M. Sudden death of cardiac origin and psychotropic drugs. Front Pharmacol. 2012;3:76. https://doi.org/10.3389/fphar.2012.00076.
14. Manolis TA, Manolis AA, Manolis AS. Cardiovascular safety of psychiatric agents: a cautionary tale. Angiology. 2018. https://doi.org/10.1177/0003319718780145.
15. Meyer JM. Novel antipsychotics and severe hyperlipidemia. J Clin Psychopharmacol. 2001;21:369–74.
16. Buckley NA, Sanders P. Cardiovascular adverse effects of antipsychotic drugs. Drug Saf. 2000;23:215–28.
17. Salvo F, Pariente A, Shakir S, Robinson P, Arnaud M, Thomas S, et al. Sudden cardiac and sudden unexpected death related to antipsychotics: a meta-analysis of observational studies. Clin Pharmacol Ther. 2016;99:306–14. https://doi.org/10.1002/cpt.250.
18. Schmedt N, Kollhorst B, Enders D, Jobski K, Krappweis J, Garbe E, et al. Comparative risk of death in older adults treated with antipsychotics: a population-based cohort study. Eur Neuropsychopharmacol. 2016;26:1390–400. https://doi.org/10.1016/j.euroneuro.2016.07.006.
19. Mehtonen OP, Aranko K, Mälkonen L, Vapaatalo H. A survey of sudden death associated with the use of antipsychotic or antidepressant drugs: 49 cases in Finland. Acta Psychiatr Scand. 1991;84:58–64.
20. Reilly JG, Ayis SA, Ferrier IN, Jones SJ, Thomas SHL. Thioridazine and sudden unexplained death in psychiatric in-patients. Br J Psychiatry. 2002;180:515–22.
21. Coulter DM, Bate A, Meyboom RH, Lindquist M, Edwards IR. Antipsychotic drugs and heart muscle disorder in international pharmacovigilance: data mining study. BMJ. 2001;322:1207–9.
22. Kilian JG, Kerr K, Lawrence C, Celermajer DS. Myocarditis and cardiomyopathy associated with clozapine. Lancet. 1999;354:1841–5.
23. De Berardis D, Rapini G, Olivieri L, Di Nicola D, Tomasetti C, Valchera A, et al. Safety of antipsychotics for the treatment of schizophrenia: a focus on the adverse effects of clozapine. Ther Adv Drug Saf. 2018;9:237–56. https://doi.org/10.1177/2042098618756261.
24. Yuen JWY, Kim DD, Procyshyn RM, White RF, Honer WG, Barr AM. Clozapine-induced cardiovascular side effects and autonomic dysfunction: a systematic review. Front Neurosci. 2018;12:203. https://doi.org/10.3389/fnins.2018.00203.
25. Ronaldson KJ, Fitzgerald PB, Taylor AJ, Topliss DJ, McNeil JJ. A new monitoring protocol for clozapine-induced myocarditis based on an analysis of 75 cases and 94 controls. Aust N Z J Psychiatry. 2011;45:458–65. https://doi.org/10.3109/00048674.2011.572 852.
26. Kay SE, Doery J, Sholl D. Clozapine associated pericarditis and elevated troponin I. Aust N Z J Psychiatry. 2002;36:143–4. https://doi.org/10.1046/j.1440-1614.2002.0988f.x.
27. Catalano G, Catalano MC, Frankel Wetter RL. Clozapine induced polyserositis. Clin Neuropharmacol. 1997;20:352–6.
28. Longhi S, Heres S. Clozapine-induced, dilated cardiomyopathy: a case report. BMC Res Notes. 2017;10:338. https://doi.org/10.1186/s13104-017-2679-5.
29. Alawami M, Wasywich C, Cicovic A, Kenedi C. A systematic review of clozapine induced cardiomyopathy. Int J Cardiol. 2014;176:315–20. https://doi.org/10.1016/j.ijcard.2014.07.103.
30. Kirpekar VC, Deshpande SM, Joshi PP. Reversible myocarditis in a patient receiving clozapine. Indian Heart J. n.d.;53:779–81.

31. Makhoul B, Hochberg I, Rispler S, Azzam ZS. Dilated cardiomyopathy: an unusual complication of clozapine therapy. Nat Clin Pract Cardiovasc Med. 2008;5:566–70. https://doi.org/10.1038/ncpcardio1 292.
32. Cohen H, Loewenthal U, Matar MA, Kotler M. Reversal of pathologic cardiac parameters after transition from clozapine to olanzapine treatment: a case report. Clin Neuropharmacol. 2001;24:106–8. https://doi.org/10.1097/00002826-200103000-00008.
33. Walker AM, Lanza LL, Arellano F, Rothman KJ. Mortality in current and former users of clozapine. Epidemiology. 1997;8:671–7.
34. Belhani D, Frassati D, Mégard R, Tsibiribi P, Bui-Xuan B, Tabib A, et al. Cardiac lesions induced by neuroleptic drugs in the rabbit. Exp Toxicol Pathol. 2006;57:207–12. https://doi.org/10.1016/j.etp.2005.09.003.
35. Warner JP, Barnes TR, Henry JA. Electrocardiographic changes in patients receiving neuroleptic medication. Acta Psychiatr Scand. 1996;93:311–3.
36. Reilly JG, Ayis SA, Ferrier IN, Jones SJ, Thomas SH. QTc-interval abnormalities and psychotropic drug therapy in psychiatric patients. Lancet. 2000;355:1048–52.
37. Miura N, Saito T, Taira T, Umebachi R, Inokuchi S. Risk factors for QT prolongation associated with acute psychotropic drug overdose. Am J Emerg Med. 2015;33:142–9. https://doi.org/10.1016/j.ajem.2014.09.048.
38. Kang UG, Kwon JS, Ahn YM, Chung SJ, Ha JH, Koo YJ, et al. Electrocardiographic abnormalities in patients treated with clozapine. J Clin Psychiatry. 2000;61:441–6.
39. Beach SR, Celano CM, Sugrue AM, Adams C, Ackerman MJ, Noseworthy PA, et al. QT prolongation, torsades de pointes, and psychotropic medications: a 5-year update. Psychosomatics. 2018;59:105–22. https://doi.org/10.1016/j.psym.2017.10.009.
40. Carrà G, Crocamo C, Bartoli F, Lax A, Tremolada M, Lucii C, et al. First-generation antipsychotics and QTc: any role for mediating variables? Hum Psychopharmacol. 2016;31:313–8. https://doi.org/10.1002/hup.2540.
41. Glassman AH. Schizophrenia, antipsychotic drugs, and cardiovascular disease. J Clin Psychiatry. 2005;66(Suppl 6):5–10.
42. Aronow WS, Shamliyan TA. Effects of atypical antipsychotic drugs on QT interval in patients with mental disorders. Ann Transl Med. 2018;6:147. https://doi.org/10.21037/atm.2018.03.17.
43. Leonard CE, Freeman CP, Newcomb CW, Bilker WB, Kimmel SE, Strom BL, et al. Antipsychotics and the risks of sudden cardiac death and all-cause death: cohort studies in Medicaid and dually-eligible Medicaid-Medicare beneficiaries of five states. J Clin Exp Cardiolog. 2013;Suppl 10:1–9. https://doi.org/10.4172/2155-9880.S10-006.
44. Nosè M, Bighelli I, Castellazzi M, Martinotti G, Carrà G, Lucii C, et al. Prevalence and correlates of QTc prolongation in Italian psychiatric care: cross-sectional multicentre study. Epidemiol Psychiatr Sci. 2016;25:532–40. https://doi.org/10.1017/S2045796015000906.
45. Novotny T, Florianova A, Ceskova E, Weislamplova M, Palensky V, Tomanova J, et al. Monitoring of QT interval in patients treated with psychotropic drugs. Int J Cardiol. 2007;117:329–32. https://doi.org/10.1016/j.ijcard.2006.04.087.
46. Milnes JT, Witchel HJ, Leaney JL, Leishman DJ, Hancox JC. hERG K^+ channel blockade by the antipsychotic drug thioridazine: an obligatory role for the S6 helix residue F656. Biochem Biophys Res Commun. 2006;351:273–80. https://doi.org/10.1016/j.bbrc.2006.10.039.
47. Schulz S, Bolz M, Bär K-J, Voss A. Central- and autonomic nervous system coupling in schizophrenia. Philos Trans R Soc A Math Phys Eng Sci. 2016;374:20150178. https://doi.org/10.1098/rsta.2015.0 178.
48. Bär KJ, Letzsch A, Jochum T, Wagner G, Greiner W, Sauer H. Loss of efferent vagal activity in acute schizophrenia. J Psychiatr Res. 2005;39:519–27. https://doi.org/10.1016/j.jpsychires.2004.12.007.
49. Aguirre RR, Mustafa MZ, Dumenigo A, Schulz S, Voss A, Goubran B, et al. Influence of acute antipsychotic treatment on cardiorespiratory coupling and heart rate variability. Cureus. 2018;10:e2066. https://doi.org/10.7759/cureus.2066.
50. Iwamoto Y, Kawanishi C, Kishida I, Furuno T, Fujibayashi M, Ishii C, et al. Dose-dependent effect of antipsychotic drugs on autonomic nervous system activity in schizophrenia. BMC Psychiatry. 2012;12:199. https://doi.org/10.1186/1471-244X-12-199.
51. Mueck-Weymann M, Rechlin T, Ehrengut F, Rauh R, Acker J, Dittmann RW, et al. Effects of olanzapine and clozapine upon pulse rate variability. Depress Anxiety. 2002;16:93–9. https://doi.org/10.1002/da.10037.
52. Pedrosa Gil F, Grohmann R, Rüther E. Asymptomatic bradycardia associated with amisulpride. Pharmacopsychiatry. 2001;34:259–61. https://doi.org/10.1055/s-2001-18033.
53. Hattori S, Kishida I, Suda A, Miyauchi M, Shiraishi Y, Fujibayashi M, et al. Effects of four atypical antipsychotics on autonomic nervous system activity in schizophrenia. Schizophr Res. 2018;193:134–8. https://doi.org/10.1016/j.schres.2017.07.004.
54. Gugger JJ. Antipsychotic pharmacotherapy and orthostatic hypotension: identification and management. CNS Drugs. 2011;25:659–71. https://doi.org/10.2165/11591710-000000000-00000.
55. Leung JYT, Barr AM, Procyshyn RM, Honer WG, Pang CCY. Cardiovascular side-effects of antipsychotic drugs: the role of the autonomic nervous system. Pharmacol Ther. 2012;135:113–22. https://doi.org/10.1016/j.pharmthera.2012.04.003.
56. Petersen EN. Pre- and postsynaptic alpha-adrenoceptor antagonism by neuroleptics in vivo. Eur J Pharmacol. 1981;69:399–405.
57. Cuffi ML, Vila E, Badia A. Effects of some antipsychotic drugs on cardiovascular catecholamine receptors in the rat. J Auton Pharmacol. 1989;9:397–409.

58. Fda. Pharmacological Drugs Advisory Committee briefing document for Zyprexa intramuscular (olanzapine for injection). 2004.
59. Fda. Risperdal (risperidone). 2006.
60. Fda. Seroquel (quetiapine fumarate) tablets 2003; 2:1–31.
61. Fda. Clozaril (clozapine) tablets prescribing information. 2014.
62. Gonsai NH, Amin VH, Mendpara CG, Speth R, Hale GM. Effects of dopamine receptor antagonist antipsychotic therapy on blood pressure. J Clin Pharm Ther. 2018;43:1–7. https://doi.org/10.1111/jcpt.12649.
63. Henderson DC, Daley TB, Kunkel L, Rodrigues-Scott M, Koul P, Hayden D. Clozapine and hypertension: a chart review of 82 patients. J Clin Psychiatry. 2004;65:686–9.
64. Woo YS, Kim W, Chae J-H, Yoon B-H, Bahk W-M. Blood pressure changes during clozapine or olanzapine treatment in Korean schizophrenic patients. World J Biol Psychiatry. 2009;10:420–5. https://doi.org/10.1080/15622970801910399.
65. Correll CU, Joffe BI, Rosen LM, Sullivan TB, Joffe RT. Cardiovascular and cerebrovascular risk factors and events associated with second-generation antipsychotic compared to antidepressant use in a non-elderly adult sample: results from a claims-based inception cohort study. World Psychiatry. 2015;14:56–63. https://doi.org/10.1002/wps.20187.
66. Jönsson AK, Schill J, Olsson H, Spigset O, Hägg S. Venous thromboembolism during treatment with antipsychotics: a review of current evidence. CNS Drugs. 2018;32:47–64. https://doi.org/10.1007/s40263-018-0495-7.
67. Jönsson AK, Spigset O, Hägg S. Venous thromboembolism in recipients of antipsychotics. CNS Drugs. 2012;26:649–62. https://doi.org/10.2165/11633920-000000000-00000.
68. Wu CS, Lin CC, Chang CM, Wu KY, Liang HY, Huang YW, et al. Antipsychotic treatment and the occurrence of venous thromboembolism: a 10-year nationwide registry study. J Clin Psychiatry. 2013; 74:918–24. https://doi.org/10.4088/JCP.12m08117.
69. Letmaier M, Grohmann R, Kren C, Toto S, Bleich S, Engel R, et al. Venous thromboembolism during treatment with antipsychotics: results of a drug surveillance programme. World J Biol Psychiatry. 2018;19:175–86. https://doi.org/10.1080/15622975.2017.1285048.
70. Allenet B, Schmidlin S, Genty C, Bosson J-L. Antipsychotic drugs and risk of pulmonary embolism. Pharmacoepidemiol Drug Saf. 2012;21:42–8. https://doi.org/10.1002/pds.2210.
71. Franchi C, Sequi M, Tettamanti M, Bonometti F, Nobili A, Fortino I, et al. Antipsychotics prescription and cerebrovascular events in Italian older persons. J Clin Psychopharmacol. 2013;33:542–5. https://doi.org/10.1097/JCP.0b013e3182968fda.
72. Hsu W-T, Esmaily-Fard A, Lai C-C, Zala D, Lee S-H, Chang S-S, et al. Antipsychotics and the risk of cerebrovascular accident: a systematic review and meta-analysis of observational studies. J Am Med Dir Assoc. 2017;18:692–9. https://doi.org/10.1016/j.jamda.2017.02.020.
73. Chen W-Y, Chen L-Y, Liu H-C, Wu C-S, Yang S-Y, Pan C-H, et al. Antipsychotic medications and stroke in schizophrenia: a case-crossover study. PLoS One. 2017;12:e0179424. https://doi.org/10.1371/journal.pone.0179424.
74. Wu CS, Wang SC, Gau SSF, Tsai HJ, Cheng YC. Association of stroke with the receptor-binding profiles of antipsychotics – a case-crossover study. Biol Psychiatry. 2013;73:414–21. https://doi.org/10.1016/j.biopsych.2012.07.006.
75. Wu C-S, Wu K-Y, Lo Y-R, Huang Y-W, Tsai Y-T, Li Y, et al. Psychotropic use and risk of stroke among patients with bipolar disorders: 10-year nationwide population based study. J Affect Disord. 2018;226: 77–84. https://doi.org/10.1016/j.jad.2017.09.020.
76. Ogłodek EA, Just MJ, Grzesińska AD, Araszkiewicz A, Szromek AR. The impact of antipsychotics as a risk factor for thromboembolism. Pharmacol Rep. 2018;70:533–9. https://doi.org/10.1016/j.pharep.2017.12.003.
77. Hare DL, Toukhsati SR, Johansson P, Jaarsma T. Depression and cardiovascular disease: a clinical review. Eur Heart J. 2014;35:1365–72. https://doi.org/10.1093/eurheartj/eht462.
78. Sauer WH, Berlin JA, Kimmel SE. Selective serotonin reuptake inhibitors and myocardial infarction. Circulation. 2001;104:1894–8.
79. Moir DC, Crooks J, Sawyer P, Turnbull MJ, Weir RD. Proceedings: cardiotoxicity of tricyclic antidepressants. Br J Pharmacol. 1972;44:371P–2P.
80. Spindelegger CJ, Papageorgiou K, Grohmann R, Engel R, Greil W, Konstantinidis A, et al. Cardiovascular adverse reactions during antidepressant treatment: a drug surveillance report of German-speaking countries between 1993 and 2010. Int J Neuropsychopharmacol. 2014;18:1–9. https://doi.org/10.1093/ijnp/pyu080.
81. Yap YG, Behr ER, Camm AJ. Drug-induced Brugada syndrome. Europace. 2009;11:989–94. https://doi.org/10.1093/europace/eup114.
82. Meert A, Vermeersch N, Beckers R, Hoste W, Brugada P, Hubloue I. Brugada-like ECG pattern induced by tricyclic antidepressants. Eur J Emerg Med. 2010;17:325–7. https://doi.org/10.1097/MEJ.0b013e328334a98f.
83. Brugada J, Campuzano O, Arbelo E, Sarquella-Brugada G, Brugada R. Present status of Brugada syndrome: JACC state-of-the-art review. J Am Coll Cardiol. 2018;72:1046–59. https://doi.org/10.1016/j.jacc.2018.06.037.
84. Minoura Y, Di Diego JM, Barajas-MartÍnez H, Zygmunt AC, Hu D, Sicouri S, et al. Ionic and cellular mechanisms underlying the development of acquired Brugada syndrome in patients treated with antidepressants. J Cardiovasc Electrophysiol. 2012;23:423–32. https://doi.org/10.1111/j.1540-8167.2011.02196.x.
85. Lusetti M, Licata M, Silingardi E, Reggiani Bonetti L, Palmiere C. Cardiac toxicity in selective serotonin

reuptake inhibitor users. Am J Forensic Med Pathol. 2015;36:293–7. https://doi.org/10.1097/PAF.0000000000000205.
86. Lapane KL, Zierler S, Lasater TM, Barbour MM, Carleton R, Hume AL. Is the use of psychotropic drugs associated with increased risk of ischemic heart disease? Epidemiology. 1995;6:376–81.
87. Cohen HW, Gibson G, Alderman MH. Excess risk of myocardial infarction in patients treated with antidepressant medications: association with use of tricyclic agents. Am J Med. 2000;108:2–8.
88. Monster TBM, Johnsen SP, Olsen ML, McLaughlin JK, Sørensen HT. Antidepressants and risk of first-time hospitalization for myocardial infarction: a population-based case-control study. Am J Med. 2004;117:732–7. https://doi.org/10.1016/j.amjmed.2004.06.027.
89. Castro VM, Clements CC, Murphy SN, Gainer VS, Fava M, Weilburg JB, et al. QT interval and antidepressant use: a cross sectional study of electronic health records. BMJ. 2013;346:f288. https://doi.org/10.1136/bmj.f288.
90. van Noord C, Straus SMJM, Sturkenboom MCJM, Hofman A, Aarnoudse A-JLHJ, Bagnardi V, et al. Psychotropic drugs associated with corrected QT interval prolongation. J Clin Psychopharmacol. 2009;29:9–15. https://doi.org/10.1097/JCP.0b013e318191c6a8.
91. Kahl KG, Westhoff-Bleck M, Krüger THC. Effects of psychopharmacological treatment with antidepressants on the vascular system. Vasc Pharmacol. 2017;96–98:11–8. https://doi.org/10.1016/j.vph.2017.07.004.
92. Jackson WK, Roose SP, Glassman AH. Cardiovascular toxicity of antidepressant medications. Psychopathology. 1987;20:64–74. https://doi.org/10.1159/000284525.
93. Hanash JA, Hansen BH, Hansen JF, Nielsen OW, Rasmussen A, Birket-Smith M. Cardiovascular safety of one-year escitalopram therapy in clinically nondepressed patients with acute coronary syndrome. J Cardiovasc Pharmacol. 2012;60:397–405. https://doi.org/10.1097/FJC.0b013e3182677041.
94. Van de Merwe TJ, Silverstone T, Ankier SI. Electrophysiological and haemodynamic changes with trazodone, amitriptyline and placebo in depressed out-patients. Curr Med Res Opin. 1984;9:339–52. https://doi.org/10.1185/03007998409109602.
95. Levenson JL. Prolonged QT interval after trazodone overdose. Am J Psychiatry. 1999;156:969–70. https://doi.org/10.1176/ajp.156.6.969a.
96. Rajamani S, Eckhardt LL, Valdivia CR, Klemens CA, Gillman BM, Anderson CL, et al. Drug-induced long QT syndrome: hERG K^+ channel block and disruption of protein trafficking by fluoxetine and norfluoxetine. Br J Pharmacol. 2006;149:481–9. https://doi.org/10.1038/sj.bjp.0706892.
97. Bhangu JS, King-Kallimanis B, Cunningham C, Kenny RA. The relationship between syncope, depression and anti-depressant use in older adults. Age Ageing. 2014;43:502–9. https://doi.org/10.1093/ageing/afu003.
98. Briggs R, Carey D, McNicholas T, Claffey P, Nolan H, Kennelly SP, et al. The association between antidepressant use and orthostatic hypotension in older people: a matched cohort study. J Am Soc Hypertens. 2018. https://doi.org/10.1016/j.jash.2018.06.002.
99. Mehta N, Vannozzi R. Lithium-induced electrocardiographic changes: a complete review. Clin Cardiol. 2017;40:1363–7. https://doi.org/10.1002/clc.22822.
100. Altinbas K, Guloksuz S, Caglar IM, Caglar FNT, Kurt E, Oral ET. Electrocardiography changes in bipolar patients during long-term lithium monotherapy. Gen Hosp Psychiatry. 2014;36:694–7. https://doi.org/10.1016/j.genhosppsych.2014.07.001.
101. Venkatarathnamma PN, Patil AR, Nanjundaiah N. Fatal lithium toxicity with therapeutic levels – a case report. Int J Clin Pharmacol Ther. 2011;49:336–8.
102. Lyman GH, Williams CC, Dinwoodie WR, Schocken DD. Sudden death in cancer patients receiving lithium. J Clin Oncol. 1984;2:1270–6. https://doi.org/10.1200/JCO.1984.2.11.1270.
103. Ide A, Kamijo Y. Intermittent complete atrioventricular block after long term low-dose carbamazepine therapy with a serum concentration less than the therapeutic level. Intern Med. 2007;46:627–9.
104. Koutsampasopoulos K, Zotos A, Papamichalis M, Papaioannou K. Carbamazepine induced atrial tachycardia with complete AV block. Hippokratia. 2014;18:185–6.
105. Kasarskis EJ, Kuo CS, Berger R, Nelson KR. Carbamazepine-induced cardiac dysfunction. Characterization of two distinct clinical syndromes. Arch Intern Med. 1992;152:186–91.
106. Alabi A, Todd A, Husband A, Reilly J. Safety profile of lamotrigine in overdose. Ther Adv Psychopharmacol. 2016;6:369–81. https://doi.org/10.1177/2045125316656707.
107. Barrett JS, Hey EB. Ventricular arrhythmias associated with the use of diazepam for cardioversion. JAMA. 1970;214:1323–4.
108. Costa A, Bosone D, Zoppi A, D'Aposangelo A, Ghiotto N, Guaschino E, et al. Effect of diazepam on 24-hour blood pressure and heart rate in healthy young volunteers. Pharmacology. 2018;101:86–91. https://doi.org/10.1159/000481665.
109. Fogari R, Costa A, Zoppi A, D'Angelo A, Ghiotto N, Battaglia D, et al. Diazepam as an oral hypnotic increases nocturnal blood pressure in the elderly. Aging Clin Exp Res. 2018. https://doi.org/10.1007/s40520-018-0991-0.
110. Jick H. Drugs – remarkably nontoxic. N Engl J Med. 1974;291:824–8. https://doi.org/10.1056/NEJM197410172911605.

Antipsychotics and Cardiac Side Effects

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Contents

Abstract

During the last decades, the diagnosis of mental illness has dramatically grown especially in the pediatric population, and, in parallel, there has been an increasing widespread use of psychotropic drugs, mainly antipsychotics and especially those of second generation (SGA). SGAs are used effectively for several conditions, such as schizophrenia, irritability and aggression in autism spectrum disorder or intellectual disability, tics or Tourette's disorder, bipolar, conduct, and eating disorders, but only few of them have regulatory approval in youths. Although effective, these drugs could potentially determine several adverse effects, which are of particular concern especially among pediatric population; here we focus on cardiac, cardiovascular, and metabolic side effects.

Keywords

Antipsychotic drugs · Second-generation antipsychotics · Cardiac side effects · Cardiovascular side effects · Metabolic side effects

Introduction

Antipsychotic drugs are the cornerstone of pharmacological treatment for several psychiatric disorders, and in the last years, there has been

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*,
https://doi.org/10.1007/978-3-030-28008-6_47

an increasing use of them, especially those of second generation. Although they effectively control symptoms and behavior associated with psychiatric disorders, accumulating evidences suggest that antipsychotics exposure could lead to an increased risk of cardiac and also metabolic side effects. These adverse events seem to be more frequent in vulnerable populations, such as patients with a first episode of schizophrenia, those who are drug-naive, children, and adolescents [1–3].

Electrocardiographic Adverse Events

Antipsychotic drugs are associated with a variety of electrocardiographic abnormalities, including minor and frequent complications, such as sinus tachycardia, and more serious arrhythmias, such as the polymorphic ventricular tachycardia torsades de pointes, which may cause sudden cardiac death [4]. The World Health Organization defined sudden cardiac death as an unexpected death occurring within 1 h of symptom onset if witnessed and, if unwitnessed, within 24 h after the person has last been observed alive and symptoms-free [5]. Antipsychotics have shown the ability of blocking the delayed rectifier potassium current (IKr), by interacting with the alpha subunit Kv11.1 of the channel, which is coded by the hERG gene (also called *KCNH2*). This blockade is dose-dependent and able to prolong cardiac repolarization, seen as corrected QT (QTc) prolongation on the electrocardiogram (ECG). In clinical settings, concern arises on QTc prolongation as it may progress to torsades de pointes in rare cases. If not immediately managed, torsades de pointes can evolve into ventricular fibrillation and cause sudden cardiac death [5]. Among antipsychotics, first-generation ones like thioridazine, droperidol, mesoridazine, and pimozide have shown a marked QTc prolongation leading to an FDA warning and for some of them to the market withdrawal [6]. In addition, a similar QTc effect was observed with chlorpromazine [7]. Haloperidol also has carried an FDA warning for the increased risk of QTc prolongation and torsades de pointes, recommending a regular ECG monitoring when intravenous (IV) haloperidol is administered [8]. Moreover, in Italy, the Italian Medicines Agency has also published a warning (GU Serie Generale n.144 del 23-06-2010) in which it has specified that, in order to reduce the risk of QTc prolongation, the vial formulation should only be used for intramuscular administration and not for IV injection. However, evidence has also suggested that in case of a dose of IV haloperidol lower than 2 mg, this drug can be administered without ECG monitoring, in patients with no cardiovascular risk factors [9]. Among second-generation antipsychotics, those associated with FDA warnings for the risk of QTc prolongation are asenapine, clozapine iloperidone, paliperidone, quetiapine, sertindole, and ziprasidone. The greater risk of QTc prolongation was found with ziprasidone compared with other second-generation antipsychotics, but this does not imply that ziprasidone is more associated with torsades de pointes and sudden cardiac death [10]. In fact, only rare cases of torsades de pointes have been reported in patients treated with ziprasidone as well as with other second-generation antipsychotics [11]. Olanzapine, quetiapine, and risperidone showed a modest QTc prolongation when used in therapeutic doses [11]. Interestingly, aripiprazole has shown a QTc-shortening effect compared with placebo and active controls [12]. Evidence on amisulpride is too limited to categorize its effect on QTc prolongation [11]. Finally, special attention deserves clozapine that has been associated with substantial heart rate increases, which may complicate QTc measurement. Therefore, whether clozapine actually cause QTc prolongation is still an unresolved question [13].

Recently, weighted recommendations on commonly used antipsychotics have been made using pharmacovigilance data [14]. In this regard, aripiprazole, perphenazine, olanzapine, and zuclopenthixol were categorized as drugs with no risk of QTc prolongation or torsades de pointes. Chlorprothixene, levomepromazine, flupentixol, paliperidone, clozapine, quetiapine, amisulpride, sulpiride, and risperidone were categorized as drugs with propensity of QTc prolongation. Finally, sertindole, pimozide, haloperidol,

and ziprasidone were categorized as drugs with a pronounced effect on QTc prolongation, documented cases of torsades de pointes, or other types of serious arrhythmias. The risk of developing torsades de pointes increases in presence of genetic risk factors like mutations of hERG gene encoding for the subunit of the potassium channel protein Kv11.1 or poor metabolizers of the cytochrome P450 (CYP) 2D6 [5, 15]. Clinical risk factors include bradycardia, conduction disturbances, coronary artery disease, structural myocardial disease, including post-MI and cardiomyopathy, and electrolyte imbalance (especially hypokalemia). Finally, female sex and age $\geq$ 65 years represent risk factors for the development of torsades de pointes. Other risk factors include polypharmacy, overdose of antipsychotics, or exposure to drug abuse of central nervous system stimulants [5].

Antipsychotics are also able to block the fast sodium current (INa) reducing peak sodium influx and causing altered voltage gradients such as those seen in Brugada syndrome, a genetic ion channel disease that can also cause sudden cardiac death [16]. However, the evidence of the association between antipsychotics and Brugada syndrome is scarce [17].

Most antipsychotics can cause sinus tachycardia, defined as heart rate $\geq$ 100 beats/min. The underlying mechanism involves a combination of both anticholinergic and antiadrenergic effects, as well as indirect effects via baroreceptor reflexes. Antipsychotics are able to block M2 cardiac receptors, reduce the parasympathetic tone, and increase heart rate. Moreover, antipsychotics through the block of adrenergic α1 receptors can cause vasodilation and reflex tachycardia [18]. As a proof of this concept, an increased risk of sinus tachycardia has been observed with antipsychotics at high affinity for M2 receptors like clozapine, quetiapine, risperidone, and chlorpromazine. A lower risk is observed instead with olanzapine and ziprasidone [6, 19] and with aripiprazole due to the scarce anticholinergic and antiadrenergic effect [20].

Antipsychotics may also cause other less common electrocardiographic adverse events that potentially could contribute to increase the risk of sudden cardiac death. In this regard, second-generation antipsychotics like risperidone, ziprasidone, clozapine, olanzapine, and quetiapine have been associated with a risk of bradycardia, atrial fibrillation, ST-segment depression and elevation, QRS prolongation, T-wave inversion, bundle branch block, and first-degree atrioventricular block [19].

Vascular Adverse Events

Antipsychotics have been associated with a risk of developing orthostatic hypotension through the blockade of adrenergic α1 receptors [20]. Low- and mid-potency first-generation antipsychotics like chlorpromazine and perphenazine have been associated with a higher risk of orthostatic hypotension than high-potency first-generation antipsychotics (haloperidol and fluphenazine) and second-generation antipsychotics. Among second-generation drugs, clozapine and quetiapine were found to have the highest risk followed by ziprasidone, olanzapine, risperidone, and aripiprazole. Among the more recently introduced second-generation antipsychotic drugs, the highest risk was observed with iloperidone followed by asenapine and lurasidone [21].

Evidence of the hypertensive effect associated with antipsychotics is limited and contradictory [22, 23]. An increased risk of hypertension was observed with mid-potency first-generation agents (like perphenazine) and the second-generation clozapine, olanzapine, and ziprasidone, whereas a lower risk was found with risperidone and quetiapine [19, 24].

Cardiac Adverse Events

Despite electrocardiographic abnormalities represent the most important clinical concern related to the antipsychotic treatment, other direct cardiac adverse events have been found, including myocardial infarction, myocarditis, and cardiomyopathy, for which the underlying mechanisms are less clear. The risk of myocardial infarction associated with the use of antipsychotic is less clear

[25]. Amisulpride, clozapine, and risperidone seem associated with an increased risk [19].

Myocarditis associated with antipsychotics is identified as a type I hypersensitivity reaction that is typically characterized by the accumulation of eosinophils and the release of toxins that could induce apoptosis and necrosis of cardiomyocytes [18]. Among antipsychotics, clozapine is most associated with myocarditis [26]. Other antipsychotics associated with this adverse event are fluphenazine, chlorpromazine, haloperidol, olanzapine, quetiapine, and risperidone [18, 27]. Myocarditis can lead to myocardial fibrosis, arrhythmias, and eventually sudden cardiac death. It can occur within the first months of treatment, and patients may present symptoms like fever, fatigue, and dyspnea. In case of myocarditis, antipsychotic treatment should be discontinued, and, if indicated, patients should start a therapy with corticosteroids [17, 20].

A less common cardiovascular adverse event of antipsychotics is cardiomyopathy, defined as a deterioration of the function of the myocardium, often caused by untreated myocarditis or other factors. Usually, its onset is slower than myocarditis [18]. Among antipsychotics, clozapine is most commonly associated with the development of cardiomyopathy [26]. Other antipsychotics associated with this risk include amisulpride and quetiapine [18]. Common symptoms are fatigue, tachypnea, and dyspnea. In case of diagnosis of cardiomyopathy, antipsychotic should be withdrawal, and patients should receive an appropriate heart failure treatment [20].

Metabolic Adverse Events

Beyond the potential direct cardiac and/or vascular effects, there is a growing body of evidence about cardio-metabolic side effects due to antipsychotics exposure. This is of concern especially for pediatric population since weight gain, dyslipidemia, or insulin resistance are known to predispose to cardiac and vascular disease in adulthood. Metabolic adverse events associated with antipsychotics are weight gain, especially abdominal obesity, impaired glucose metabolism, and dyslipidemia. Several studies and meta-analyses have shown a different degree of weight gain associated with individual antipsychotics [28–34]. Among first-generation drugs, those with low potency, such as chlorpromazine and thioridazine, are associated with a higher risk of weight gain than mid- (molindone and perphenazine) or high-potency antipsychotics (fluphenazine, haloperidol, and pimozide). Among second-generation antipsychotics, a high risk of weight gain was observed with clozapine and olanzapine; an intermediate risk with iloperidone, quetiapine, risperidone, paliperidone, sertindole, and zotepine; and a smaller risk with amisulpride, aripiprazole, asenapine, lurasidone, and ziprasidone [35]. Despite this different risk's magnitude, we can consider all antipsychotics associated with weight gain, with a risk even higher in those patients who have taken them for the first time [32, 36, 37]. In fact, in a 12-month trial conducted on patients with a first episode of schizophrenia, antipsychotics at low risk such as amisulpride, ziprasidone, and low doses of haloperidol were associated with a significant weight gain [32]. The period at major risk for gaining weight in drug-naive patients with schizophrenia is the first few months of therapy. In this regard, a meta-analysis has shown a mean gain in BMI and weight within the first 12 weeks of antipsychotic treatment in previously drug-naive patients older than 15 years [36]. Predictors of antipsychotic-induced weight gain are shown in Table 1.

In children and adolescents, second-generation antipsychotics such as aripiprazole, olanzapine, quetiapine, and risperidone are used for the treatment of bipolar mania, schizophrenia, irritability, and aggression associated with autistic disorder. Evidence has shown a greater orexigenic effect in this subpopulation than in adults [32]. In fact, young patients treated with antipsychotics have an increased risk of being obese or overweight [1, 29, 31]. However, long-term data on this metabolic risk during antipsychotic treatment are limited. In a systematic review of randomized, placebo-controlled trials of patients aged <18 years treated with second-generation antipsychotic drugs, a similar hierarchy was found in the risk of weight gain than that observed

Table 1 Predictors of antipsychotic-induced weight gain

Predictors	Predictors related to
Family history of obesity	Familial factors
Parental BMI	
Cannabis use	Patients
Young age (children and adolescents)	
Sex (mixed evidence)	
High levels of negative symptoms (such as alogia, affective flattening, avolition)	
Lack of cognitive restraint in the presence of increased appetite	
Low BMI (<25 kg/m^2)	
Non-smoking status	
Nonwhite ethnicity	
Improved symptom reduction (limited or inconclusive data)	Psychiatric illness
First-episode status of psychiatric illness	
Lack of prior antipsychotic treatment	
Early weight gain (within the first 2–4 weeks of antipsychotic treatment)	Treatment
Good treatment adherence	
High antipsychotic dose	
Polypharmacy (limited or inconclusive data)	
Long-term treatment	
Specific medications (such as clozapine and olanzapine, which have a high risk of metabolic dysregulation)	

in adult patients [1], whereby clozapine and olanzapine were associated with the great weight gain, followed by risperidone, quetiapine, aripiprazole, and ziprasidone. Finally, it is important to consider that despite the differential risk of weight gain associated with the antipsychotics seems consistent across adults, adolescents, and children, the high inter-individual variability in weight gain among patients treated with a specific drug suggests that other factors like personal, familial, or genetic factors can come into play influencing the degree of weight gain [3, 31, 36]. In fact, allelic variants of CYP-2D6 and -3A4 were found to alter the metabolic pathways of antipsychotics [38, 39]. Similarly, allelic variants of ABCB1 and ABCG2 genes, codifying for transport proteins belonging to the ATP-binding cassette superfamily, were found to influence the plasma concentrations of antipsychotics [40–42]. In this regard, a pharmacogenetic study has investigated the impact of allelic variants of CYP3A, CYP2D6, ABCB1, and ABCG2 genes on second-generation antipsychotics plasma concentrations and their association with the occurrence of adverse drug reactions, finding no association for the investigated allelic variants of CYP3A (CYP3A4*22 C > T C_59013445_10, CYP3A5*3A > G C_26201809_30) and CYP2D6 (*3 del A C_32407232_50, *6 del T C_32407243_20, *4 G > A C_27102431_D0, and assay ID Hs00010001_cn gene duplication), while the ABCB1 haplotype (G2677 T/A-C3435T) and the ABCG2 (c.421 C>A) allelic variants were associated with lower plasma concentrations of aripiprazole and risperidone. Moreover, the ABCG2 c.421 CA/AA functional variant was found associated with a higher risk of developing metabolism and nutrition disorders [43]. These results, if confirmed in larger studies, underline the importance of combining therapeutic drug monitoring, pharmacogenetic, and pharmacovigilance methods to tailor the treatment with these drugs in the pediatric population.

The underlying mechanisms involved in antipsychotic-induced weight gain include different functional pathways and neurotransmissions [3]. Among them, the histaminergic transmission seems to recover an important role as histamine H1 receptors are involved in the energy homeostasis. In fact, the extent of H1 receptor antagonism of antipsychotic drugs has been identified as predictor of the magnitude of the weight gain in clinical studies [44, 45]. Moreover, serotonin 5-HT2a and 5-HT2c receptors can also play a role in the control of food intake and body weight. Accordingly, most second-generation antipsychotics such as clozapine and olanzapine are potent 5-HT2c antagonists. On the contrary, although aripiprazole and ziprasidone have a high affinity for 5-HT2c receptors, they have shown only a weak association with metabolic dysregulation. This could be explained by the influence of other receptors that can potentially counterbalance the inhibition of 5HT2c receptors like the partial agonist effect of aripiprazole on 5-HT1a receptors [46]. Another potential

mechanism involved in antipsychotic drug-induced weight gain is the block of dopamine D2 and D3 receptors as this blockade has been associated with a strong effect on feeding behavior [3]. This can also explain the effect on weight observed with antipsychotic agents that interact exclusively with dopaminergic receptors, such as amisulpride [32]. Polymorphism of the promoter region of the 5-HT2C receptor gene has been associated with antipsychotic-induced weight gain [47], and polymorphisms of the MTHFR gene [48] and the D2 receptor gene [49] have been associated with an increased risk of metabolic syndrome in patients receiving second-generation antipsychotics. Evidence of the role of adrenergic α1 and α2 receptors blockade in inducing weight gain or metabolic dysregulation is instead lacking [31]. Finally, genetic data suggest a role for G-protein signalling, promelanin-concentrating hormone signalling, leptin signalling and leptin receptor activity, and cannabinoid receptor activity in antipsychotic drug-induced weight gain [3, 50].

Another adverse event associated with antipsychotic drugs is the potential to cause or exacerbate the metabolic syndrome, which appears with central obesity, hypertension, dyslipidemia, and glucose intolerance or insulin resistance. In general, the risk of developing the metabolic syndrome is high with clozapine, olanzapine, and chlorpromazine, moderate with quetiapine, mild with risperidone, paliperidone, amisulpride, and sertindole, and low with aripiprazole and ziprasidone [29, 35, 37, 51, 52]. Among second-generation antipsychotics, olanzapine and clozapine have been associated with the highest risk of dyslipidemia whereas risperidone and quetiapine with an intermediate risk and aripiprazole and ziprasidone with a low risk of this metabolic abnormality. Moreover, the risk of dyslipidemia with olanzapine, clozapine, and quetiapine was found independent of BMI or in addition to weight-related effects [3, 53]. In fact, dyslipidemia should be considered as a separate and direct adverse event of antipsychotic drugs other than a consequence of weight gain. The dyslipidemic adverse effects of clozapine, olanzapine, and quetiapine display as abnormal elevations in serum triglyceride levels and as an increase in total cholesterol, low-density lipoprotein (LDL), and non-high-density lipoprotein (non-HDL) cholesterol levels. The lowest risk of serum lipid abnormalities has been found with risperidone [31], although a significant elevation of serum triglyceride levels was observed in young, antipsychotic-drug-naive patients [53]. Finally, a neutral effect on lipid levels was observed with aripiprazole and ziprasidone [3, 53]. The receptors involved in the antipsychotic-drug-associated dyslipidemia are not completely understood; however, transcriptional regulators of lipid and carbohydrate metabolism, peroxisome proliferator-activated receptors, and the inhibition of AMP-activated protein kinase activity may play a relevant role [54, 55].

Clozapine and olanzapine treatment has been also associated with the dysregulation of glucose homeostasis (hyperglycemia and insulin resistance), independent of weight gain and adiposity [33]. Quetiapine has been associated with a moderate risk of hyperglycemia, lower than that associated with clozapine or olanzapine but higher than risperidone. As with dyslipidemia, the lowest risk of hyperglycemia was observed with aripiprazole and ziprasidone [35]. Antipsychotics have also been associated with the risk of developing type 2 diabetes mellitus [56], with a higher risk found in patients treated with second-generation antipsychotics than in those treated with first-generation drugs [57]. Furthermore, the risk of diabetes mellitus differs for individual drugs. In this regard, olanzapine and clozapine, followed by quetiapine and risperidone, are associated with a significant increase in the risk of diabetes mellitus [58–60]. Patients aged 0–24 years seem to have the highest risk of diabetes mellitus associated with antipsychotic drugs [61], although the incidence rates of diabetes mellitus generally increase with age. This contradiction seems to be related to the low risk for diabetes mellitus at a younger age, which makes the effect of antipsychotic drugs on the glycemic control more noticeable, whereas at an older age, the effect of other risk factors can become more pronounced than that related to the antipsychotic treatment. In inducing impaired glucose metabolism, a role

seems to be played by muscarinic M2 and M3 receptors that are expressed on the surface of pancreatic cells. The affinity of second-generation antipsychotic agents for these receptors is relevant as M3 receptors can control insulin release [31, 62, 63]. In fact, some antipsychotics with a high affinity for the M3 receptor (such as clozapine and olanzapine) might unbalance both cholinergic-dependent and glucose-dependent insulin secretion from pancreatic cells promoting glucose dysregulation and type 2 diabetes mellitus [31].

Finally, all these metabolic abnormalities seen above have shown a dose-dependent relationship with the serum concentrations of the second-generation antipsychotics [46, 64].

Conclusion

Antipsychotic medications have been implicated in the development of cardiovascular disorders via direct and indirect effects. These agents are frequently cited as causing electrocardiographic adverse events especially QTc prolongation that rarely may progress in torsades de pointes. In this regard both FDA and the Italian Medicines Agency published a warning on the parenteral use of haloperidol. These agents have also been directly linked to vascular effects such as increased or reduced blood pressure. Less clear is their association with the risk of myocarditis, myocardial infarction, and cardiomyopathy, although some evidences have shown this association for both first and second generation of antipsychotics. On the contrary, several findings suggest the correlation between antipsychotic use, both first- (chlorpromazine and thioridazine) and second-generation (clozapine, olanzapine, risperidone) antipsychotics, and metabolic side effects, such as weight gain, impaired glucose metabolism, and dyslipidemia. The underlying mechanisms involved in antipsychotic-induced metabolic effects are strongly related to their effects on serotoninergic, histaminergic, and dopaminergic receptors. It's important to highlight that this risk can be higher in children and adolescents. In fact, young patients treated with antipsychotics have an increased risk of being obese or overweight. However, long-term data on this metabolic risk during antipsychotic treatment are limited. Finally, it is important to consider that also genetic factors can influence the risk and severity of metabolic side effects.

Cross-References

- ▶ Cardiovascular Adverse Effects of Psychotropic Drugs
- ▶ Cardiovascular Manifestations in Schizophrenia

References

1. De Hert M, Dobbelaere M, Sheridan EM, Cohen D, Correll CU. Metabolic and endocrine adverse effects of second-generation antipsychotics in children and adolescents: a systematic review of randomized, placebo controlled trials and guidelines for clinical practice. Eur Psychiatry. 2011;26:144–58.
2. Maayan L, Vakhrusheva J, Correll CU. Effectiveness of medications used to attenuate antipsychotic-related weight gain and metabolic abnormalities: a systematic review and metaanalysis. Neuropsychopharmacology. 2010;35:1520–30.
3. Correll CU, Lencz T, Malhotra AK. Antipsychotic drugs and obesity. Trends Mol Med. 2011;17:97–107.
4. Nielsen J. The safety of atypical antipsychotics: does QTc provide all the answers? Expert Opin Drug Saf. 2011;10:341–4.
5. Nielsen J, Graff C, Kanters JK, et al. Assessing QT interval prolongation and its associated risks with antipsychotics. CNS Drugs. 2011;25:473–90.
6. Michelsen JW, Meyer JM. Cardiovascular effects of antipsychotics. Expert Rev Neurother. 2007;7:829–39.
7. Shah AA, Aftab A, Coverdale J. QTc prolongation with antipsychotics: is routine ECG monitoring recommended? J Psychiatr Pract. 2014;20:196–206.
8. Hassaballa HA, Balk RA. Torsade de pointes associated with the administration of intravenous haloperidol: a review of the literature and practical guidelines for use. Expert Opin Drug Saf. 2003;2:543–7.
9. Meyer-Massetti C, Cheng CM, Sharpe BA, et al. The FDA extended warning for intravenous haloperidol and torsades de pointes: how should institutions respond? J Hosp Med. 2010;5:E8E16.
10. Citrome L. Drug safety evaluation of ziprasidone. Expert Opin Drug Saf. 2011;10:437–48.
11. Hasnain M, Vieweg WV. QTc interval prolongation and torsade de pointes associated with second-generation antipsychotics and antidepressants: a comprehensive review. CNS Drugs. 2014;28:887–920.
12. Polcwiartek C, Sneider B, Graff C, et al. The cardiac safety of aripiprazole treatment in patients at high risk

for torsade: a systematic review with a meta-analytic approach. Psychopharmacology. 2015;232:3297–308.
13. Nielsen J. QTc prolongation and clozapine: fact or artefact? Aust N Z J Psychiatry. 2012;46:793–4.
14. Fanoe S, Kristensen D, Fink-Jensen A, et al. Risk of arrhythmia induced by psychotropic medications: a proposal for clinical management. Eur Heart J. 2014;35:1306–15.
15. Brown CS, Farmer RG, Soberman JE, et al. Pharmacokinetic factors in the adverse cardiovascular effects of antipsychotic drugs. Clin Pharmacokinet. 2004;43:33–56.
16. Sicouri S, Antzelevitch C. Sudden cardiac death secondary to antidepressant and antipsychotic drugs. Expert Opin Drug Saf. 2008;7:181–94.
17. Polcwiartek C, Kragholm K, Schjerning O, Graff C, Nielsen J. Cardiovascular safety of antipsychotics: a clinical overview. Expert Opin Drug Saf. 2016; 15:679–88.
18. Leung JY, Barr AM, Procyshyn RM, et al. Cardiovascular side-effects of antipsychotic drugs: the role of the autonomic nervous system. Pharmacol Ther. 2012;135:113–22.
19. Feinstein RE. Cardiovascular effects of novel antipsychotic medications. Heart Dis. 2002;4:184–90.
20. Nielsen J, Correll CU, Manu P, et al. Termination of clozapine treatment due to medical reasons: when is it warranted and how can it be avoided? J Clin Psychiatry. 2013;74:603–13.
21. Gugger JJ. Antipsychotic pharmacotherapy and orthostatic hypotension: identification and management. CNS Drugs. 2011;25:659–71.
22. Henderson DC, Daley TB, Kunkel L, et al. Clozapine and hypertension: a chart review of 82 patients. J Clin Psychiatry. 2004;65:686–9.
23. Lund BC, Perry PJ, Brooks JM, et al. Clozapine use in patients with schizophrenia and the risk of diabetes, hyperlipidemia, and hypertension: a claims-based approach. Arch Gen Psychiatry. 2001;58:1172–6.
24. Bodén R, Edman G, Reutfors J, et al. A comparison of cardiovascular risk factors for ten antipsychotic drugs in clinical practice. Neuropsychiatr Dis Treat. 2013;9:371–7.
25. Brauer R, Douglas I, Smeeth L. The association between antipsychotic agents and the risk of myocardial infarction: a systematic review. Br J Clin Pharmacol. 2011;72:871–8.
26. Fitzsimons J, Berk M, Lambert T, et al. A review of clozapine safety. Expert Opin Drug Saf. 2005;4: 731–44.
27. Vang T, Rosenzweig M, Bruhn CH, et al. Eosinophilic myocarditis during treatment with olanzapine – report of two possible cases. BMC Psychiatry. 2016;16:70.
28. Leucht S, Corves C, Arbter D, Engel RR, Li C, Davis JM. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. Lancet. 2009;373:31–41.
29. Rummel-Kluge C, Komossa K, Schwarz S, Hunger H, Schmid F, Kissling W, Davis JM, Leucht S. Second-generation antipsychotic drugs and extrapyramidal side effects: a systematic review and meta-analysis of head-to-head comparisons. Schizophr Bull. 2012;38: 167–77.
30. Parsons B, Allison DB, Loebel A, Williams K, Giller E, Romano S, Siu C. Weight effects associated with antipsychotics: a comprehensive database analysis. Schizophr Res. 2009;110:103–10.
31. Coccurello R, Moles A. Potential mechanisms of atypical antipsychotic-induced metabolic derangement: clues for understanding obesity and novel drug design. Pharmacol Ther. 2010;127:210–51.
32. Kahn RS, Fleischhacker WW, Boter H, Davidson M, Vergouwe Y, Keet IP, Gheorghe MD, Rybakowski JK, Galderisi S, Libiger J, Hummer M, Dollfus S, López-Ibor JJ, Hranov LG, Gaebel W, Peuskens J, Lindefors N, Riecher-Rössler A, Grobbee DE, EUFEST Study Group. Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial. Lancet. 2008;371:1085–97.
33. Newcomer JW. Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review. CNS Drugs. 2005;19(Suppl 1): 1–93.
34. Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, Keefe RS, Davis SM, Davis CE, Lebowitz BD, Severe J, Hsiao JK, Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med. 2005;353:1209–23.
35. DE Hert M, Correll CU, Bobes J, Cetkovich-Bakmas-M, Cohen D, Asai I, Detraux J, Gautam S, Möller HJ, Ndetei DM, Newcomer JW, Uwakwe R, Leucht S. Physical illness in patients with severe mental disorders. I. Prevalence, impact of medications and disparities in health care. World Psychiatry. 2011;10:52–77.
36. Tarricone I, Ferrari Gozzi B, Serretti A, Grieco D, Berardi D. Weight gain in antipsychotic-naive patients: a review and metaanalysis. Psychol Med. 2010;40:187–200.
37. Alvarez-Jiménez M, González-Blanch C, Crespo-Facorro B, Hetrick S, Rodríguez-Sánchez JM, Pérez-Iglesias R, Vázquez-Barquero JL. Antipsychotic-induced weight gain in chronic and first-episode psychotic disorders: a systematic critical reappraisal. CNS Drugs. 2008;22:547–62.
38. de Leon J, Armstrong SC, Cozza KL. The dosing of atypical antipsychotics. Psychosomatics. 2005;46: 262–73.
39. Spina E, de Leon J. Clinical applications of CYP genotyping in psychiatry. J Neural Transm. 2015;122: 5–28.
40. Gunes A, Spina E, Dahl M-L, Scordo MG. ABCB1 polymorphisms influence steady-state plasma levels of 9-hydroxyrisperidone and risperidone active moiety. Ther Drug Monit. 2008;30:628–33.

41. Yoo H-D, Lee S-N, Kang H-A, Cho H-Y, Lee I-K, Lee Y-B. Influence of ABCB1 genetic polymorphisms on the pharmacokinetics of risperidone in healthy subjects with CYP2D6∗10/∗10. Br J Pharmacol. 2011;164:433–43.
42. Xiang Q, Zhao X, Zhou Y, Duan JL, Cui YM. Effect of CYP2D6, CYP3A5, and MDR1 genetic polymorphisms on the pharmacokinetics of risperidone and its active moiety. J Clin Pharmacol. 2010;50:659–66.
43. Rafaniello C, Sessa M, Bernardi FF, Pozzi M, Cheli S, Cattaneo D, Baldelli S, Molteni M, Bernardini R, Rossi F, Clementi E, Bravaccio C, Radice S, Capuano A. The predictive value of ABCB1, ABCG2, CYP3A4/5 and CYP2D6 polymorphisms for risperidone and aripiprazole plasma concentrations and the occurrence of adverse drug reactions. Pharmacogenomics J. 2018;18:422–30.
44. Kim SF, Huang AS, Snowman AM, Teuscher C, Snyder SH. From the cover: antipsychotic drug-induced weight gain mediated by histamine H1 receptor-linked activation of hypothalamic AMP-kinase. Proc Natl Acad Sci U S A. 2007;104:3456–9.
45. Kroeze WK, Hufeisen SJ, Popadak BA, Renock SM, Steinberg S, Ernsberger P, Jayathilake K, Meltzer HY, Roth BL. H1-histamine receptor affinity predicts short-term weight gain for typical and atypical antipsychotic drugs. Neuropsychopharmacology. 2003;28:519–26.
46. Correll CU. From receptor pharmacology to improved outcomes: individualizing the selection, dosing, and switching of antipsychotics. Eur Psychiatry. 2010;25:S12–21.
47. Reynolds GP, Hill MJ, Kirk SL. The 5-HT2C receptor and antipsychotic induced weight gain: mechanisms and genetics. J Psychopharmacol. 2006;20:15–8.
48. van Winkel R, Rutten BP, Peerbooms O, Peuskens J, van Os J, De Hert M. MTHFR and risk of metabolic syndrome in patients with schizophrenia. Schizophr Res. 2010;121:193–8.
49. Hong CJ, Liou YJ, Bai YM, Chen TT, Wang YC, Tsai SJ. Dopamine receptor D2 gene is associated with weight gain in schizophrenic patients under long-term atypical antipsychotic treatment. Pharmacogenet Genomics. 2010;20:359–66.
50. De Hert M, Detraux J, van Winkel R, Yu W, Correll CU. Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. Nat Rev Endocrinol. 2011;8:114–26.
51. De Hert M, Dekker JM, Wood D, Kahl KG, Holt RI, Möller HJ. Cardiovascular disease and diabetes in people with severe mental illness position statement from the European Psychiatric Association (EPA), supported by the European Association for the Study of Diabetes (EASD) and the European Society of Cardiology (ESC). Eur Psychiatry. 2009;24:412–24.
52. Nielsen J, Skadhede S, Correll CU. Antipsychotics associated with the development of type 2 diabetes in antipsychotic-naive schizophrenia patients. Neuropsychopharmacology. 2010;35:1997–2004.
53. Correll CU, Manu P, Olshanskiy V, Napolitano B, Kane JM, Malhotra AK. Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. JAMA. 2009;302:1765–73.
54. Nasrallah HA. Atypical antipsychotic-induced metabolic side effects: insights from receptor binding profiles. Mol Psychiatry. 2008;13:27–35.
55. Oh KJ, Park J, Lee SY, Hwang I, Kim JB, Park TS, Lee HJ, Koo SH. Atypical antipsychotic drugs perturb AMPK-dependent regulation of hepatic lipid metabolism. Am J Physiol Endocrinol Metab. 2011;300:E624–32.
56. Liao CH, Chang CS, Wei WC, Chang SN, Liao CC, Lane HY, Sung FC. Schizophrenia patients at higher risk of diabetes, hypertension and hyperlipidemia: a population-based study. Schizophr Res. 2011;126:110–6.
57. Smith M, Hopkins D, Peveler RC, Holt RI, Woodward M, Ismail K. First- v. second-generation antipsychotics and risk for diabetes in schizophrenia: systematic review and meta-analysis. Br J Psychiatry. 2008;192:406–11.
58. Ramaswamy K, Masand PS, Nasrallah HA. Do certain atypical antipsychotics increase the risk of diabetes? A critical review of 17 pharmacoepidemiologic studies. Ann Clin Psychiatry. 2006;18:183–94.
59. Yood MU, DeLorenze G, Quesenberry CP Jr, Oliveria SA, Tsai AL, Willey VJ, McQuade R, Newcomer J, L'Italien G. The incidence of diabetes in atypical antipsychotic users differs according to agent – results from a multisite epidemiologic study. Pharmacoepidemiol Drug Saf. 2009;18:791–9.
60. Starrenburg FC, Bogers JP. How can antipsychotics cause diabetes mellitus? Insights based on receptor-binding profiles, humoral factors and transporter proteins. Eur Psychiatry. 2009;24:164–70.
61. Hammerman A, Dreiher J, Klang SH, Munitz H, Cohen AD, Goldfracht M. Antipsychotics and diabetes: an age-related association. Ann Pharmacother. 2008;42:1316–22.
62. Johnson DE, Nedza FM, Spracklin DK, Ward KM, Schmidt AW, Iredale PA, Godek DM, Rollema H. The role of muscarinic receptor antagonism in antipsychotic-induced hippocampal acetylcholine release. Eur J Pharmacol. 2005;506:209–19.
63. Silvestre JS, Prous J. Research on adverse drug events. I. Muscarinic M3 receptor binding affinity could predict the risk of antipsychotics to induce type 2 diabetes. Methods Find Exp Clin Pharmacol. 2005;27:289–304.
64. Simon V, van Winkel R, De Hert M. Are weight gain and metabolic side effects of atypical antipsychotics dose dependent? A literature review. J Clin Psychiatry. 2009;70:1041–50.

Psychiatric and Neurological Effects of Cardiovascular Drugs

45

Stefano Govoni

Contents

Abstract

This chapter deals with the psychiatric effects of cardiovascular drugs. It is a rather intriguing topic with two distinct aspects. A psychiatric effect of a cardiovascular treatment may represent an unwanted side effect, for example, depression associated with an antihypertensive drug, which can be predicted and avoided by using the appropriate agent. These effects are more frequent with molecules acting on the adrenergic transmission. However this aspect does not reflect the whole picture of the psychiatric effects of cardiovascular treatments. Psychiatric and cardiovascular illnesses are frequently strictly intermingled, and some psychiatric symptoms due to cardiovascular

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*,
https://doi.org/10.1007/978-3-030-28008-6_46

events (e.g., anxiety associated with atrial fibrillation) may be corrected by the combined use of the appropriate cardiovascular and, upon careful assessment, psychiatric drugs. Finally, there are some psychiatric conditions that may take advantage of cardiovascular drugs purposely targeted, in this case, to the psychiatric symptoms (e.g., beta-blockers in post-traumatic stress disorder).

These actions are not surprising since many of the cardiovascular drugs do recognize targets present both at the level of the cardiovascular apparatus and in the brain. Moreover, several cardiovascular drugs may cross the blood-brain barrier and reach central nervous system (CNS) targets. Finally, it should be underscored that several cardiovascular therapies are lifelong standing, thus increasing the importance of well understanding the full spectrum of the pharmacological activities of the drugs prescribed and also acknowledging that as the patient ages, his/her sensibility to the CNS effects of the decided therapy may change. The chapter refers to a well-established literature for general concepts and to current papers for applied examples.

Keywords

Anxiety · Adrenergic blockers · Clonidine · Dementia · Depression · Drug repurposing · Psychiatric side effects · PTSD · Reserpine · Statins

Introduction

It should be stressed that it is not easy to collect literature data on the psychiatric adverse effects of cardiovascular drugs since papers are rather focused on the cardiovascular effects of psychiatric drugs and of substances of abuse.

Indeed, the literature is dominated by the concerns on the cardiovascular side effects of psychotropic drugs, in particular on the QT effects of several widely used compounds [1], which are undoubtedly important, but not necessarily the most clinically relevant cardiovascular risk associated with CNS-active drugs. Simply, QT effects are easy to predict, to prevent, and to detect. Less frequent are the concerns on the reverse situations, that is, the psychiatric side effects of cardiovascular drugs which may be more subtle and difficult to detect.

It is worth to make some general considerations. In particular, a brief overview on the psychiatric side effect of cardiovascular drugs should (a) acknowledge the various mechanisms by which a cardiovascular drug (and illness) may affect psychic conditions; (b) take into account also the reverse condition, that is, to appreciate the mechanisms by which a psychotropic drug may affect cardiovascular function; (c) to be very careful to the potential interactions between cardiovascular and psychotropic drugs, at the level of both pharmacokinetics and pharmacodynamics, not forgetting pharmacogenetics; (d) try to understand whether the side effect profile of cardiovascular drugs has the same characteristics in psychiatric or neurologic patients as in otherwise "normal" patients; and (e) to recognize the importance of assessing the potential psychiatric consequences of cardiovascular illnesses themselves and of their treatments. Several of these items are discussed also in other chapters of this publication. The present chapter will be mainly focused on the potential adverse or favorable psychiatric effects of established cardiovascular drugs.

The complex relationship between cardiovascular disease, treatment, and mental status is well represented by a case described in *The New England Journal of Medicine* [2] concerning a 62-year-old man with atrial fibrillation evaluated in a psychiatric clinic because of depression and anxiety. It is a complex case. The patient had a history (15 years before the described episode) of depression and anxiety treated for some 13 years, and then treatments were discontinued. The patient after a relatively brief (1 year) period of remission presented intermittently cardiac and psychiatric symptoms for a year and half including anxiety, accelerated heart, palpitations, restlessness, and fatigue. These symptoms do not allow to discriminate between a cardiac or psychiatric diagnosis. After a thorough medical

screening, the final diagnosis was symptomatic atrial fibrillation with associated anxiety. Accurate choices were made in order to select the drugs to be used to treat the cardiovascular component not unfavorably affecting the psychiatric profile. The physicians followed the principle that the border between medical and psychiatric causes is increasingly eroded when the reciprocal brain-heart interactions are considered and when the possibility that drugs affecting one compartment may also act upon the other one and interact. As an example, patients in which atrial fibrillation and anxiety coexist may benefit more from a treatment based on beta-blockers rather than calcium antagonists because the antiadrenergic effects of beta-blockers may limit anxiety.

From a general point of view, it should be mentioned that most cardiovascular drugs (as well as, on the other hand, most of the CNS-active drugs) are prescribed for long periods, sometimes for a lifelong therapy. This is true, for example, for beta-blockers, antihypertensive associations, statins, and antiplatelet agents. Accordingly, the risk for psychiatric side effects should be analyzed with great attention since, due to the very long times of treatment, the onset of psychiatric symptoms may well be a comorbidity rather than an adverse effect of the treatment.

An important paper published in a journal focused on medical informatics and decision-making [3] has studied the pharmacological risk factors associated with hospital readmission rates of a cohort of 1275 psychiatric patients. Using this powerful new approach to gain information on real-world drug use and to make research also on new biological hypotheses, the authors have studied the pharmacological factors influencing readmission following an index psychiatric admission. The data were based on the analysis of prescriptions from electronic medical records from the Mount Sinai Data Warehouse (NY, USA). In addition to the pharmacological data, also comorbidities and shared genetic architecture were examined. Pharmacotherapy data on both primary side effects and secondary side effects (drug-drug interaction induced) associated with readmission risk were studied. The authors identified 28 drugs associated with the readmission risk among which, somewhat surprisingly, pravastatin had the highest risk (OR = 13.1); the readmitted patients also presented an enrichment of side effects both primary and secondary. Another observation stemming out of the analysis is that psychiatric conditions and cardiovascular disease are comorbid and present shared genes (e.g., cardiomyopathy and anxiety disorder).

In several cases, readmission was due to the fact that several psychiatric drugs have known cardiovascular and metabolic effects, among which prominent are antipsychotics, but also the reverse is true, i.e., drugs used in cardiovascular therapy may have direct effects on brain function if they cross the blood-brain barrier (BBB). Obvious examples are the depressive effects and suicidal intention associated with several antihypertensive drugs, but also the less obvious actions of some antithrombotic such as clopidogrel on neuronal plasticity (see below). Psychiatric patients may be more susceptible to such actions of cardiovascular drugs. The data strongly support the concept that medicaments have pleiotropic effects hitting several biological targets which may participate both in their therapeutic action and in their side effect profile. As an example, 5-HT receptors are a common target of laxatives, psycholeptics, antiemetics, and beta-blockers suggesting the possibility of superimposed side effects while used for their principal purpose.

Mechanisms Through Which Cardiovascular Drugs May Affect Psychic Functions

Upon a request of a general and broadly inclusive classification, a pharmacologist will categorize most of the presently available cardiovascular drugs as agents characterized by multiple and coexisting activities on receptors, enzymes, membranes, and ionic channels. Many of them will reach not only peripheral targets but also central synapses. Many of them may not have sufficient selectivity for peripheral versus CNS molecular targets at therapeutically active concentrations. Therefore, the possibility of affecting psychiatric functions is plausible.

Also, the reverse is true. In fact, psychotropic drugs are characterized by multiple and coexisting activities on receptors, neurotransmitter transporters, and ionic channels and by a large volume of distribution being, in general, small lipophilic molecules. As such it is obvious to predict that many of them will reach not only the brain but also peripheral synapses and cells acting upon molecular targets that in most cases may not present a sufficient brain-periphery selectivity or for which the compound has not sufficient selectivity. Just two examples are α_2-adrenergic receptors and nicotine. The α_2-adrenergic receptors in the brain and in the periphery are indistinguishable, and drugs such as clonidine may act on both central and peripheral targets as receptor agonists simultaneously decreasing the sympathetic output (a CNS-mediated action decreasing blood pressure as intended) and interfering with other CNS noradrenergic synapses increasing the risk of depression. In the periphery the α_2-agonist effect of clonidine will rather produce temporarily an arteriolar smooth muscle direct contraction, followed by relaxation when the presynaptic action at both peripheral and central noradrenergic terminals prevails.

Nicotinic cholinergic receptors do present tissue-specific differences, but nicotine may act on all of them producing both psychic symptoms (stimulation and alertness) and cardiovascular and muscle effects acting, respectively, on cholinergic ganglion cells and at the level of the neuromuscular junction.

The picture of the psychiatric side effects of cardiovascular drugs needs some additional "a priori" reasoning based on the mode of action of the most diffuse cardiovascular therapeutic agents, used in millions of people and for long-term, sometimes lifelong, treatments. Historically, the main physiological targets of cardiovascular drugs since the 1960s are relatively few: the control of blood pressure, the control of heart rate and, later on, the control of cholesterol. Let us forget for the moment the more recent advances in cardiovascular pharmacology, since the vast majority of the patients are treated with well-known, frequently over 40 years old, drugs acting on the abovementioned targets. In the case of hypertension, the control is exerted using drugs active on (a) adrenergic transmission (both alpha and beta receptor blockers or, in the past, amine-depleting compounds (such as reserpine); (b) plasma volume (diuretics); (c) vascular smooth muscle relaxants such as calcium channel blockers; and (d) agents acting upon the renin-angiotensin system, either diminishing the production of angiotensin II or blocking its receptors. The control of heart rate is exerted with compounds active on sodium, potassium, and calcium ion channels and on beta-adrenergic stimulus. Cholesterol control has several players, among which the most prominent drugs are statins. From a general pharmacological point of view, effects at brain level are expected in the case of agents active on adrenergic transmission and on ion channels. On the other hand, also the other drugs may have complex pharmacological profiles that may include actions on the nervous system. For example, both statins and angiotensin receptor blockers may have actions upon inflammatory processes involving the production of cytokines which may act as signal molecules for the brain (see below). Finally, as further detailed, activities at brain level of cardiovascular drugs are not necessarily negative, some may be beneficial for the patient and even considered for a development of independent indications.

Antihypertensive Drugs Acting upon Aminergic Transmission: The Cases of Reserpine, Clonidine, Alpha Methyldopa, and Adrenergic Receptor Blockers

The negative psychiatric effects of cardiovascular drugs are dominated by the adrenergic blockers that may induce depression in the treated patients. The historical and emblematic example is provided by reserpine. This drug, which is now obsolete, has been used both in psychiatry in manic patients and as an antihypertensive treatment, associated with a diuretic. The main mode of action of reserpine (for a reappraisal review, see [4]) is to inhibit the vesicular transport that recovers the reuptaken neurotransmitter (noradrenaline, dopamine, or serotonin) into the synaptic vesicles protecting it from cytoplasmic

degradation, mainly by monoamine oxidase (MAO). When the transport mechanism is blocked by reserpine as long as the nerve terminal fires, the transmitter is released, recovered in the terminal, and degraded until aminergic terminals are depleted. This occurs both in the periphery and within the CNS blunting noradrenergic, dopaminergic, and serotoninergic transmission. Both in the periphery and within the CNS, the impairment of noradrenergic transmission contributes to the antihypertensive action of reserpine being somewhat equivalent to a sympathetic denervation. At brain level, the aminergic impairment mimics the proposed neurotransmitter defects associated with depression, i.e., noradrenergic and serotoninergic dysfunction. The effects on dopamine in addition of being related to anhedonia may also produce parkinsonian side effects. Notably, reserpine treatment has been used to produce animal models (both in rodents and in primates) of depressive illness. Accordingly, the clinical use of reserpine in cardiovascular patients has been associated with depression as side effect [5], although the depressive symptoms associated with use of reserpine have been questioned because they may not meet formal criteria for major depression challenging the more common theory [5, 6].

Also, other antihypertensive drugs affecting adrenergic transmission do present the risk of depression. Among them clonidine and alpha methyldopa share the mechanism of being agonists at alpha 2-adrenergic receptors [5]. Alpha 2 receptors are present both in the brain and in the periphery at both presynaptic and postsynaptic level. The agonism at presynaptic level exerts an inhibition of noradrenaline (not exclusively) release, therefore decreasing synaptic terminal activity. Applied to the cardiovascular effects, it is proposed that the central action of both drugs prevail decreasing the sympathetic outflow; indeed both drugs have been classified as central-acting antihypertensives. The blunting of noradrenergic nerve terminal activity within the CNS has been associated with depressive-like symptoms. Notably mianserin, an alpha 2 receptor antagonist, is used as an antidepressant drug [7].

Recently, Nayak and Nachane [8] have shown that the use of alpha methyldopa to treat hypertension in pregnancy is associated with postpartum depression. It is a small study (only 100 consecutive women attending the immunization outpatient department were recruited) that needs repetition working on large numbers (perhaps using registry data). However, the data are intriguing; near 78% of the women treated with alpha methyldopa developed postpartum depression, with an OR for the increased risk of depression over six times that observed in women not treated with this drug. Fortunately, the increased depression risk was not associated with increased suicidal risk. Again, the study is too small to draw firm conclusions (only 9 out of the 100 recruited women were treated with alpha methyldopa, 7 of which developed postpartum depression; moreover, the authors do not specify the treatments received by the whole group and misinterpret the mechanism of action of alpha methyldopa).

As far as depression outcome in depressed patients with coronary artery disease (CAD), Vitinius et al. [9] described in 570 patients with CAD and a score at the Hospital Anxiety and Depression Scale indicating the presence of depression a variety of factors affecting either favorably or negatively the depression outcome. Among the conditions associated with an adverse effect on the depression outcome, there was the use of various classes of drugs among which are beta-blockers. Indeed, the study, while contributing to the identification of various somatic and sociodemographic predictors of depression in patients with CAD, identified several drug treatments, including cardiovascular drugs, worsening depression. The exact causal relationships and mechanisms involved have to be further explored. In the case of beta-blockers, the increased risk of depression compared to other cardiovascular drugs is consistent with literature data published since the late 1970s (see also [5, 10]).

Adrenergic Cardiovascular Agents Potentially Useful in Psychiatry

The effects of some cardiovascular drugs, in particular the alpha 1 receptor blocker prazosin, and various beta (beta-1) blockers have been studied for potential beneficial effects in post-traumatic stress disorder (PTSD) and in panic disorders.

Traumatic memories are taught to be linked to a strong adrenergic response due to the trauma experienced by the subject. Accordingly, beta-blockers have been studied as potential treatments for PTSD (with questionable results, see [11–13]). In a controlled randomized trial, Brunet et al. [14] assessed the efficacy of trauma memory reactivation while treating the patients with propranolol. In brief, the patients with a long-standing PTSD were treated with propranolol one and a half hour before a session of memory reactivation, once a week for 6 weeks. The treatment with propranolol was efficacious in reducing the symptoms of BPSD as evaluated both by the clinician and by the patient. The size of the study is small, but the results are consistent with the reconsolidation theory and suggest the importance of further exploring various trauma populations and long-term effects.

Interestingly enough, Meli et al. [15] have studied the association of administration of a beta-blocker during the evaluation for an acute coronary syndrome in the emergency room and the symptoms of PTSD 1 month later. The beta-blocker was administered for cardiologic reasons. The effect was small but significant in reducing PTSD symptoms suggesting that beta-blockade during a period relevant for fear consolidation may have later on beneficial effects on the psychological health of the patient.

One beta-blocker has been studied also in relation to panic disorders; in particular Bernik et al. [16] evaluated the effect of a single dose of pindolol on acute anxiety caused by the experimental administration of flumazenil, the benzodiazepine receptor antagonist, in panic disorder patients. It should be underscored that (a) pindolol had no significant effect and (b) pindolol has a complex mode of action and in addition of being a beta-blocker is a high-affinity 5-HT_{1A} receptor blocker and exactly for this reason it was used by the authors. Indeed, drugs acutely enhancing serotoninergic transmission may decrease panic attacks and positively cooperate with SSRI (selective serotonin reuptake inhibitors) antidepressants. In turn somatodendritic 5-HT_{1A} receptors inhibit the firing of serotoninergic neurons; hence their blockade will favor serotoninergic activity. In spite of the failure of the reported study, potential central serotoninergic activity of pindolol when used as a cardiovascular drug may be taken into consideration as possible source of psychiatric effects.

Furthermore, the alpha blocker prazosin has been studied in relation to PTSD as reported by Raskind et al. [17]. The rationale behind the use of the adrenergic alpha 1 receptor blocker is similar to the one considered for beta antagonist, i.e., that PTSD is based on the coincidence of a strong adrenergic activation and emotional activation by a stressor producing traumatic memories which are based on a catecholaminergic trace and altered responsiveness to noradrenergic signaling [18]. In addition, there are literature data showing that prazosin may be effective in attenuating nightmares associated with PTSD [19]. The study published by Raskind et al. [17] recruited some 300 participants from 13 departments of veteran's affair medical centers. The recruited patients were equally assigned to placebo or prazosin for 26 weeks. Prazosin was administered in escalating divided doses up to a maximum of 12 and 20 mg/day, respectively, for women and men. However, the results did not support an effect of the treatment in attenuating the symptoms; indeed prazosin did not alleviate distressing dreams or improve sleep quality. The reasons for the failure can be several and induce caution in the interpretation of the available literature when based on sporadic nonconfirmed observations in few patients dealing with advantageous psychiatric effects of a cardiovascular therapy. On the other hand, further studies including a more refined characterization of autonomic nervous system activity are needed to determine whether there might be subgroups of patients with PTSD who can benefit from prazosin. At the doses used, prazosin daily administration had an effect on blood pressure that was actually considered a side effect in these patients, which, however, was small.

Prazosin has been investigated also in relation to alcohol use disorder [20], which is an interesting application since preclinical data suggest the involvement of the noradrenergic transmission in alcohol reinforcement, although the noradrenergic

pathways have not been yet targeted in alcohol abuse disorders. The quoted authors treated 92 subjects with alcohol use disorder without PTSD which were randomly assigned to receive placebo or prazosin. The treatment was titrated to a target dosing schedule of 16 mg/day in divided doses (morning, afternoon, bedtime). The daily alcohol consumption was registered. The number of drinks per day, the number of heavy drinking days, and the probability of heavy drinking were reduced in the prazosin-treated group which reported more drowsiness and edema compared to the placebo group. Due to the very limited number of efficacious pharmacological treatments available for this disorder, this observation deserves further investigation.

Nitro Derivatives and Schizophrenia

There is a puzzling relationship between some vasodilator compounds acting through the nitric oxide (NO) production and schizophrenia. In particular the prodrug sodium nitroprusside, which has been used in clinical practice as an arterial and venous vasodilator for 40 years in acute hemodynamic applications, has been administered in a small study [21] to 20 schizophrenic patients randomly assigned to receive either sodium nitroprusside or placebo. At the doses used (infusion of 0.5 μg/kg/min for 4 h), sodium nitroprusside did not alter systolic blood pressure, diastolic blood pressure, blood oxygen saturation level, and heart rate. These observations are in line with the fact that the dose used was the minimum one required to lower blood pressure in hypertensive patients, while normotensive individuals require higher doses to respond to the drug. The authors [21] observed a safe, rapid, and long-lasting improvement of positive, negative, anxiety, and depressive symptoms in patients with schizophrenia after a single intravenous injection of sodium nitroprusside. The results are in line with preclinical data from the same group and may be explained by the observation that defects in the glutamate-nitric oxide-cyclic guanosine monophosphate (cGMP) network have been described in individuals with schizophrenia. Even if the results have not been confirmed by others [22], possibly because of methodological differences in the experimental settings, they are intriguing in delineating a possible mechanism through which a category of cardiovascular drug may exert CNS actions.

Revisiting and Repurposing Calcium Antagonists

A peculiar aspect is represented by calcium antagonists. This is a class of cardiovascular drugs including several molecules belonging to at least three different chemical reference structures, i.e., dihydropyridines (prototype nifedipine), phenylalkyl amines (prototype verapamil), and benzothiazepines (prototype diltiazem). The various agents have individually both common and specific uses. All of them are antihypertensive, some of them (e.g., verapamil) are also used as class IV antiarrhythmics, and others can be prescribed as coronary-dilating agents in angina (nifedipine and verapamil). Interestingly enough, when they were first introduced in cardiovascular pharmacology, some potential activities at the level of the CNS were also proposed, mainly as neuroprotectants; in particular a dihydropyridine, nimodipine, was developed for vascular dementia and cerebral vasospasm. However, their use in neurological/psychiatric conditions was never fully developed. Moreover, one of them, flunarizine, originally prescribed for ameliorating cerebral circulation exhibited problems of depression and parkinsonism [23], which was due to a peculiar pharmacological profile of this compound, being also an antagonist of dopamine D2 receptors [24], a property not shared by other calcium antagonists. Indeed, iatrogenic depression was also described in elderly patients presenting hypertension and coronary disease treated with atenolol but not in those receiving verapamil-sustained-release treatment [25]. In particular, the authors propose that given a choice between these equally effective high blood pressure treatment strategies, it may be prudent to use a verapamil-based strategy if there is the risk of the occurrence of a mood-related side effect of the beta-blocker.

Recently the studies on the potential usefulness of calcium antagonist as CNS-active drugs have been revitalized [26] in appreciation of the fact that voltage-dependent calcium channels of various types, including the L channels targeted by calcium antagonists, are present in the brain. In particular, data are reported showing potential uses of isradipine for Parkinson's disease and dependency, nimodipine for febrile seizures, and cilnidipine for pain and tremor, all the three having as main indication hypertension. Besides the mentioned molecules, the knowledge has increased about the activity of several other molecules (including some antiepileptics) on the various calcium channel subtypes. Therefore, to be more precise, the repurposing of already marketed drugs able to interact with the various calcium channels concerns molecules including, but not being limited to, calcium antagonists used in cardiovascular diseases. Within this context also the use of calcium antagonists in dementias proposed more than 20 years ago has been re-evaluated in a trial on nilvadipine on 511 patients affected by mild-moderate Alzheimer's disease [27]. However, as in the past, the treatment didn't produce benefits in the patients. The attention to the repurposing of calcium antagonists is underscored by an ongoing trial on the use of nicardipine in young adults with mood instability. Notably the study also considers the effect of the CACNA1C polymorphism related to the gene encoding the alpha 1C subunit of the L-type voltage-gated calcium channel [28].

Cardiovascular Drugs Secondarily Acting on the Neuroinflammatory Component: The Case of Statins

As already stated, and shown, not always the potential psychiatric effects of cardiovascular drugs are considered negative. In several occasions their use has been associated with potential advantages for the patient. From a general point of view, beyond specific mechanisms, it should be reminded that alterations in cerebral blood flow may participate in the expression of brain pathologies and that a preserved good cerebrovascular function is important. Within this context all the measures that contribute to sustain vascular functions (including both drugs and lifestyle) may exert beneficial effects on brain functions (dementias are a particularly relevant topic). On the other hand, more specific mechanisms have been also considered in specific cases in the process of drug repurposing, so far with no particular success. Within this context statins have been studied in relation to depression and dementias. The treatments with statins, when lifestyle corrections are insufficient to control effectively cholesterol levels, or when the cardiovascular risk is high, are usually very long. On the other hand, it has been convincingly shown that long-term statin treatment may reduce cardiovascular mortality in at-risk patients. Statins are potent drugs that, in addition to inhibit cholesterol synthesis, have other not yet fully described mechanisms of action among which a potent anti-inflammatory activity, not forgetting about the inflammatory hypothesis of atherosclerosis [29]. Interestingly enough, inflammatory processes have been claimed to be at the basis of several neuropsychiatric diseases, including, but not limited to, Alzheimer's disease, Parkinson's disease, and depression (see, e.g. [30],). In particular, in the case of depression, it has been proposed that the combined treatment of a statin with an SSRI antidepressant is superior to the antidepressant alone. On the other hand, small trials and observational studies provided contrasting results with both decreased and increased risk for depression in statin users. Recently, a Danish group [31] has explored the relationship between statin and depression by examining in a large study the data on almost 388,000 patients equally divided between statin users and statin nonusers over a period of more than 15 years, using a nationwide register-based cohort study. The study is based on a sophisticated statistical analysis and the propensity score, correcting and considering the possible confounders. The results indicate that statins reduced, as expected, cardiovascular mortality and mortality for all the causes and that statin users and nonusers are equally likely to develop depression. No additive beneficial effects on depression of statins and antidepressants were described.

Statins have also been studied for their potential beneficial effects in patients affected by Alzheimer's disease (AD), based on the relationship between cholesterol metabolism and beta-amyloid accumulation in the brain of AD patients. However, in the case of their use in dementia, the final conclusions are negative [32].

Another example related to the use of a cardiovascular drug against dementia based on its activity on neuroinflammation is represented by losartan. From a mechanistic point of view, systemic inflammation launches through several route signals to the brain that may trigger cytokine derangement at brain level. Angiotensin II participates in the inflammation process by actions on angiotensin 1 receptors. Salmani et al. [33] in a preclinical study have shown that the pretreatment and treatment with losartan for 24 days prevented in the rat the behavioral and brain effects of neuroinflammation induced by a peripheral injection of lipopolysaccharide. The study has obvious limitations and still documents additional mechanisms that may contribute to the multifarious effects of angiotensin II receptor blockers.

Based on a similar reasoning about the role of neuroinflammation in depression and also considering the involvement of phosphodiesterase (PDE) activity, El-Haggar et al. [34] have conducted a small proof-of-concept randomized double-blind placebo-controlled trial on the effect of pentoxifylline (PTX; 400 mg b.i.d. for 3 months) in addition to escitalopram (20 mg/day) administered to patients affected by major depressive disorder (MDD). PTX is usually prescribed for peripheral arterial disease. The authors observed a greater improvement in Hamilton Rating Scale for Depression in PTX-treated patients compared to the control group. As a biological correlate, the serum levels of inflammation markers (TNF-α, IL-6, IL-10, 8-OHdG) showed a statistically significant reduction, while the neurotrophin BDNF (brain-derived neurotrophic factor) displayed a significant increase. The authors conclude that this drug may represent a promising adjunct to the antidepressants. The published study is small (totaling 80 patients divided into two groups of treatment) and needs independent confirmation; on the other hand, it underscores the potential favorable psychiatric effects of this cardiovascular drug, again stressing the importance of the drug-repurposing studies.

Antiplatelet Agents

The antithrombotic clopidogrel deserves a comment even if the data are based so far almost exclusively on preclinical studies. In particular, Sipe et al. [35] in an elegant study on ocular dominance plasticity have demonstrated the importance of P2Y12 purinergic receptors which are selectively expressed in non-activated microglia and participate in modulating microglial activity during early injury responses. The disruption of this receptor activity, as it occurs during the treatment with clopidogrel, abrogates visual cortex plasticity responses to closure of one eye during development. Moreover, it should be noted that P2Y12 receptor has a myriad of subtypes with pharmacologic effects involving adenosine and uridine nucleotides.

By extension it can be proposed that clopidogrel may affect brain's plastic response, an effect to which psychiatric patients may be more sensitive. Indeed, in the previous quoted study by Shameer et al. [3], clopidogrel was one of the 28 drugs associated with rehospitalization. Moreover, a case report [36] in line with post-marketing reports describes a case of clopidogrel-induced auditory and visual hallucinations in an 83-year-old white woman. The dose of clopidogrel was 75 mg daily, and the patient exhibited auditory and visual hallucinations 5 h after starting the medication. Hallucinosis resolved with discontinuation of the drug.

In these cases, alternative antiplatelet drugs not crossing the BBB may be chosen.

Further exploring the field of antiplatelet therapies, the use of low doses of acetylsalicylic acid (ASA, 75–160 mg daily) should be commented. Few years ago, Kern et al. [37] examined the effect of ASA on cognitive function and dementia. It should be mentioned that several studies have investigated the relationship between the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and dementia with contrasting results based on

the tenuous rationale of a NSAID-sensitive neuroinflammatory process participating in the pathogenesis of dementia. In contrast, no study examined the effect of ASA on cognitive function in persons at high cardiovascular risk in spite of the fact that ASA is the most widely prescribed drug to prevent cardiovascular disease. The sample of patients studied by the quoted authors was derived from the Prospective Population Study of Women and from the H70 Birth Cohort Study in Gothenburg, Sweden, and included near 790 women aged 72–90 years. Subjects demented or using warfarin, clopidogrel, or heparin at the baseline were excluded. Over 95% of the participants had a high cardiovascular risk. The primary and secondary outcomes of the study were cognitive decline and dementia incidence in relation to the use of low-dose ASA and cardiovascular risk factors. The results show that low-dose ASA assumption in women with high cardiovascular risk was associated with less cognitive decline at follow-up. The authors comment on a potential neuroprotective effect of the treatment. From my point of view, even considering the multiple mode of action of ASA, and its activity in controlling expression factors involved in neurodegenerative processes, I suggest that the vascular effects of the drug may prevail in assuring a better cerebral circulation in the treated population, rather than claiming direct neuroprotective mechanisms. However, this point can and should be explored by means of further studies.

Dementing Diseases

The following notes are an adjunct to the paragraphs that in the case of calcium antagonists, statins and acetylsalicylic acid have anticipated experiences in demented patients.

The view that sustaining optimal cardiovascular competence may have protective effects against dementia has been intensively explored in the case of antihypertensive treatments. The SPRINT (Systolic Blood Pressure Intervention Trial) MIND investigators published a trial [38] on 9361 hypertensive adults randomized to a systolic blood pressure target of less than 120 mmHg compared with less than 140 mmHg. The primary outcome of the study, i.e., a reduction in the occurrence of dementia, was not reached. However, the results of the trial showed that reducing the blood pressure below 150 mmHg was not associated with increased risk of cerebral hypoperfusion resulting in negative effects on brain function. Indeed, intensive blood pressure control did not result in impaired cognition following a period of treatment over 3 years and a follow-up of over 5 years. In addition, the published results do show that the intensive blood pressure control may have some benefits as indicated by the reduced occurrence of mild cognitive impairment (MCI) even if the progression of MCI to dementia is not certain and reversion and stability of the defect are possible. The question on how much to lower blood pressure in the elderly is still on the table, but the concept that controlling it will reduce the risk of cognitive impairment is consistent across the various studies.

A Note on Cardiovascular Supplements and Integrators

A comment on the use of supplementation in cardiovascular pharmacology and their psychiatric aspects is timely. It is a growing field both commercially and scientifically. More and more patients do use integrators either prescribed or self-prescribed. The basic attitude is that integrators do not harm and may be beneficial, which is incorrect. New researches in the last few years do document precise mechanism of action of active compounds present in several integrators. Some of these modes of action do involve recognized multiple molecular targets including epigenetic modifications [39]. The number of involved substances is enormous and there are no systematic data. As a general comment, I would suggest that if there is a proven beneficial cardiovascular effect, cardiovascular protection may positively reverberate on cerebrovascular competence and be usefully framed within therapeutic interventions in the aged patient aimed also at preserving CNS functions through the improvement of cerebral circulation. Also, in the case of these

Table 1 Psychiatric/neurologic effects of cardiovascular drugs, selected examples

Class and/or mechanism	Vesicular transport inhibitors	Central antihypertensive drugs acting as α_2-receptor agonists	Beta-blockers	α_1-Blockers	Nitrates	Calcium antagonists	Antiplatelet agents	Phosphodiesterase inhibitor
Drug	Reserpine	Clonidine, alpha methyldopa (α-MD)	Various or as specified	Prazosin		Various or as specified	Clopidogrel, ASA as specified	Pentoxifylline
Potentially harmful effects								
	Depression [as reviewed in 5]	Fatigue, sedation, depression [both clonidine and α-MD, as reviewed in 5] Postpartum depression [α-MD; 8]	Depression [5, 9, 10] Depression in elderly patients [atenolol; 25]			Parkinsonism and depression [23]	Auditory and visual hallucinations [clopidogrel, case report; 36]	
Potentially beneficial effects								
	Sedation of agitated patients, one of the original psychiatric uses of reserpine	Attention deficit hyperactivity disorder (ADHD) [clonidine, as reviewed in 5]	Potential treatment of PTSD [questionable results; 11–13] Flumazenil-induced panic attack [pindolol, no effect; 16] Reduction of PTSD symptoms [propranolol; 14]. Reduction of PTSD symptoms associated with acute coronary syndrome [15]	Attenuation of PTSD-associated nightmares [19]. Treatment of PTSD [no effect; 20] Treatment of alcohol use disorder [20].	Treatment of schizophrenia [beneficial (20); no effect (21)]	Cerebrovascular disorders Various calcium antagonists and uses [26] Alzheimer's disease [nilvadipine, no effect; [27] Mood disorders [nicardipine, ongoing evaluation [28]; verapamil as reviewed in [5]	Favorable effects of ASA on cognitive decline [37].	Favorable effect in depressed patients [34]

Note: The potentially useful effects reported are frequently controversial and do represent off-label use and effects examined in drug-repurposing studies. See the text for the detailed references and the review by Huffman et al. [5] for further comments

molecules, it will be important to have a full knowledge of the map of their targets and to be informed on their ability to cross the BBB and to reach the CNS at active concentrations. Indeed, preclinical data, frequently in vitro, which are insufficient to make a decision, do document the potential for CNS activities. Most of these preparations are simply introduced on the market without a clinical investigation making really difficult to provide a sound scientifically grounded clinical advice beyond the cautionary: further studies are needed.

Take-Home Messages

What are the practical consequences and the take-home messages stemming out from the present chapter and after reading Table 1 which summarizes the adverse and the favorable psychiatric effects of several cardiovascular drugs as detailed in the text? To be conservative it can be affirmed that:

(a) Convincingly several cardiovascular drugs have mechanisms of action that may hit targets in the brain as well as at cardiovascular levels (e.g., aminergic receptors, ion channels), provided the crossing of the blood-brain barrier.
(b) Some of these actions are at the basis of adverse psychiatric effects (e.g., depression).
(c) The full pharmacological profile of the chosen cardiovascular drugs should be carefully evaluated and the possibility of psychiatric side effects considered.
(d) In psychiatric and elderly patients, the susceptibility to psychiatric adverse effects may be greater; in particular a comorbid psychiatric condition may require a careful choice of the cardiovascular drug avoiding molecules that can aggravate the psychiatric status.
(e) Favorable psychiatric effects of cardiovascular drugs can be explored and fruitfully exploited, but ad hoc well-designed randomized placebo-controlled trials are needed.
(f) The field may benefit of the new approaches based on the analysis of prescription data from electronic medical records of a large number of patients.

References

1. Brouillette J, Nattel S. A practical approach to avoiding cardiovascular adverse effects of psychoactive medications. Can J Cardiol. 2017;33(12):1577–86.
2. Chen JA, Ptaszek LM, Celano CM, Beach SR. Case 9-2019: a 62-year-old man with atrial fibrillation, depression, and worsening anxiety. N Engl J Med. 2019;380(12):1167–74.
3. Shameer K, Perez-Rodriguez MM, Bachar R, Li L, Johnson A, Johnson KW, Dudley JT. Pharmacological risk factors associated with hospital readmission rates in a psychiatric cohort identified using prescriptome data mining. BMC Med Inform Decis Mak. 2018;18(S3):1–11. https://doi.org/10.1186/s12911-018-0653-3.
4. Slim HB, Black HR, Thompson PD. Older blood pressure medications-do they still have a place? Am J Cardiol. 2011;108(2):308–16.
5. Huffman JC, Stern TA. Neuropsychiatric consequences of cardiovascular medications. Dialogues Clin Neurosci. 2007;9(1):29–45.
6. Baumeister AA, Hawkins MF, Uzelac SM. The myth of reserpine-induced depression: role in the historical development of the monoamine hypothesis. J Hist Neurosci. 2003;12(2):207–20.
7. Tremblay P, Blier P. Catecholaminergic strategies for the treatment of major depression. Curr Drug Targets. 2006;7(2):149–58.
8. Nayak AS, Nachane HB. Risk analysis of suicidal ideations and postpartum depression with antenatal alpha methyldopa use. Asian J Psychiatr. 2018;38:42–4.
9. Vitinius F, Escherich S, Deter HC, Hellmich M, Jünger J, Petrowski K, et al. Somatic and sociodemographic predictors of depression outcome among depressed patients with coronary artery disease – a secondary analysis of the SPIRR-CAD study. BMC Psychiatry. 2019;19(1):57.
10. Boal AH, Smith DJ, McCallum L, Muir S, Touyz RM, Dominiczak AF, et al. Monotherapy with major antihypertensive drug classes and risk of hospital admissions for mood disorders. Hypertension. 2016;68:1132–8.
11. Amos T, Stein DJ, Ipser JC. Pharmacological interventions for preventing post-traumatic stress disorder (PTSD). Cochrane Database Syst Rev. 2014;7:CD006239.

12. Giustino TF, Fitzgerald PJ, Maren S. Revisiting propranolol and PTSD: memory erasure or extinction enhancement? Neurobiol Learn Mem. 2016;130:26–33.
13. Sijbrandij M, Kleiboer A, Bisson JI, Barbui C, Cuijpers P. Pharmacological prevention of post-traumatic stress disorder and acute stress disorder: a systematic review and meta-analysis. Lancet Psychiatry. 2015;2(5):413–21.
14. Brunet A, Saumier D, Liu A, Streiner DL, Tremblay J, Pitman RK. Reduction of PTSD symptoms with pre-reactivation propranolol therapy: a randomized controlled trial. Am J Psychiatry. 2018;175(5):427–33.
15. Meli L, Chang BP, Shimbo D, Swan BW, Edmondson D, Sumner JA. Beta blocker administration during emergency department evaluation for acute coronary syndrome is associated with lower post-traumatic stress symptoms 1-month later. J Trauma Stress. 2017;30(3):313–7.
16. Bernik M, Ramos RT, Hetem LAB, Graeff F. Effect of single doses of pindolol and d-fenfluramine on flumazenil-induced anxiety in panic disorder patients. Behav Brain Res. 2019;357–358:82–7.
17. Raskind MA, Peskind ER, Chow B, Harris C, Davis-Karim A, Holmes HA, et al. Trial of prazosin for post-traumatic stress disorder in military veterans. N Engl J Med. 2018;378(6):507–17.
18. Hendrickson RC, Raskind MA, Millard SP, Sikkema C, Terry GE, Pagulayan KF, Li G, Peskind ER. Evidence for altered brain reactivity to norepinephrine in veterans with a history of traumatic stress. Neurobiol Stress. 2018;8:103–11.
19. Raskind MA, Peskind ER. Prazosin for post-traumatic stress disorder. N Engl J Med. 2018;378(17):1649–50.
20. Simpson TL, Saxon AJ, Stappenbeck C, Malte CA, Lyons R, Tell D, Millard SP, Raskind M. Double-blind randomized clinical trial of prazosin for alcohol use disorder. Am J Psychiatry. 2018;175(12):1216–24.
21. Hallak JE, Maia-de-Oliveira JP, Abrao J, Evora PR, Zuardi AW, Crippa JA, Belmonte-de-Abreu P, Baker GB, Dursun SM. Rapid improvement of acute schizophrenia symptoms after intravenous sodium nitroprusside: a randomized, double-blind, placebo-controlled trial. JAMA Psychiat. 2013;70(7):668–76.
22. Stone JM, Morrison PD, Koychev I, Gao F, Reilly TJ, Kolanko M, Mohammadinasab A, Kapur S, McGuire PK. The effect of sodium nitroprusside on psychotic symptoms and spatial working memory in patients with schizophrenia: a randomized, double-blind, placebo-controlled trial. Psychol Med. 2016;46(16):3443–50.
23. Chouza C, Scaramelli A, Caamaño JL, De Medina O, Aljanati R, Romero S. Parkinsonism, tardive dyskinesia, akathisia, and depression induced by flunarizine. Lancet. 1986;1(8493):1303–4.
24. Govoni S, Di Giovine S, Moresco RM, Battaini F, Trabucchi M. Effect of chronic calcium antagonist treatment on dopamine recognition sites in rat striatum. Neurosci Lett. 1988;87(1-2):173–7.
25. Wilson DL, Ried LD. Identifying iatrogenic depression using confirmatory factor analysis of the Center for Epidemiologic Studies Depression Scale in patients prescribed a verapamil-sustained-release-led or atenolol-led hypertension treatment strategy. Res Social Adm Pharm. 2012;8(4):309–20.
26. Zamponi GW. Targeting voltage-gated calcium channels in neurological and psychiatric diseases. Nat Rev Drug Discov. 2016;15(1):19–34.
27. Lawlor B, Segurado R, Kennelly S, Olde Rikkert MGM, Howard R, et al. Nilvadipine in mild to moderate Alzheimer disease: a randomised controlled trial. PLoS Med. 2018;15(9):e1002660.
28. Atkinson LZ, Colbourne L, Smith A, Harmer CH, Nobre AC, Rendell J, et al. The Oxford study of calcium channel antagonism, cognition, mood instability and sleep (OxCaMS): study protocol for a randomised controlled, experimental medicine study. Trials. 2019;20(1):120.
29. Diamantis E, Kyriakos G, Quiles-Sanchez LV, Farmaki P, Troupis T. The anti-inflammatory effects of statins on coronary artery disease: an updated review of the literature. Curr Cardiol Rev. 2017;13(3):209–16.
30. Zuzarte P, Duong A, Figueira ML, Costa-Vitali A, Scola G. Current therapeutic approaches for targeting inflammation in depression and cardiovascular disease. Curr Drug Metab. 2018;19(8):674–87.
31. Köhler-Forsberg O, Gasse C, Petersen L, Nierenberg AA, Mors O, Østergaard SD. Statin treatment and the risk of depression. J Affect Disord. 2019;246:706–15.
32. McGuinness B, Craig D, Bullock R, Passmore P. Statins for the prevention of dementia. Cochrane Database Syst Rev. 2016;1:CD003160.
33. Salmani H, Hosseini M, Beheshti F, Baghcheghi Y, Sadeghnia HR, Soukhtanloo M, Khazaei M. Angiotensin receptor blocker, losartan ameliorates neuroinflammation and behavioral consequences of lipopolysaccharide injection. Life Sci. 2018;203:161–70.
34. El-Haggar SM, Eissa MA, Mostafa TM, El-Attar KS, Abdallah MS. The phosphodiesterase inhibitor Pentoxifylline as a novel adjunct to antidepressants in major depressive disorder patients: a proof-of-concept, randomized, double-blind, placebo-controlled trial. Psychother Psychosom. 2018;87(6):331–9.
35. Sipe GO, Lowery RL, Tremblay M-È, Kelly EA, Lamantia CE, Majewska AK. Microglial P2Y12 is necessary for synaptic plasticity in mouse visual cortex. Nat Commun. 2016;7:10905.
36. Osuagwu FC, Parashar S, Amalraj B, Tinklepaugh M, Dillon J, Bradley RH. Clopidogrel-induced auditory and visual hallucinations. Prim Care Companion CNS Disord. 2016;18(3). https://doi.org/10.4088/PCC.15l01894

37. Kern S, Skoog I, Ostling S, Kern J, Börjesson-Hanson A. Does low-dose acetylsalicylic acid prevent cognitive decline in women with high cardiovascular risk? A 5-year follow-up of a non-demented population-based cohort of Swedish elderly women. BMJ Open. 2012;2 (5):pii: e001288.
38. Williamson JD, The SPRINT-MIND Investigators for the SPRINT Research Group, et al. Effect of intensive vs standard Blood pressure control on probable dementia. A randomized clinical trial. JAMA. 2019;321:553–61.
39. Ferguson JF, Allayee H, Gerszten RE, Ideraabdullah F, Kris-Etherton PM, Ordovás JM, et al. Nutrigenomics, the microbiome, and gene-environment interactions: new directions in cardiovascular disease research, prevention, and treatment: a scientific statement from the American Heart Association. Circ Cardiovasc Genet. 2016;9(3):291–313.

Adrenoceptor Blockers

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Influence on Depression and Anxiety

Donato Cappetta, Konrad Urbanek, Liberato Berrino, and Antonella De Angelis

Contents

Abstract

The prominent role of norepinephrine in the regulation of cognitive functions is suggested by the distribution of noradrenergic circuits in specific regions of the central nervous system. Adrenergic receptors play a role in the regulation of the noradrenergic system in the central nervous system, both at pre- and postsynaptic levels, and their modulation permits a dynamic system to respond and adapt to stimuli. Evidence suggests that norepinephrine system dysregulation is a mechanism involved in the occurrence of pathological anxiety and depression. The stimulated adrenergic activity in the central nervous system provides a rationale for the use of antiadrenergic medications. Studies support antagonism of the postsynaptic α_1-adrenergic receptor as a target for post-traumatic stress disorder treatment.

Pharmacological action of epinephrine/norepinephrine on the heart and vessels is a basis of backbone medical therapies of cardiovascular diseases. A link between depression and the use of β-blockers has been postulated for a long time, but the association between their use and depression remains debated with conflicting results reported.

Future research will help to clarify the role of adrenergic system in mood and anxiety

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*,
https://doi.org/10.1007/978-3-030-28008-6_49

disorders in order to develop new treatments that not only alleviate symptoms but also affect underlying pathophysiology of these maladies.

Keywords

Adrenergic receptors · Norepinephrine neurotransmission · α- and β-blockers · Post-traumatic stress disorder · Depression

Introduction

Norepinephrine is an essential neurotransmitter, distributed throughout the central nervous system (CNS) with multiple effects. The noradrenergic system modulates several cognitive functions, such as learning/memory and stress response, and its dysregulation, by means of prolonged stressor stimuli, is associated with a variety of behavioral pathologies, such as drug abuse and cognitive deficits, leading to stress- and/or anxiety-related disorders [i.e., post-traumatic stress disorder (PTSD) and depression] [1, 2]. The largest cluster of noradrenergic neurons is represented by the locus coeruleus, implicated in a wide array of physiological and behavioral functions. Stressful stimuli activate locus coeruleus neurons, alter their electrophysiological activity, and induce a massive norepinephrine release [3].

In the light of the contribution of noradrenergic system to the etiology of several neuropsychiatric conditions, deciphering its role and the involvement of regulatory mechanisms may reveal new therapeutic targets for tailoring pharmacotherapy but also understand the background for CNS-related adverse reactions.

Distribution of Adrenergic Receptors

Adrenergic receptors (adrenoceptors) are membrane-bound receptors that belong to the superfamily of G protein-coupled receptors. They are found in almost all peripheral tissues and in many districts within the CNS where they mediate the physiological response to endogenous ligands, norepinephrine and epinephrine, and to a lesser extent dopamine [4]. Adrenergic receptors are classified into two major types, α and β, on the base of their affinity for specific agonists. The current classification has been defined by studies of molecular cloning identifying nine distinct genes encoding three α_1 (α_{1A}, α_{1B}, α_{1D}), three α_2 (α_{2A}, α_{2B}, α_{2C}), and three β (β_1, β_2, β_3) subtypes [5]. The α_1-adrenergic receptors are located in the peripheral and CNS at postsynaptic level, where they exert excitatory functions by stimulating Ca^{2+} channels as well as protein kinase C and phospholipase A_2 and promoting cyclic AMP production. In the CNS, they are found in hippocampus and cortex, whereas in periphery they are expressed in vascular and nonvascular smooth muscle cells and mediate vasoconstriction [6, 7]. On the other hand, the α_2-adrenergic receptors mediate an inhibitory action, by inhibiting adenylate cyclase and formation of cyclic AMP in the peripheral and CNS, at both pre- and postsynaptic level. In the CNS, their activation is associated with a reduced release of neurotransmitters on noradrenergic (autoreceptors) and non-noradrenergic (heteroreceptors) nerve terminals. The functional role of the diverse adrenergic receptor family members, α_1-adrenergic receptor subtypes among others, is still poorly understood, and because most currently available drugs are not selective enough to differentiate between the α_1 subtypes, it is difficult to determine how each subtype is able to modulate cognitive functions. Peripheral functions include inhibition of lipolysis in fat cells and insulin release from the pancreas [8–10]. The β-adrenergic receptors are positively coupled to adenylate cyclase through activation of a stimulatory G protein, resulting in increased cyclic AMP and cyclic AMP-dependent protein kinase. Moreover, their activation regulates the function of voltage-gated Ca^{2+} channels in muscle fibers. They are distributed on several organs, mainly the heart (β_1) but also in the lung, kidney, liver, vasculature, and adipose tissue [5, 11]. Therefore, adrenergic neurotransmission plays key role in the modulation of CNS activity, and the adrenergic part of autonomic nervous system is vital for the organism, since it regulates a variety of physiological processes and the response to stress. Pharmacological action of epinephrine/norepinephrine on the heart and vessels is one of

the bases of backbone medical therapies for cardiovascular diseases.

Noradrenergic System in Cognitive Processes and Behavior

Most of the noradrenergic neuronal network arises from the locus coeruleus and projects to different cortical and subcortical areas (hippocampus, amygdala, hypothalamus, etc.). The locus coeruleus provides the unique source of norepinephrine to hippocampus and neocortex, which are essential for cognitive and affective functions. Norepinephrine increases the organism's ability to process salient stimuli while suppressing responses to irrelevant information [12, 13]. Changes in norepinephrine activity can influence a wide range of psychobiologic functions. These include executive capabilities involved in decision-making mediated by the prefrontal cortex (PFC), hippocampal memory encoding, stress response mediated by the hypothalamus, and fear learning processed by the amygdala [14, 15].

Several adrenergic receptors have a role in the modulation of the noradrenergic system in the CNS, both pre- and postsynaptically, and functional interactions among different subtypes permit a dynamic system to respond and adapt to continuous stimuli [16]. Indeed, mRNA localization studies have revealed differential distributions of α and β receptors throughout the brain, suggesting that different adrenergic receptor subtypes mediate distinctive actions based on their differential localization across neuronal subpopulations and/or neuronal compartments [10, 17]. Moreover, evidence that adrenergic receptors are expressed by glial cells points to the influence of the locus coeruleus-noradrenergic system on glial function and, consequently, on neighboring neurons [18].

The Involvement of Norepinephrine in Depression

Depression is associated with potential morbidity and mortality contributing to suicide, medical illness, and disruption of interpersonal relationships and often leading to substance abuse. In spite of new mechanistic insights underlying pathophysiology of depression, the monoamine hypothesis, which postulates a deficiency of serotonin and/or norepinephrine neurotransmission in the brain, remains the most popular theory compatible with the clinical activity of most antidepressant medications. Although serotonin has been the most studied neurotransmitter in depression, a considerable proportion of patients fail to respond to selective serotonin reuptake inhibitors (SSRIs).

Noradrenergic Antidepressants

Accumulating evidence has indicated that norepinephrine is of major importance in the pathophysiology and treatment of depressive disorder. Clinical analysis has suggested that a specific set of symptoms poorly respond to serotonergic antidepressants and that antidepressants that enhance norepinephrine offer a therapeutic advantage in the treatment of symptoms [2]. Imaging studies have shown that major depression is associated with abnormal metabolism in limbic structures of the PFC and that metabolism normalization occurs in patients with a persistent antidepressant response [19]. Moreover, the mutual interactions between the serotonergic and the noradrenergic neurotransmission in the brainstem affect cellular plasticity and strengthen the functional cross talk between these systems, leading to development of emotion-related behaviors. In particular, elevation of norepinephrine in the serotoninergic neurons of the raphe is likely to activate the α_2 autoreceptor on noradrenergic neurotransmission and the α_2 heteroreceptor on the raphe serotoninergic neurons. Treatment with dual-action antidepressants (serotonin-norepinephrine reuptake inhibitors) in anxious depression may restore norepinephrine system through normalizing the upregulated α_2-adrenergic receptors and increasing raphe serotoninergic neurons [15]. Thus, the role of noradrenergic neurotransmission is being increasingly recognized and appears to be a key mechanism involved in the occurrence of pathological depression. The use of pharmacological interventions that facilitate norepinephrine release may promote

cell plasticity and adaptations that restore the regulatory control of norepinephrine and can strengthen regulation of behavior in patients.

The Noradrenergic Antagonism in Post-Traumatic Stress Disorder

Substantial evidence has indicated an excessive reactivity of noradrenergic system in stress-related disorders, evidencing a causal relationship between norepinephrine responsiveness and PTSD. An elevated norepinephrine release has been evidenced, with a raised firing of the locus coeruleus. PTSD is a debilitating mental health condition that can occur when a person has experienced or witnessed an extremely distressing and life-threatening event. In the USA, 5–10% population is affected, and the percentage is even higher in special populations that have been exposed to severe trauma, such as veterans and active-duty soldiers. The symptoms include hyperarousal, the avoidance of trauma reminders, the re-experiencing of traumatic events, as well as alteration of cognition and mood, commonly associated with aggressive behavior and suicide. Among the most characteristic symptoms of PTSD is sleep disruption, which is due in part to nightmares related to the traumatic events and to nighttime arousal [20]. Imaging and postmortem studies have provided consistent evidence of dysfunction at the PFC level in patients with PTSD. Difficulties in memory retrieval, lower performance in task depending on the PFC, impaired inhibition of the fear response, and altered pattern in the PFC activity suggest functional alterations in PTSD patients [21, 22].

The stimulated adrenergic activity in the CNS and its continuation during sleep provide a rationale for the use of antiadrenergic medications to ameliorate these symptoms. Animal models support antagonism of the postsynaptic α_1-adrenergic receptor in the CNS as a target for PTSD treatment. Of the clinically available α_1-adrenergic antagonists, prazosin that crosses the blood-brain barrier has demonstrated efficacy in antagonizing central α_1-adrenergic receptors when administered peripherally [23].

Treatment of Post-Traumatic Stress Disorder: Clinical Studies

During the last decade, six randomized placebo-controlled clinical trials have been conducted on combat soldiers and civilians. These studies, recruiting a number of participants ranged from 10 to 100, have shown moderate to large effects of prazosin in alleviating sleep disturbance and improving global clinical status. In these early trials, prazosin treatment has been effective and well tolerated, showing clinical benefits on total PTSD symptoms with improvements in trauma nightmares, sleep quality, and daytime symptoms, in both military veterans and civilians. These effects have been observed in some, but not in other, measurements of sleep quality and total PTSD symptoms [24–29]. However, as major limitation, these positive trials had a short duration (less than 15 weeks) and were of moderate size.

The ability of prazosin to sustain efficacy for chronic PTSD symptoms over longer periods (26 weeks) has been tested in a recent trial in which 304 participants were randomized in 1:1 ratio to receive either prazosin or placebo. The study has recruited US combat veterans who had chronic PTSD and reported frequent nightmares. In contrast with previous smaller randomized trials of prazosin, this trial has failed to show a benefit of prazosin over placebo in reducing the frequency and intensity of trauma nightmares [30]. A possible explanation for these negative results may stand from recruitment of patients who had clinically stable conditions. Acute or unstable medical illness and psychosocial instability were the criteria of exclusion in this trial, not taken into consideration in the other studies. Therefore, the clinical characteristics of patients recruited in this trial may well explain why PTSD symptoms were less likely to be ameliorated with antiadrenergic treatment.

PTSD is a complex syndrome with several subtypes and variations that can manifest with different combinations of symptoms. Despite the understanding of neurobiological pathways underlying PTSD, the different variants with different biologic phenotypes explain the failure in

the identification of one distinctive treatment that fits all. This extreme variability forces a more complete definition of the PTSD based on biologic markers that may call for a specific targeted pharmacotherapy and psychotherapy. Future trials should demonstrate the biologic basis that enlarges our current understanding of this disorder so that each subgroup of the millions of patients with PTSD may respond to proper pharmacological approach.

Since norepinephrine hyperactivity has been established as a critical signaling of the stress response implicated in anxiety-related behavior, the search for novel agents to treat PTSD and other anxiety disorders has shown alternative pharmacological approaches to disrupt the catecholamine activity. Nepicastat, a selective dopamine β-hydroxylase inhibitor, is being tested for the treatment of PTSD in veterans who have previously served in combat zone (NCT00659230, NCT00641511). The scientific rationale is based on the reduction of noradrenergic synaptic signaling by the inhibition of β-hydroxylase, the enzyme that converts dopamine to norepinephrine.

Neuropsychiatric Effects of Cardiovascular Adrenergic Antagonists

Chronic medical condition and associated medication have been linked with development of depressive symptoms. However, the shortage of systemic investigations and the relatively high percentage of depression in chronically treated patients may also indicate a coincidence rather than a drug effect. Although it has been postulated that cardiovascular medications may have impact on neuropsychiatric symptoms, it is problematic to associate a specific neuropsychiatric symptom to the particular cardiovascular drug. This is partially because anxiety and major depressive disorder are relatively common in patients with acute and chronic cardiovascular diseases [31–33]. Still, a link between depression and the use of β-blockers (BBs) has been postulated for a long time. In general, the presumed increase in rates of neuropsychiatric effects has been thought to depend on the chemical properties of BBs, as lipophilic molecules (propranolol and metoprolol) can penetrate through blood-brain barrier easier than non-lipophilic drugs (atenolol). Yet, meta-analysis of 15 trials with more than 35,000 patients has showed that the risk of adverse effects (depressive symptoms, fatigue, or sexual dysfunction) did not differ significantly following the use of lipophilic and non-lipophilic drugs [34]. Overall, the association between the use of BBs and depression remains debated with conflicting results reported. Observational studies and case reports have related the use of propranolol with depression, and the analysis of the drug prescription pattern has found that this BB was associated with increased prescription of an antidepressant. High rates of new prescriptions for antidepressants were more frequently seen in patients having prescribed propranolol, as compared with diuretics [35–38]. Also, the quality of life analysis, by assessing psychological functioning, has shown lower scores in patients taking propranolol when compared to captopril, enalapril, and atenolol [39]. In more extended studies, however, the link of BBs and depressive symptoms is weaker than initially thought. Large meta-analysis of 15 trials has not revealed such association, and the following reviews have confirmed this notion [34, 40]. On the other end, the more recent 5-year follow-up study in patients with monotherapy of hypertension has shown the association of treatment with BBs with the higher risk of hospitalization for mood disorders. While this study is consistent with the possibility of depression as a rare side effect of BBs, the necessity of hospital admission reflects the severity of mood disorder and does not consider bipolar and depressive disorders treated within the community [41]. The evidence has also shown that both lipophilic and non-lipophilic BBs can be accompanied with adverse neuropsychiatric effects other than depression, such as fatigue and sedation [42, 43]. Fatigue, anxiety, and sleep disturbance can also occur in patients assuming α_1 antagonists as antihypertensive agents and to treat symptoms of benign prostatic hypertrophy (prazosin, doxazosin, and alfuzosin). This class of drugs was not consistently

linked to depression with only rare cases being reported for prazosin [44–46].

Aside from adverse effects, BBs find therapeutic application in the field of neuropsychiatry. They are considered as medication of choice for short-term relief of social and performance anxiety and, as doping, are prohibited in particular sports as archery and shooting. It has been reported that the risk of PTSD may be reduced by the immediate, post-trauma, administration of propranolol [47]. BBs are used to treat aggression following a traumatic brain injury and in aggressive patients affected by schizophrenia and other neuropsychiatric conditions [48, 49]. Finally, BBs can be utilized in patients with alcohol or benzodiazepine withdrawal-related symptoms and suffering from restlessness related to the use of antagonists of dopamine signaling (e.g., antipsychotic drugs) [50, 51].

Pindolol and Antidepressive Therapy

Pindolol, used for the treatment of hypertension and angina, is a moderately lipophilic, non-selective β-receptor antagonist with intrinsic sympathomimetic activity. It is also an antagonist of serotonin 5-HT_{1A} receptor. The inhibition of reuptake of serotonin that is common to various antidepressant drugs occurs within hours of administration of reuptake inhibitor, but the clinical effect is not clearly apparent before 2–3 weeks. When serotonin transporter at synaptic endings is blocked by the reuptake inhibitor, the extracellular rise of serotonin triggers inhibitory 5-HT_{1A} autoreceptors that, in turn, inhibit the firing of serotonergic neurons [52]. The feedback can be responsible for the abovementioned clinical delay and may last until the receptor is desensitized. In efforts to develop strategies that might shorten that undesirable delay, the attention has been directed to pindolol, because of its effects on 5-HT_{1A} autoreceptors. The studies of pindolol as a potential augmenting agent for patients with depression have yielded mixed results. Meta-analysis of clinical trials has found that pindolol speeds up the response to SSRIs although it does not improve overall response rate [53]. Interestingly, experimental data and human PET studies have shown an increase in serotonin synthesis in PFC when pindolol is combined with a reuptake inhibitor [54, 55]. It has also been shown that response acceleration and steadiness are higher in patients with a first depressive episode but not in recurrent patients, indicating that the augmentation with pindolol may depend on previous exposure to antidepressants [56]. In patients with reuptake inhibitor-resistant depression, systematic review of clinical data has not found evidence for efficacy of add-on pindolol and SSRI therapy, which is consistent with previous studies [57]. Further investigation is needed to clarify this issue. The use of pindolol is currently considered as a third-line augmentation strategy for patients with obsessive-compulsive disorder.

In summary, BBs as a class are not evidently linked with depression, and the evidence regarding the use of propranolol is not definitive. On the other hand, intensification of fatigue and sedation are more consistently reported. It seems that in a daily clinical practice, the importance of mental well-being of hypertensive and cardiomyopathic patients may be underestimated, and clinicians need to keep in mind the possible link between neuropsychiatric symptoms and cardiovascular drug therapy.

Conclusion

More research is needed to understand the role of adrenergic system in mood and anxiety disorders to develop new treatments that not only alleviate symptoms but also affect underlying pathophysiology of these maladies. The links between adrenergic antagonists and mental health together with ongoing real-life observations can allow not only developing more personalized prescribing attitude but also stimulating the research on the pathobiology of neuropsychiatric diseases.

References

1. Berridge CW, Waterhouse BD. The locus coeruleus-noradrenergic system: modulation of behavioral state and state-dependent cognitive processes. Brain Res Brain Res Rev. 2003;42:33–84.
2. Moret C, Briley M. The importance of norepinephrine in depression. Neuropsychiatr Dis Treat. 2011;7:9–13.

3. Smith SM, Vale WW. The role of the hypothalamic-pituitary-adrenal axis in neuroendocrine responses to stress. Dialogues Clin Neurosci. 2006;8:383–95.
4. Dohlman HG, Thorner J, Caron MG, Lefkowitz RJ. Model systems for the study of seven-transmembrane-segment receptors. Annu Rev Biochem. 1991; 60:653–88.
5. Bylund DB, Eikenberg DC, Hieble JP, Langer SZ, Lefkowitz RJ, Minneman KP, et al. International Union of Pharmacology nomenclature of adrenoceptors. Pharmacol Rev. 1994;46:121–36.
6. Hieble JP, Bylund DB, Clarke DE, Eikenburg DC, Langer SZ, Lefkowitz RJ, et al. International Union of Pharmacology. X. Recommendation for nomenclature of alpha 1-adrenoceptors: consensus update. Pharmacol Rev. 1995;47:267–70.
7. Berridge MJ, Irvine RF. Inositol phosphates and cell signalling. Nature. 1989;341:197–205.
8. Ruffolo RR Jr, Hieble JP. Alpha-adrenoceptors. Pharmacol Ther. 1994;61:1–64.
9. Knaus AE, Muthig V, Schickinger S, Moura E, Beetz N, Gilsbach R, Hein L. Alpha2-adrenoceptor subtypes – unexpected functions for receptors and ligands derived from gene-targeted mouse models. Neurochem Int. 2007;51:277–81.
10. Hein L, Altman JD, Kobilka BK. Two functionally distinct alpha2-adrenergic receptors regulate sympathetic neurotransmission. Nature. 1999;402:181–4.
11. O'Donnell JM. Effect of the beta-2 adrenergic agonist zinterol on norepinephrine turnover. Res Commun Chem Pathol Pharmacol. 1993;80:113–6.
12. Delfs JM, Zhu Y, Druhan JP, Aston-Jones GS. Origin of noradrenergic afferents to the shell subregion of the nucleus accumbens: anterograde and retrograde tract-tracing studies in the rat. Brain Res. 1998;806:127–40.
13. Borodovitsyna O, Flamini M, Chandler D. Noradrenergic modulation of cognition in health and disease. Neural Plast. 2017;2017:6031478.
14. Arnsten AF. Stress weakens prefrontal networks: molecular insults to higher cognition. Nat Neurosci. 2015;18:1376–85.
15. Goddard AW, Ball SG, Martinez J, Robinson MJ, Yang CR, Russell JM, Shekhar A. Current perspectives of the roles of the central norepinephrine system in anxiety and depression. Depress Anxiety. 2010;27: 339–50.
16. Berridge CW. Noradrenergic modulation of arousal. Brain Res Rev. 2008;58:1–17.
17. Nicholas AP, Pieribone VA, Hokfelt T. Cellular localization of messenger RNA for beta-1 and beta-2 adrenergic receptors in rat brain: an in situ hybridization study. Neuroscience. 1993;56:1023–39.
18. Stone EA, John SM. Further evidence for a glial localization of rat cortical beta-adrenoceptors: studies of in vivo cyclic AMP responses to catecholamines. Brain Res. 1991;549:78–82.
19. Drevets WC, Bogers W, Raichle ME. Functional anatomical correlates of antidepressant drug treatment assessed using PET measures of regional glucose metabolism. Eur Neuropsychopharmacol. 2002;12: 527–44.
20. Ross RJ, Ball WA, Sullivan KA, Caroff SN. Sleep disturbance as the hallmark of posttraumatic stress disorder. Am J Psychiatry. 1989;146:697–707.
21. Pitman RK, Rasmusson AM, Koenen KC, Shin LM, Orr SP, Gilbertson MW, et al. Biological studies of posttraumatic stress disorder. Nat Rev Neurosci. 2012;13:769–87.
22. Arnsten AF, Raskind MA, Taylor FB, Connor DF. The effects of stress exposure on prefrontal cortex: translating basic research into successful treatments for post-traumatic stress disorder. Neurobiol Stress. 2015;1:89–99.
23. Togno J, Eaton S. Is there a role for prazosin in the treatment of post-traumatic stress disorder? Aust Family Physician. 2015;44:647–9.
24. Raskind MA, Peskind ER, Kanter ED, Petrie EC, Radant A, Thompson CE, et al. Reduction of nightmares and other PTSD symptoms in combat veterans by prazosin: a placebo-controlled study. Am J Psychiatry. 2003;160:371–3.
25. Raskind MA, Peskind ER, Hoff DJ, Hart KL, Holmes HA, Warren D, et al. A parallel group placebo controlled study of prazosin for trauma nightmares and sleep disturbance in combat veterans with post-traumatic stress disorder. Biol Psychiatry. 2007; 61:928–34.
26. Taylor FB, Martin P, Thompson C, Williams J, Mellman TA, Gross C, et al. Prazosin effects on objective sleep measures and clinical symptoms in civilian trauma posttraumatic stress disorder: a placebo-controlled study. Biol Psychiatry. 2008;63:629–32.
27. Germain A, Richardson R, Moul DE, Mammen O, Haas G, Forman SD, et al. Placebo-controlled comparison of prazosin and cognitive-behavioral treatments for sleep disturbances in US military veterans. J Psychosom Res. 2012;72:89–96.
28. Raskind MA, Peterson K, Williams T, Hoff DJ, Hart K, Holmes H, et al. A trial of prazosin for combat trauma PTSD with nightmares in active-duty soldiers returned from Iraq and Afghanistan. Am J Psychiatry. 2013;170:1003–10.
29. Ahmadpanah M, Sabzeiee P, Hosseini SM, Torabian S, Haghighi M, Jahangard L, et al. Comparing the effect of prazosin and hydroxyzine on sleep quality in patients suffering from posttraumatic stress disorder. Neuropsychobiology. 2014;69:235–42.
30. Raskind MA, Peskind ER, Chow B, Harris C, Davis-Karim A, Holmes HA, et al. Trial of prazosin for post-traumatic stress disorder in military veterans. N Engl J Med. 2018;378:507–17.
31. Connerney I, Shapiro PA, McLaughlin JS, Bagiella E, Sloan RP. Relation between depression after coronary artery bypass surgery and 12-month outcome: a prospective study. Lancet. 2001;358:1766–71.
32. Konstam V, Moser DK, De Jong MJ. Depression and anxiety in heart failure. J Card Fail. 2005;11:455–63.
33. van Melle JP, de Jonge P, Spijkerman TA, Tijssen JG, Ormel J, van Veldhuisen DJ, et al. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: a meta-analysis. Psychosom Med. 2004;66:814–22.

34. Ko DT, Hebert PR, Coffey CS, Sedrakyan A, Curtis JP, Krumholz HM. Beta-blocker therapy and symptoms of depression, fatigue, and sexual dysfunction. JAMA. 2002;288:351–7.
35. McNeil GN, Shaw PK, Dock DS. Substitution of atenolol for propranolol in a case of propranolol-related depression. Am J Psychiatry. 1982;139:1187–8.
36. Oppenheim G. Propranolol-induced depression: mechanism and management. Aust N Z J Psychiatry. 1983;17:400–2.
37. Thiessen BQ, Wallace SM, Blackburn JL, Wilson TW, Bergman U. Increased prescribing of antidepressants subsequent to beta-blocker therapy. Arch Intern Med. 1990;150:2286–90.
38. Hallas J. Evidence of depression provoked by cardiovascular medication: a prescription sequence symmetry analysis. Epidemiology. 1996;7:478–84.
39. Steiner SS, Friedhoff AJ, Wilson BL, Wecker JR, Santo JP. Antihypertensive therapy and quality of life: a comparison of atenolol, captopril, enalapril and propranolol. J Hum Hypertens. 1990;4:217–25.
40. Verbeek DE, van Riezen J, de Boer RA, van Melle JP, de Jonge P. A review on the putative association between beta-blockers and depression. Heart Fail Clin. 2011;7:89–99.
41. Boal AH, Smith DJ, McCallum L, Muir S, Touyz RM, Dominiczak AF, Padmanabhan S. Monotherapy with major antihypertensive drug classes and risk of hospital admissions for mood disorders. Hypertension. 2016;68:1132–8.
42. Dimsdale JE, Newton RP, Joist T. Neuropsychological side effects of beta-blockers. Arch Intern Med. 1989;149:514–25.
43. Paykel ES, Fleminger R, Watson JP. Psychiatric side effects of antihypertensive drugs other than reserpine. J Clin Psychopharmacol. 1982;2:14–39.
44. Carruthers SG. Adverse effects of alpha 1-adrenergic blocking drugs. Drug Saf. 1994;11:12–20.
45. MacDonald R, Wilt TJ, Howe RW. Doxazosin for treating lower urinary tract symptoms compatible with benign prostatic obstruction: a systematic review of efficacy and adverse effects. BJU Int. 2004;94:1263–70.
46. Guay DR. Extended-release alfuzosin hydrochloride: a new alpha adrenergic receptor antagonist for symptomatic benign prostatic hyperplasia. Am J Geriatr Pharmacother. 2004;2:14–23.
47. Vaiva G, Ducrocq F, Jezequel K, Averland B, Lestavel P, Brunet A, Marmar CR. Immediate treatment with propranolol decreases posttraumatic stress disorder two months after trauma. Biol Psychiatry. 2003;54:947–9.
48. Fleminger S, Greenwood RJ, Oliver DL. Pharmacological management for agitation and aggression in people with acquired brain injury. Cochrane Database Syst Rev. 2003;1:CD003299.
49. Fava M. Psychopharmacologic treatment of pathologic aggression. Psychiatr Clin North Am. 1997;20:427–51.
50. Sachdev PS. Neuroleptic-induced movement disorders: an overview. Psychiatr Clin North Am. 2005;28:255–74.
51. Horwitz RI, Gottlieb LD, Kraus ML. The efficacy of atenolol in the outpatient management of the alcohol withdrawal syndrome. Results of a randomized clinical trial. Arch Intern Med. 1989;149:1089–93.
52. Artigas F, Romero L, de Montigny C, Blier P. Acceleration of the effect of selected antidepressant drugs in major depression by 5-HT1A antagonists. Trends Neurosci. 1996;19:378–83.
53. Ballesteros J, Callado LF. Effectiveness of pindolol plus serotonin uptake inhibitors in depression: a meta-analysis of early and late outcomes from randomised controlled trials. J Affect Disord. 2004;79:137–47.
54. Nguyen KQ, Tohyama Y, Watanabe A, Hasegawa S, Skelin I, Diksic M. Acute effects of combining citalopram and pindolol on regional brain serotonin synthesis in sham operated and olfactory bulbectomized rats. Neurochem Int. 2009;54:161–71.
55. Berney A, Nishikawa M, Benkelfat C, Debonnel G, Gobbi G, Diksic M. An index of 5-HT synthesis changes during early antidepressant treatment: alpha-[11C]methyl-L-tryptophan PET study. Neurochem Int. 2008;52:701–8.
56. Portella MJ, de Diego-Adeliño J, Puigdemont D, Pérez-Egea R, Alvarez E, Artigas F, Pérez V. Pindolol augmentation enhances response outcomes in first depressive episodes. Eur Neuropsychopharmacol. 2009;19:516–9.
57. Liu Y, Zhou X, Zhu D, Chen J, Qin B, Zhang Y, et al. Is pindolol augmentation effective in depressed patients resistant to selective serotonin reuptake inhibitors? A systematic review and meta-analysis. Hum Psychopharmacol. 2015;30:132–42.

Therapeutic Drug Monitoring in Neuropsychiatric Disorders

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Shivakumar Kolachalam, Stefano Aringhieri, and Marco Scarselli

Contents

Abstract

Despite enormous medical and economic efforts in treating psychiatric and neurologic disorders, more than 1/3 of patients do not benefit from the pharmacological therapy. In particular, since patients respond differently to the same dose of the same drug, the variability of pharmacological effectiveness among different patients is often difficult to explain and/or predict. Among the many factors relevant for the success of the pharmacologic treatments, the pharmacokinetic characteristics of individuals can be responsible for the lack of therapeutic response. In fact, interindividual pharmacokinetic differences, uncertain drug adherence, or drug-drug interactions are key issues to be seriously taken into consideration. Therefore, ongoing research, besides developing safe and effective drugs, also focuses on proper use of currently available ones.

For all these issues, therapeutic drug monitoring (TDM) is an effective tool to improve current therapies applied in daily clinical practice, further in the direction of a "personalized medicine" to identify each individual patient's best therapeutic concentration. However, in order to achieve maximum benefits, TDM should be adequately integrated in the clinical practice to help the specialist in making the right and timely decisions.

In this chapter, we examine the benefits of TDM in clinical practice for antidepressants, mood stabilizers, and antipsychotics widely used in treating brain disorders.

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*,
https://doi.org/10.1007/978-3-030-28008-6_48

Keywords

TDM · Neuropsychiatric disorders · Antidepressants · Mood stabilizers · Antipsychotics · Personalized medicine

Introduction

The success of the pharmacologic treatment, including neuropsychiatric medications, is influenced by several factors, mostly related to the pharmacodynamic and pharmacokinetic characteristics of the patient (Fig. 1). In particular, since patients respond differently to the same dose of the same drug, the variability of pharmacological effectiveness among different patients is often difficult to explain and/or predict. However, some of these variables can be easily controlled and their monitoring can strongly improve the therapeutic success. In fact, suboptimal drug plasma concentration or patient non-adherence can be relevant factors responsible for the lack of a pharmacological response.

In this perspective, therapeutic drug monitoring (TDM) is an important tool that helps to optimize current therapies utilized in daily clinical practice. TDM measures the drug's (and/or its metabolite's) concentration in the blood or serum, and it proposes an optimal therapeutic range reference for the best probability of pharmacological response combined with reduced risk of adverse drug reactions/toxicity [1]. Historically, in neuropsychiatric disorders, TDM was introduced to avoid the toxicity of drugs, for e.g., lithium, which have a narrow therapeutic index, i.e., a drug with a toxic concentration close to its therapeutic effective concentration [2]. Nowadays, TDM can also be employed for the so-called "personalized medicine" to identify each individual patient's best therapeutic concentration.

Most importantly, besides the quantification of plasma drug concentration (Cp), TDM should interpret this value with respect to the dose in order to improve the pharmacological treatments considering non-response at therapeutic doses,

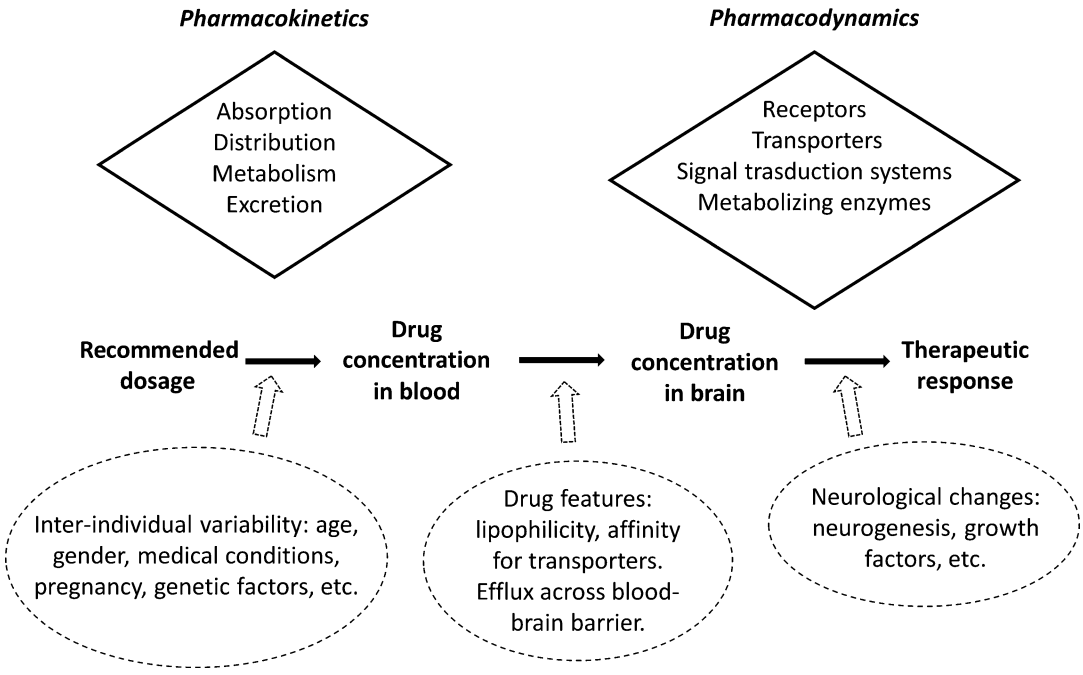

Fig. 1 From prescribed dose to pharmacological response: pharmacokinetic and pharmacodynamic factors responsible for interindividual variability. (Adapted from [1])

uncertain drug compliance, and polytherapy with potential drug-drug interactions.

The pharmacokinetic variability among individuals is influenced by many factors such as age, sex, comorbidity, enzymatic genetic polymorphisms, polytherapy, etc. At the same dose of some drugs (e.g., tricyclic antidepressants), a 10- to 20-fold difference can be found at steady state as patients mostly differ in their ability to absorb, metabolize (cytochrome p450 polymorphism), distribute, and excrete [3–7].

Special categories that may particularly benefit from TDM are children, adolescents, pregnant women, elderly patients, and patients with substance abuse disorders, considering their peculiar characteristics that make them more vulnerable to toxicity and side effects. The Cp should be constantly monitored in elderly patients [8], considering the progressive impairments of some of their organs, such as the kidney and liver, whose function may decrease significantly [4, 9].

In particular, in neuropsychiatric disorders, we can estimate that about 1/3 of patients do not benefit from the therapy, and about 20–60% of them suspend drug usage during chronic treatment. In addition, about half of the medications used for treating chronic diseases are not taken as prescribed [10]. For example, for antiepileptic drugs, subtherapeutic levels were found in most patients attending hospitals due to seizures [11]. Therefore, besides developing new effective drugs, current research has put many efforts in order to improve the proper use of available ones [12–15].

Indeed, a good practice with TDM delivers important advantages in terms of cost-benefits, mainly through reduced length of hospital stay and thus healthcare costs.

According to AGNP (*Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie*) guidelines, TDM is mandatory for lithium and carbamazepine, where lithium monitoring has become the gold standard of TDM due to its narrow therapeutic window [16–18]. For many other drugs, TDM is strongly recommended, especially for patients with polytherapy, for patients with uncertain adherence to medication, and for "non-responders." Evidence of a relationship between clinical outcome and Cps has been found for anticonvulsant drugs [19], tricyclic antidepressants (TCAs) [20], antipsychotics (APs) [21], and mood stabilizers [22].

TDM is strongly recommended for TCAs for their risk of toxicity [23–26], and use of TDM has indeed reduced this risk [24, 27, 28]. The typical (first-generation) APs such as haloperidol and the atypical (second-generation) APs such as amisulpride, clozapine, and olanzapine are also suitable candidates for TDM, since their overdosing may lead to extrapyramidal syndrome or other side effects. In the case of clozapine, there is a strong correlation between clozapine concentration in blood and incidence of seizures.

Another indication for TDM is to reduce the risk of relapse by controlling patient's compliance to the medication. Furthermore, for some drugs, such as clozapine, Cp fluctuations can be deleterious for relapses, and hence controlling its Cp may help to limit rehospitalization of patients [29, 30].

Unfortunately, TDM is often misused in neuropsychiatric disorders [31–35], and its improper application might lead to misleading results and wrong clinical decisions. For example, typical errors can be measuring plasma concentrations not at steady-state conditions or transcription errors on the request form. Studies for antidepressant and mood-stabilizing drugs have revealed the imperfect use of TDM [36, 37], and around half of the requests were found to be incorrect in case of antiepileptic drugs [32].

Indeed, an optimal use of TDM is far from trivial, revealing that the gap between clinicians and pharmacologists is still relevant. In fact, often, on one side, the pharmacologists have limited knowledge of the clinical conditions of the patients, while on the other side, the physicians are not familiar with the pharmacokinetic problematics [38, 39]. Therefore, it is essential to improve the interactions between laboratory activity, pharmacologists and clinical experts in the direction of a real interdisciplinary approach, where patients would strongly benefit from such a multidisciplinary process.

TDM for Mood Stabilizers

The class of mood stabilizers is the most important category of drugs used for treating severe and complex mental illnesses, such as bipolar disorder (BD), which can be characterized by psychotic features. BD is a psychiatric disorder distinguished by depressive and manic or hypomanic episodes, which alternate with euthymic phases. BD patients are prone to cause self-harm, and in severe cases, they may try to commit suicide.

The gold standard treatment for BD is lithium; however, other categories of drugs such as anticonvulsants, APs and antidepressants are also used, mostly in association. Lithium and anticonvulsant drugs (e.g., valproic acid/valproate) are used for the long-term treatment, especially to prevent the relapse, while APs and antidepressants are generally used for shorter periods for their specific action on psychotic and depressive episodes, respectively [40–43]. The association of lithium with valproic acid seems to be safe, well tolerated, and the most effective [44], particularly for patients who do not benefit from lithium monotherapy [45] or those with residual symptoms [46]. There are some predictive factors of poor response to lithium, such as mixed states, comorbidities with substance abuse, or states of anxiety. The *Balance* study showed that lithium monotherapy and the association of lithium and valproate were more likely to prevent relapse than valproate monotherapy [47]. However, there is no clear evidence that lithium and valproate is better than lithium alone in preventing recurrence of episodes or reducing hospitalization [48]. The concomitant use of lithium and valproate provides a valid alternative for the treatment of rapid cycling disorders, with a particular improvement in depression within 24–48 h of the start of combined use [49].

In clinical practice, the lithium therapeutic window is 0.50–1.20 mmol/l in the acute phase, but it decreases to 0.50–0.80 mmol/l during the chronic treatment in order to avoid the deleterious side effects as much as possible, particularly referring to nephrotoxicity (Fig. 2). On this aspect, several studies have been carried out regarding the long-term treatment, and most of them pointed

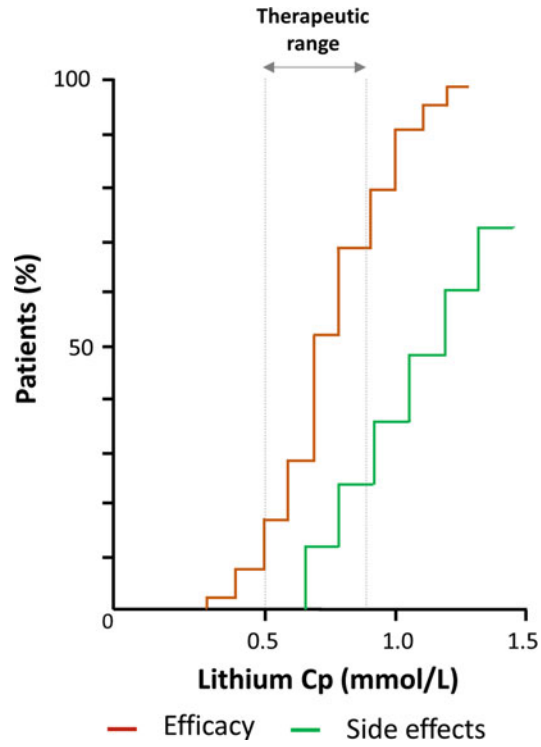

Fig. 2 Relationship between lithium Cp and its efficacy and relevant side effects among patients. (Adapted from [56])

out that lithium treatment should be considered a risk factor for kidney functional impairment [50]. The value above 1.20 mmol/l is considered as alert level, where the physician, and eventually the patient, should be informed. Although TDM is often used to avoid high concentration and toxicity of lithium, attention should be paid not only to the upper threshold, but also to the lower threshold, below which the efficacy of lithium is questionable. In our experience of TDM, lithium is often used in dosages that determine serum levels of 0.40 mmol/l or below, even if there is little evidence of lithium efficacy at this Cp. A study proposed that 0.40 mmol/l could be the minimum Cp to achieve clinical efficacy in patients affected by BD, with the possibility of maintaining a lower concentration in euthymic patients. However, the same study also pointed out that 0.60–0.75 mmol/l is the optimal Cp to benefit from the therapy, and Cp levels beyond this though may give additional control of manic episodes but offer no

improvements for depressive symptoms [51]. In contrast, a randomized double-blind study conducted in 94 patients with BD showed that the range 0.40–0.50 mmol/l is associated with greater probability of recurrence and variability of psychiatric symptoms in weekly evaluations [52, 53]. Another study conducted by the University of Pisa on patients undergoing lithium therapy showed that patients with lithium concentration 0.50 mmol/l or above displayed a significantly higher clinical improvement than the rest [54]. In addition, it was proposed that when lithium was associated with valproate in 75 bipolar patients, the lithium concentration between 0.40 and 0.60 mmol/l seemed enough to be effective [55], suggesting that the association between these two drugs might reduce the risk of lithium toxicity.

Historically, early studies by Amdisen [56] clearly indicated that lithium efficacy increases with its Cp; however, this also correlates for side effects such as nephrotoxicity. Therefore, the therapeutic range is a rational compromise between these two aspects, i.e., the best probability of clinical efficacy combined with reduced risk of toxicity.

Regarding other mood stabilizers like valproate and carbamazepine, their therapeutic ranges and toxic levels are well-defined [1]. TDM is strongly recommended for valproate, considering the linear relationship between its Cp and clinical efficacy. The therapeutic window of valproate is 50–100 μg/ml, with an alert threshold of 120 μg/ml. According to one study in acute mania, the target blood level of valproate for the best response was more than 94 μg/ml [57]. Other studies have confirmed this therapeutic range in the chronic treatments with valproate [58].

TDM for Antipsychotics

Antipsychotics (APs) are usually prescribed for treating schizophrenia, BD, and other brain diseases characterized by delusional thoughts. Generally, these drugs are divided into typical antipsychotics (TAPs) or first-generation antipsychotics and atypical antipsychotics (AAPs) or second-generation antipsychotics, based on the concept that AAPs have lesser side effects such as parkinsonism and tardive dyskinesia [59] and eventually a better profile in terms of social and cognitive improvement.

In clinical practice, haloperidol and chlorpromazine are the two most widely prescribed TAPs that act as dopamine D2 receptor antagonists. On the other side, AAPs, such as clozapine, olanzapine, quetiapine, and risperidone, have a mechanism of action that goes beyond the D2 receptor blockade and involves serotonin, muscarinic, adrenergic, and glutamatergic receptors. Recently our group has revisited the mechanism of action of AAPs and based on the different clinical characteristics among these compounds belonging to the same category grouped them into three different levels of "atypia," where, besides D2 and 5-HT2A/2C receptor antagonism, other mechanisms such as 5-HT1 partial agonism, D3 antagonism, H1 antagonism, α2 antagonism, moderate muscarinic antagonism, M1-positive allosterism, BDNF production, and GlyT blocking have received particular attention [60].

Regarding the use of APs in clinical practice, TDM represents a rational approach for optimizing their effectiveness, where the Cp can be a relevant parameter for drug efficacy and tolerability. Indeed, some APs have shown a good correlation between their Cp and the highest probability of clinical response with minimized risk of adverse drug reactions. In particular, TDM of APs is useful for identifying a non-response at therapeutic doses, uncertain drug adherence, pharmacokinetic drug-drug interactions, and for reducing side effects. It is worth noting that Cp is a good predictor for drug cerebral concentration, especially for lipophilic drugs where the blood-brain barrier efflux transporters are poorly involved.

Neuroimaging studies have demonstrated that motor side effects, such as extrapyramidal syndrome, may occur when more than 80% of D2 receptors in the striatum are blocked. Conversely, receptor occupancy between 65 to 80% seems to be the best condition for AP effectiveness with lower probability of inducing extrapyramidal side effects [61]. Importantly, a correlation was found between the D2 receptor occupancy and the Cp of some APs, whereas such a relationship with dosage was less clear. This correlation was recently confirmed by

Grundmann et al. [62]. Studies have also found that the relationship between Cp and D2 receptor occupancy is fit by a hyperbolic saturation curve, where risperidone and olanzapine, at higher concentration, may exceed 80% of receptor occupancy [63]. These curves show a good correlation between predicted and observed receptor occupancy in relation to the drug Cp. The prediction of D2 receptor occupancy in relation to Cp is particularly valid for olanzapine, less for risperidone, and not significant for clozapine. For risperidone, the blood-brain barrier efflux transporters such as P-glycoprotein (P-gp) may be responsible for lowering its concentration in the brain, which reduces the abovementioned correlation [64].

Recently, some in vivo studies have analyzed the possible relationship between Cp and receptor occupancy for other targets such as the 5-HT2A receptor in the cortex and GlyT1 transporters; however, the information is still too preliminary [65].

Many studies related to the variability between AAP dose and Cp have been carried out with clozapine, which nowadays is frequently monitored, because of its relevant side effects. The Cp of clozapine is difficult to predict due to its large interindividual variability factors such as sex, age, weight, smoking, and concomitant use of other medications that influence CYP450 activity (e.g., CYP1A2) [66]. In particular, a fixed dose of clozapine of 400 mg/day showed a very large Cp variability among patients [67]. Moreover, smoking lowers the Cp of clozapine by inducing CYP1A2 [68]. While on one hand CYP inhibitors, such as fluvoxamine, were shown to increase the Cp of clozapine up to ten times, on the other hand, co-administration with carbamazepine (a CYP3A4- and CYP1A2-inducing drug) resulted in a substantial decrease in the Cp of clozapine [69]. Similar interactions were found with other AAPs like olanzapine and risperidone when they were co-administered either with carbamazepine or selective serotonin reuptake inhibitors (SSRIs) fluoxetine and paroxetine, which are mostly CYP2D6- and CYP2C19-inhibiting drugs [70].

Regarding drug efficacy, several studies have found a good correlation between AP response and its Cp, especially for clozapine and olanzapine. In fact, TDM of these two drugs is strongly recommended as indicated in AGNP consensus guidelines (Level I recommendation) [1]. Perry et al. [71] for the first time showed in treatment-resistant schizophrenic patients that a Cp of clozapine greater than 350 ng/ml resulted in a 64% clinical response, while below this level the response was only 22%. Other studies have also confirmed a cutoff for clozapine efficacy at 350 ng/ml [72] or 420 ng/ml [73]. In addition, a correlation was found between Cp of clozapine and increased risk of epileptic seizures and hence the proposed therapeutic range with an alert value of 1000 ng/ml [1, 73]. Moreover, a fluctuation of clozapine Cp can predict relapses and rehospitalization in schizophrenic patients, where TDM may help reduce such risks and provide cost-effective advantages [1].

Taken together, these data clearly show the importance of routine TDM in patients undergoing AP treatment.

TDM for Antidepressants

Antidepressants are the most common drugs in psychopharmacology, primarily for treating depression and anxiety disorders; besides, they have recently been recommended for treating chronic pain and insomnia [74, 75]. Regarding the mechanism of action, these medications rapidly increase release of serotonin and norepinephrine in the synaptic cleft; however their clinical effects are not immediate and require few weeks, i.e., lag of clinical response. Hence, other mechanisms have been indicated for antidepressants' action, and among them, the increase of adult hippocampal neurogenesis and synaptogenesis seem to correlate with the clinical improvement [76].

Both the first-generation (e.g., TCA) and the second-generation (e.g., SSRI and serotonin-norepinephrine reuptake inhibitor *aka* SNRI) antidepressants are used in clinical practice, with a particular preference for the second category due to their reduced side effects and better tolerability.

Indeed, severe side effects of TCAs are still a concern for physicians compelling a constant monitoring of patients' conditions [25], mainly due to a substantial variability in therapeutic drug response among patients, where only 1/3

have a complete remission from their illness [10], evidently making clear about the benefits the TDM could provide for TCAs. In fact, for TCAs, a 10- to 20-fold difference can be found in their steady-state Cp for patients taking the same dose as a consequence of interindividual metabolic variability caused by CYP2D6 polymorphism [77]. Furthermore, TDM is strongly recommended for most TCAs to reduce the risk of toxicity [28]. Therefore, taking into consideration the high variability on CYP2D6 activity among patients, prior genotyping should be considered. For example, the anticholinergic activity of nortriptyline increases with increasing blood concentrations, and this activity might occur even at therapeutic concentrations [78]. Animal studies have shown that steady-state Cps of TCAs correlate well with concentrations in brain but less with dosages [79]. In fact, a concentration-clinical effectiveness relationship has been demonstrated for many TCAs [80].

For SSRIs, a weak (but significant) dose-dependent clinical improvement was reported with tolerability decreased at high doses [81]. Though acceptance of TDM is actually limited in clinical practice, evidence for its usefulness is growing. Magnetic resonance spectroscopy has shown that brain concentrations of fluoxetine and norfluoxetine correlate with concentrations in blood in some patients [82]. In addition, positron-emission tomography neuroimaging studies using a serotonin transporter (SERT) radioligand showed that the Cps of SSRIs correlate quite well with SERT occupancy, where at least 70% occupancy must be attained for optimal clinical outcome [83, 84]. For citalopram, TDM was shown to be advantageous in the early phase of treatment, in 1 week after start of the medical treatment [85]. In fact, knowing the lag of efficacy by few weeks for antidepressants, TDM could be used initially in order to optimize Cp without waiting for the clinical response, which may either be achieved or not. A study on citalopram has shown good cost-benefit advantage in terms of decreased duration of hospitalization for the patients. In fact, citalopram now has the maximal recommendation level for the application of TDM [86]. The same study group also found that citalopram Cp below 50 ng/ml on day 7 of treatment was predictive for treatment failure later on [87]. For paroxetine, a positive correlation was found between the drug concentration in blood and serotonin syndrome symptoms [88].

Besides above, evidence for a statistically significant relationship between drug concentration and therapeutic outcome is still lacking for TCA mianserin, antidepressants mirtazapine and trazodone, norepinephrine reuptake inhibitor (NRI) reboxetine, and monoamine oxidase inhibitors (MAOs) moclobemide and tranylcypromine. Interestingly, some animal studies have shown that P-gp efflux transporter can also influence drug availability in the brain for TCA nortriptyline and SSRI citalopram [89–91].

Conclusion

The success of the pharmacologic treatments in neuropsychiatric disorders is influenced by several factors, and among those, the pharmacokinetic differences between individuals should be seriously taken into consideration. In fact, suboptimal Cp or higher than expected concentrations, even if the drug dosage is correct, can be responsible for the lack of therapeutic response or the manifestation of relevant side effects, respectively. In addition, patient nonadherence and incorrect drug use can be relevant factors responsible for the lack of the pharmacological response.

For all these issues, TDM should be a relatively easy tool to improve current therapies applied in daily clinical practice, further in the direction of a "personalized medicine" to identify each individual patient's best therapeutic concentration.

Most importantly, besides the quantification of Cp, TDM should interpret this value (especially for patients in polytherapy) to help the specialist make correct and timely decision(s) related to either the dosage or change of the drug in case the current regime is not effective.

In situations where the drug and/or its metabolite(s) concentrations are found different than expected, pharmacogenetic tests on the most relevant polymorphisms of CYP450 (e.g., CYP2D6)

would help to understand each patient's metabolic characteristics.

All these strategies are far from trivial, especially if we notice that many patients do not benefit from the standard therapy, or they might suspend/discontinue the therapy during chronic treatment or might use them not as prescribed.

In summary, though the utility of TDM in clinical practice is clear, there is still a wide window for improvement. In fact, besides helping the specialist in making the right decisions, TDM also seems to offer some cost-benefit advantages, including reduced length of hospital stay for patients; however, more studies are required to seal such claims.

Cross-References

► Bipolar Disorder

References

1. Hiemke C, Bergemann N, Clement HW, Conca A, Deckert J, Domschke K, et al. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: update 2017. Pharmacopsychiatry. 2018;51(01–02):9–62. https://doi.org/10.1055/s-0043-116492.
2. Gupta N. Guidelines for lithium monitoring: are they ideal? Acta Psychiatr Scand. 2001;104(1):76–7. https://doi.org/10.1034/j.1600-0447.2001.104001076.x.
3. Egberts KM, Mehler-Wex C, Gerlach M. Therapeutic drug monitoring in child and adolescent psychiatry. Pharmacopsychiatry. 2011;44(6):249–53. https://doi.org/10.1055/s-0031-1286291.
4. Klotz U. Pharmacokinetics and drug metabolism in the elderly. Drug Metab Rev. 2009;41(2):67–76. https://doi.org/10.1080/03602530902722679.
5. Hiemke C. Clinical utility of drug measurement and pharmacokinetics: therapeutic drug monitoring in psychiatry. Eur J Clin Pharmacol. 2008;64(2):159–66. https://doi.org/10.1007/s00228-007-0430-1.
6. Jaquenoud Sirot E, Knezevic B, Morena GP, Harenberg S, Oneda B, Crettol S, et al. ABCB1 and cytochrome P450 polymorphisms: clinical pharmacogenetics of clozapine. J Clin Psychopharmacol. 2009;29(4):319–26. https://doi.org/10.1097/JCP.0b013e3181acc372.
7. Jaquenoud Sirot E, van der Velden JW, Rentsch K, Eap CB, Baumann P. Therapeutic drug monitoring and pharmacogenetic tests as tools in pharmacovigilance. Drug Saf. 2006;29(9):735–68. https://doi.org/10.2165/00002018-200629090-00001.
8. Uchida H, Mamo DC, Mulsant BH, Pollock BG, Kapur S. Increased antipsychotic sensitivity in elderly patients: evidence and mechanisms. J Clin Psychiatry. 2009;70(3):397–405. https://doi.org/10.4088/JCP.08r04171.
9. Kinirons MT, O'Mahony MS. Drug metabolism and ageing. Br J Clin Pharmacol. 2004;57(5):540–4. https://doi.org/10.1111/j.1365-2125.2004.02096.x.
10. Zullig LL, Peterson ED, Bosworth HB. Ingredients of successful interventions to improve medication adherence. JAMA. 2013;310(24):2611–2. https://doi.org/10.1001/jama.2013.282818.
11. Stepanova D, Beran RG. The benefits of antiepileptic drug (AED) blood level monitoring to complement clinical management of people with epilepsy. Epilepsy Behav. 2015;42:7–9. https://doi.org/10.1016/j.yebeh.2014.09.069.
12. Ceskova E. The need to improve current psychopharmacotherapy before developing new drugs. Expert Opin Pharmacother. 2014;15(14):1969–73. https://doi.org/10.1517/14656566.2014.941806.
13. Crettol S, de Leon J, Hiemke C, Eap CB. Pharmacogenomics in psychiatry: from therapeutic drug monitoring to genomic medicine. Clin Pharmacol Ther. 2014;95(3):254–7. https://doi.org/10.1038/clpt.2013.221.
14. de Leon J. Focusing on drug versus disease mechanisms and on clinical subgrouping to advance personalised medicine in psychiatry. Acta Neuropsychiatr. 2014;26(6):327–33. https://doi.org/10.1017/neu.2014.14.
15. Shin C, Han C, Pae CU, Patkar AA. Precision medicine for psychopharmacology: a general introduction. Expert Rev Neurother. 2016;16(7):831–9. https://doi.org/10.1080/14737175.2016.1182022.
16. Collins N, Barnes TR, Shingleton-Smith A, Gerrett D, Paton C. Standards of lithium monitoring in mental health trusts in the UK. BMC Psychiatry. 2010;10:80. https://doi.org/10.1186/1471-244X-10-80.
17. Greenblatt DJ, Gan L, Harmatz JS, Shader RI. Pharmocokinetics and pharmacodynamics of single-dose triazolam: electroencephalography compared with the Digit-Symbol Substitution Test. Br J Clin Pharmacol. 2005;60(3):244–8. https://doi.org/10.1111/j.1365-2125.2005.02409.x.
18. Licht RW, Vestergaard P, Kessing LV, Larsen JK, Thomsen PH, Danish Psychiatric Association and the Child and Adolescent Psychiatric Association in Denmark. Psychopharmacological treatment with lithium and antiepileptic drugs: suggested guidelines from the Danish Psychiatric Association and the Child and Adolescent Psychiatric Association in Denmark. Acta Psychiatr Scand Suppl. 2003;108(419):1–22. https://doi.org/10.1034/j.1600-0447.108.s419.1.x.
19. Patsalos PN, Berry DJ, Bourgeois BF, Cloyd JC, Glauser TA, Johannessen SI, et al. Antiepileptic drugs – best practice guidelines for therapeutic drug monitoring: a position paper by the subcommission on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies. Epilepsia. 2008;49(7):1239–76. https://doi.org/10.1111/j.1528-1167.2008.01561.x.

20. Müller MJ, Dragicevic A, Fric M, Gaertner I, Grasmäder K, Härtter S, et al. Therapeutic drug monitoring of tricyclic antidepressants: how does it work under clinical conditions? Pharmacopsychiatry. 2003;36(3):98–104. https://doi.org/10.1055/s-2003-39983.
21. Perry PJ. Therapeutic drug monitoring of antipsychotics. Psychopharmacol Bull. 2001;35(3):19–29.
22. Connolly KR, Thase ME. The clinical management of bipolar disorder: a review of evidence-based guidelines. Prim Care Companion CNS Disord. 2011;13(4). https://doi.org/10.4088/PCC.10r01097.
23. Preskorn SH, Jerkovich GS. Central nervous system toxicity of tricyclic antidepressants: phenomenology, course, risk factors, and role of therapeutic drug monitoring. J Clin Psychopharmacol. 1990;10(2):88–95.
24. Preskorn SH, Fast GA. Therapeutic drug monitoring for antidepressants: efficacy, safety, and cost effectiveness. J Clin Psychiatry. 1991;52(Suppl):23–33.
25. Perry PJ, Zeilmann C, Arndt S. Tricyclic antidepressant concentrations in plasma: an estimate of their sensitivity and specificity as a predictor of response. J Clin Psychopharmacol. 1994;14(4):230–40.
26. Wille SM, Cooreman SG, Neels HM, Lambert WE. Relevant issues in the monitoring and the toxicology of antidepressants. Crit Rev Clin Lab Sci. 2008;45(1):25–89. https://doi.org/10.1080/10408360701713112.
27. Preskorn SH, Fast GA. Tricyclic antidepressant-induced seizures and plasma drug concentration. J Clin Psychiatry. 1992;53(5):160–2.
28. Burke MJ, Preskorn SH. Therapeutic drug monitoring of antidepressants: cost implications and relevance to clinical practice. Clin Pharmacokinet. 1999;37(2):147–65.
29. Bodén R, Brandt L, Kieler H, Andersen M, Reutfors J. Early non-adherence to medication and other risk factors for rehospitalization in schizophrenia and schizoaffective disorder. Schizophr Res. 2011;133(1–3):36–41. https://doi.org/10.1016/j.schres.2011.08.024.
30. Stieffenhofer V, Saglam H, Schmidtmann I, Silver H, Hiemke C, Konrad A. Clozapine plasma level monitoring for prediction of rehospitalization schizophrenic outpatients. Pharmacopsychiatry. 2011;44(2):55–9. https://doi.org/10.1055/s-0030-1267178.
31. Zernig G, Lechner T, Kramer-Reinstadler K, Hinterhuber H, Hiemke C, Saria A. What the clinician still has to be reminded of. Ther Drug Monit. 2004;26(5):582.
32. Sharma S, Joshi S, Mukherji S, Bala K, Tripathi CB. Therapeutic drug monitoring: appropriateness and clinical utility in neuropsychiatry practice. Am J Ther. 2009;16(1):11–6. https://doi.org/10.1097/MJT.0b013e31817fd85f.
33. Conca A, Schmidt E, Pastore M, Hiemke C, Duffy D, Giuppony G. Therapeutic drug monitoring in Italian psychiatry. Pharmacopsychiatry. 2011;44(6):259–62. https://doi.org/10.1055/s-0031-1286281.
34. Loayza N, Crettol S, Riquier F, Eap CB. Adherence to antidepressant treatment: what the doctor thinks and what the patient says. Pharmacopsychiatry. 2012;45(5):204–7. https://doi.org/10.1055/s-0032-1306311.
35. Guo W, Guo GX, Sun C, Zhang J, Rong Z, He J, et al. Therapeutic drug monitoring of psychotropic drugs in China: a nationwide survey. Ther Drug Monit. 2013;35(6):816–22. https://doi.org/10.1097/FTD.0b013e318296a2ff.
36. Mann K, Hiemke C, Schmidt LG, Bates DW. Appropriateness of therapeutic drug monitoring for antidepressants in routine psychiatric inpatient care. Ther Drug Monit. 2006;28(1):83–8. https://doi.org/10.1097/01.ftd.0000189897.16307.65.
37. Mann K, Hiemke C, Lotz J, Schmidt LG, Lackner KJ, Bates DW. Appropriateness of plasma level determinations for lithium and valproate in routine care of psychiatric inpatients with affective disorders. J Clin Psychopharmacol. 2006;26(6):671–3. https://doi.org/10.1097/01.jcp.0000246208.11153.b6.
38. Hiemke C. Therapeutic drug monitoring in neuropsychopharmacology: does it hold its promises? Eur Arch Psychiatry Clin Neurosci. 2008;258(Suppl 1):21–7. https://doi.org/10.1007/s00406-007-1005-y.
39. Sjöqvist F. Development of clinical pharmacology as a medical speciality in Europe – the roles of WHO, IUPHAR and EACPT. Basic Clin Pharmacol Toxicol. 2014;115(2):172–8. https://doi.org/10.1111/bcpt.12278.
40. Goodwin FK. Rationale for using lithium in combination with other mood stabilizers in the management of bipolar disorder. J Clin Psychiatry. 2003;64(Suppl 5):18–24.
41. Frye MA, Yatham LN, Calabrese JR, Bowden CL, Ketter TA, Suppes T, et al. Incidence and time course of subsyndromal symptoms in patients with bipolar I disorder: an evaluation of 2 placebo-controlled maintenance trials. J Clin Psychiatry. 2006;67(11):1721–8.
42. Lin D, Mok H, Yatham LN. Polytherapy in bipolar disorder. CNS Drugs. 2006;20(1):29–42. https://doi.org/10.2165/00023210-200620010-00003.
43. Salvi V, Cat Berro A, Bechon E, Bogetto F, Maina G. Lithium and anticonvulsants in the treatment of mania and in the prophylaxis of recurrences [Article in Italian]. Riv Psichiatr. 2011;46(3):172–81. https://doi.org/10.1708/889.9807.
44. Freeman MP, Stoll AL. Mood stabilizer combinations: a review of safety and efficacy. Am J Psychiatry. 1998;155(1):12–21. https://doi.org/10.1176/ajp.155.1.12.
45. Post RM. Chapter 14, Complex combination therapy for long-term stability in bipolar disorder. In: Akiskal HS, Tohen M, editors. Bipolar psychopharmacotherapy: caring for the patient. 2nd ed. West Sussex: Wiley; 2011. p. 285–98. https://doi.org/10.1002/9780470975114.
46. Juruena MF, Ottoni GL, Machado-Vieira R, Carneiro RM, Weingarthner N, Marquardt AR, et al. Bipolar I and II disorder residual symptoms: oxcarbazepine and carbamazepine as add-on treatment to lithium in a double-blind, randomized trial. Prog Neuropsychopharmacol Biol Psychiatry. 2009;33(1):94–9. https://doi.org/10.1016/j.pnpbp.2008.10.012.
47. Baldessarini RJ. Commentary: the Bipolar Affective Disorder: Lithium/Anticonvulsant Evaluation (BALANCE)

study. Bipolar Disord. 2010;12(7):669–72. https://doi.org/10.1111/j.1399-5618.2010.00860.x.
48. Cipriani A, Reid K, Young AH, Macritchie K, Geddes J. Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder. Cochrane Database Syst Rev. 2013;(10):CD003196. https://doi.org/10.1002/14651858.CD003196.pub2.
49. Sharma V, Persad E, Mazmanian D, Karunaratne K. Treatment of rapid cycling bipolar disorder with combination therapy of valproate and lithium. Can J Psychiatry. 1993;38(2):137–9. https://doi.org/10.1177/070674379303800213.
50. Davis J, Desmond M, Berk M. Lithium and nephrotoxicity: a literature review of approaches to clinical management and risk stratification. BMC Nephrol. 2018;19(1):305. https://doi.org/10.1186/s12882-018-1101-4.
51. Severus WE, Kleindienst N, Seemüller F, Frangou S, Möller HJ, Greil W. What is the optimal serum lithium level in the long-term treatment of bipolar disorder – a review? Bipolar Disord. 2008;10(2):231–7. https://doi.org/10.1111/j.1399-5618.2007.00475.x.
52. Keller MB, Lavori PW, Kane JM, Gelenberg AJ, Rosenbaum JF, Walzer EA, et al. Subsyndromal symptoms in bipolar disorder. A comparison of standard and low serum levels of lithium. Arch Gen Psychiatry. 1992;49(5):371–6.
53. Spies M, Knudsen GM, Lanzenberger R, Kasper S. The serotonin transporter in psychiatric disorders: insights from PET imaging. Lancet Psychiatry. 2015;2(8):743–55. https://doi.org/10.1016/S2215-0366(15)00232-1.
54. Del Grande C, Muti M, Musetti L, Pergentini I, Corsi M, Turri M, et al. Long-term treatment of bipolar disorder: how should we use lithium salts? [Article in Italian]. Riv Psichiatr. 2012;47(6):515–26. https://doi.org/10.1708/1178.13058.
55. Muti M, Del Grande C, Musetti L, Marazziti D, Pergentini I, Corsi M, et al. Prescribing patterns of lithium or lithium+valproate in manic or mixed episodes: a naturalistic study. Int Clin Psychopharmacol. 2013;28(6):305–11. https://doi.org/10.1097/YIC.0b013e3283642348.
56. Amdisen A. Serum level monitoring and clinical pharmacokinetics of lithium. Clin Pharmacokinet. 1977;2(2):73–92. https://doi.org/10.2165/00003088-197702020-00001.
57. Allen MH, Hirschfeld RM, Wozniak PJ, Baker JD, Bowden CL. Linear relationship of valproate serum concentration to response and optimal serum levels for acute mania. Am J Psychiatry. 2006;163(2):272–5. https://doi.org/10.1176/appi.ajp.163.2.272.
58. Fleming J, Chetty M. Therapeutic monitoring of valproate in psychiatry: how far have we progressed? Clin Neuropharmacol. 2006;29(6):350–60. https://doi.org/10.1097/01.WNF.0000228209.69524.E8.
59. Meltzer HY. Update on typical and atypical antipsychotic drugs. Annu Rev Med. 2013;64:393–406. https://doi.org/10.1146/annurev-med-050911-161504.
60. Aringhieri S, Carli M, Kolachalam S, Verdesca V, Cini E, Rossi M, et al. Molecular targets of atypical antipsychotics: from mechanism of action to clinical differences. Pharmacol Ther. 2018;192:20–41. https://doi.org/10.1016/j.pharmthera.2018.06.012.
61. Uchida H, Takeuchi H, Graff-Guerrero A, Suzuki T, Watanabe K, Mamo DC. Predicting dopamine D_2 receptor occupancy from plasma levels of antipsychotic drugs: a systematic review and pooled analysis. J Clin Psychopharmacol. 2011;31(3):318–25. https://doi.org/10.1097/JCP.0b013e318218d339.
62. Grundmann M, Kacirova I, Urinovska R. Therapeutic drug monitoring of atypical antipsychotic drugs. Acta Pharm. 2014;64(4):387–401. https://doi.org/10.2478/acph-2014-0036.
63. Lako IM, van den Heuvel ER, Knegtering H, Bruggeman R, Taxis K. Estimating dopamine D_2 receptor occupancy for doses of 8 antipsychotics: a meta-analysis. J Clin Psychopharmacol. 2013;33(5):675–81. https://doi.org/10.1097/JCP.0b013e3182983ffa.
64. Gunes A, Spina E, Dahl ML, Scordo MG. ABCB1 polymorphisms influence steady-state plasma levels of 9-hydroxyrisperidone and risperidone active moiety. Ther Drug Monit. 2008;30(5):628–33. https://doi.org/10.1097/FTD.0b013e3181858ca9.
65. Alberati D, Moreau JL, Lengyel J, Hauser N, Mory R, Borroni E, et al. Glycine reuptake inhibitor RG1678: a pharmacologic characterization of an investigational agent for the treatment of schizophrenia. Neuropharmacology. 2012;62(2):1152–61. https://doi.org/10.1016/j.neuropharm.2011.11.008.
66. Rostami-Hodjegan A, Amin AM, Spencer EP, Lennard MS, Tucker GT, Flanagan RJ. Influence of dose, cigarette smoking, age, sex, and metabolic activity on plasma clozapine concentrations: a predictive model and nomograms to aid clozapine dose adjustment and to assess compliance in individual patients. J Clin Psychopharmacol. 2004;24(1):70–8. https://doi.org/10.1097/01.jcp.0000106221.36344.4d.
67. Potkin SG, Bera R, Gulasekaram B, Costa J, Hayes S, Jin Y, et al. Plasma clozapine concentrations predict clinical response in treatment-resistant schizophrenia. J Clin Psychiatry. 1994;55(Suppl B):133–6.
68. Lopez LV, Kane JM. Plasma levels of second-generation antipsychotics and clinical response in acute psychosis: a review of the literature. Schizophr Res. 2013;147(2–3):368–74. https://doi.org/10.1016/j.schres.2013.04.002.
69. Jerling M, Lindström L, Bondesson U, Bertilsson L. Fluvoxamine inhibition and carbamazepine induction of the metabolism of clozapine: evidence from a therapeutic drug monitoring service. Ther Drug Monit. 1994;16(4):368–74.
70. Spina E, de Leon J. Metabolic drug interactions with newer antipsychotics: a comparative review. Basic Clin Pharmacol Toxicol. 2007;100(1):4–22. https://doi.org/10.1111/j.1742-7843.2007.00017.x.
71. Perry PJ, Miller DD, Arndt SV, Cadoret RJ. Clozapine and norclozapine plasma concentrations and clinical response of treatment-refractory schizophrenic

patients. Am J Psychiatry. 1991;148(2):231–5. https://doi.org/10.1176/ajp.148.2.231.
72. Kronig MH, Munne RA, Szymanski S, Safferman AZ, Pollack S, Cooper T, et al. Plasma clozapine levels and clinical response for treatment-refractory schizophrenic patients. Am J Psychiatry. 1995;152(2):179–82. https://doi.org/10.1176/ajp.152.2.179.
73. Mauri MC, Volonteri LS, Colasanti A, Fiorentini A, De Gaspari IF, Bareggi SR. Clinical pharmacokinetics of atypical antipsychotics: a critical review of the relationship between plasma concentrations and clinical response. Clin Pharmacokinet. 2007;46(5):359–88. https://doi.org/10.2165/00003088-200746050-00001.
74. Urquhart DM, Wluka AE, van Tulder M, Heritier S, Forbes A, Fong C, et al. Efficacy of low-dose amitriptyline for chronic low back pain: a randomized clinical trial. JAMA Intern Med. 2018;178(11):1474–81. https://doi.org/10.1001/jamainternmed.2018.4222.
75. Yi XY, Ni SF, Ghadami MR, Meng HQ, Chen MY, Kuang L, et al. Trazodone for the treatment of insomnia: a meta-analysis of randomized placebo-controlled trials. Sleep Med. 2018;45:25–32. https://doi.org/10.1016/j.sleep.2018.01.010.
76. Popova D, Castrén E, Taira T. Chronic fluoxetine administration enhances synaptic plasticity and increases functional dynamics in hippocampal CA3-CA1 synapses. Neuropharmacology. 2017;126:250–6. https://doi.org/10.1016/j.neuropharm.2017.09.003.
77. Porcelli S, Fabbri C, Spina E, Serretti A, De Ronchi D. Genetic polymorphisms of cytochrome P450 enzymes and antidepressant metabolism. Expert Opin Drug Metab Toxicol. 2011;7(9):1101–15. https://doi.org/10.1517/17425255.2011.597740.
78. Chew ML, Mulsant BH, Pollock BG, Lehman ME, Greenspan A, Mahmoud RA, et al. Anticholinergic activity of 107 medications commonly used by older adults. J Am Geriatr Soc. 2008;56(7):1333–41. https://doi.org/10.1111/j.1532-5415.2008.01737.x.
79. Glotzbach RK, Preskorn SH. Brain concentrations of tricyclic antidepressants: single-dose kinetics and relationship to plasma concentrations in chronically dosed rats. Psychopharmacology (Berl). 1982;78(1):25–7. https://doi.org/10.1007/BF00470582.
80. Ostad Haji E, Hiemke C, Pfuhlmann B. Therapeutic drug monitoring for antidepressant drug treatment. Curr Pharm Des. 2012;18(36):5818–27. https://doi.org/10.2174/138161212803523699.
81. Jakubovski E, Varigonda AL, Freemantle N, Taylor MJ, Bloch MH. Systematic review and meta-analysis: dose-response relationship of selective serotonin reuptake inhibitors in major depressive disorder. Am J Psychiatry. 2016;173(2):174–83. https://doi.org/10.1176/appi.ajp.2015.15030331.
82. Karson CN, Newton JE, Livingston R, Jolly JB, Cooper TB, Sprigg J, et al. Human brain fluoxetine concentrations. J Neuropsychiatry Clin Neurosci. 1993;5(3):322–9. https://doi.org/10.1176/jnp.5.3.322.
83. Meyer JH. Imaging the serotonin transporter during major depressive disorder and antidepressant treatment. J Psychiatry Neurosci. 2007;32(2):86–102.
84. Meyer JH, Wilson AA, Sagrati S, Hussey D, Carella A, Potter WZ, et al. Serotonin transporter occupancy of five selective serotonin reuptake inhibitors at different doses: an [11C]DASB positron emission tomography study. Am J Psychiatry. 2004;161(5):826–35. https://doi.org/10.1176/appi.ajp.161.5.826.
85. Ostad Haji E, Tadic A, Wagner S, Dragivevic A, Müller MJ, Boland K, et al. Early improvement and serum concentrations of citalopram to predict antidepressant drug response of patients with major depression. Pharmacopsychiatry. 2013;46(7):261–6. https://doi.org/10.1055/s-0033-1354370.
86. Ostad Haji E, Mann K, Dragicevic A, Müller MJ, Boland K, Rao ML, et al. Potential cost-effectiveness of therapeutic drug monitoring for depressed patients treated with citalopram. Ther Drug Monit. 2013;35(3):396–401. https://doi.org/10.1097/FTD.0b013e3182885d9d.
87. Ostad Haji E, Tadić A, Wagner S, Dragicevic A, Müller MJ, Boland K, et al. Association between citalopram serum levels and clinical improvement of patients with major depression. J Clin Psychopharmacol. 2011;31(3):281–6. https://doi.org/10.1097/JCP.0b013e318218f503.
88. Hegerl U, Bottlender R, Gallinat J, Kuss HJ, Ackenheil M, Möller HJ. The serotonin syndrome scale: first results on validity. Eur Arch Psychiatry Clin Neurosci. 1998;248(2):96–103. https://doi.org/10.1007/s004060050024.
89. Doran A, Obach RS, Smith BJ, Hosea NA, Becker S, Callegari E, et al. The impact of P-glycoprotein on the disposition of drugs targeted for indications of the central nervous system: evaluation using the MDR1A/1B knockout mouse model. Drug Metab Dispos. 2005;33(1):165–74. https://doi.org/10.1124/dmd.104.001230.
90. Suzuki T, Mihara K, Nakamura A, Kagawa S, Nagai G, Nemoto K, et al. Effects of genetic polymorphisms of CYP2D6, CYP3A5, and ABCB1 on the steady-state plasma concentrations of aripiprazole and its active metabolite, dehydroaripiprazole, in Japanese patients with schizophrenia. Ther Drug Monit. 2014;36(5):651–5. https://doi.org/10.1097/FTD.0000000000000070.
91. Uhr M, Grauer MT, Holsboer F. Differential enhancement of antidepressant penetration into the brain in mice with abcb1ab (mdr1ab) P-glycoprotein gene disruption. Biol Psychiatry. 2003;54(8):840–6. https://doi.org/10.1016/S0006-3223(03)00074-X.

Cardiovascular and Central Nervous System Toxicity by Anticancer Drugs in Breast Cancer Patients

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Gianfranco Natale and Guido Bocci

Contents

Abstract

Breast cancer is one of the most malignant diseases, associated with high rate mortality. In this chapter a particular attention is paid on cardiovascular and central nervous system toxicity induced by chemotherapeutic agents used for both primary and metastatic treatment of this life-threatening pathology. With respect to traditional drugs, including anthracyclines, taxanes, fluoropyrimidines, and endocrine therapy, the more recent targeted therapies, such as human epidermal growth factor receptor 2 (HER2) and vascular endothelial growth factor (VEGF), aimed to ameliorate anticancer activity and to reduce toxic effects by affecting more specific molecular sites. However, despite the improvement in breast cancer treatment, these novel drugs were also found to be associated, even if at a lesser extent, with important side effects, such as cardiotoxicity, with consequent heart failure. For this reason, the cardiovascular and neuropsychiatric safety profiles of all anticancer drugs and protocols

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*,
https://doi.org/10.1007/978-3-030-28008-6_50

remain important items to be carefully evaluated in breast cancer patients.

Keywords

Alkylating agents · Anthracyclines · Brain toxicity · Cardioprotection · Cardiotoxicity · Endocrine therapy · ERB2 inhibitors · Fluoropyrimidines · Taxanes · VEGF inhibitors

Introduction

During the last decades, the prognosis of tumor malignancies has been highly improved by the progress in cancer prevention and diagnosis, as well as in therapeutic protocol design. In this respect, several diseases can now be efficiently treated or maintained in remission for a long time, allowing cancer patients to live for many years after diagnosis.

Considering the severity and the high mortality rate of breast cancer, prevention tests remain an important tool to protect potential patients from the disease. Apart from age and hormonal, dietetic, and metabolic factors, genetic mutations also represent an important high risk factor for developing breast cancer [1]. Screening of general population, including self-palpation and mammography, also promotes incidence and mortality reduction [2]. In particular, the American Institute of Ultrasound in Medicine [3] released a Practice Guideline for the Performance of a Breast Ultrasound Examination in order to improve the safe and effective use of ultrasound in medicine through professional and public education and research. More in depth, assistance is provided to medical practitioners when performing sonographic examinations of the breast for palpable masses and implant detection, as well as interventional procedures [4].

Once breast cancer is diagnosed, surgery, radiotherapy, and chemotherapy are the main tools to treat primary and metastatic tumor and to manage the possible occurrence of cancer relapse. However efficacious, innovative, and improved it is, anticancer therapy still includes the onset of mild to severe side effects that involve several organs in survivor patients. In particular, the present chapter focuses its attention on cardiovascular and central nervous system (CNS) toxicity induced by chemotherapeutic agents used for primary and metastatic cancer breast treatment (Fig. 1). With respect to the traditional drugs (e.g., anthracyclines, taxanes, and fluoropyrimidines), which merely act on DNA biochemistry, the more recent targeted therapies aimed to improve anticancer activity and to reduce toxic effects by affecting more specific molecular sites, such as the human epidermal growth factor receptor 2 (HER2) and the vascular endothelial growth factor (VEGF). Unfortunately, in spite of the progress in breast cancer treatment, in the past decades, these novel drugs were also found to be associated, even if at a lesser extent, with important side effects such as life-threatening cardiotoxicity, with consequent heart failure, and cognitive impairment. For this reason, the cardio- and CNS-safety profiles of all anticancer drugs and protocols remain important items to be carefully evaluated in cancer breast patients. Finally, although this is not the aim of the present chapter, it should be remembered that chest radiation in breast cancer treatment is cardiotoxic as well, with pericarditis, premature coronary artery disease, valvular heart disease, arrhythmias, and restrictive/constrictive cardiomyopathy, until heart failure [5–8].

Anticancer Drug-Induced Cardiotoxicity

Anticancer drug-induced cardiotoxicity can include both acute (transient) and chronic injury. In this respect, the latter is more severe and can be classified into type I (early onset) and type II (late onset). Type I is associated with irreversible cardiac cell damage, including vacuole formation, myocyte loss, and necrosis, with permanent and cumulative cell death, and it is typically induced by traditional chemotherapeutic agents, whereas type II is mainly caused by novel targeted drugs and is associated with dose-independent, noncumulative, and reversible myocardial

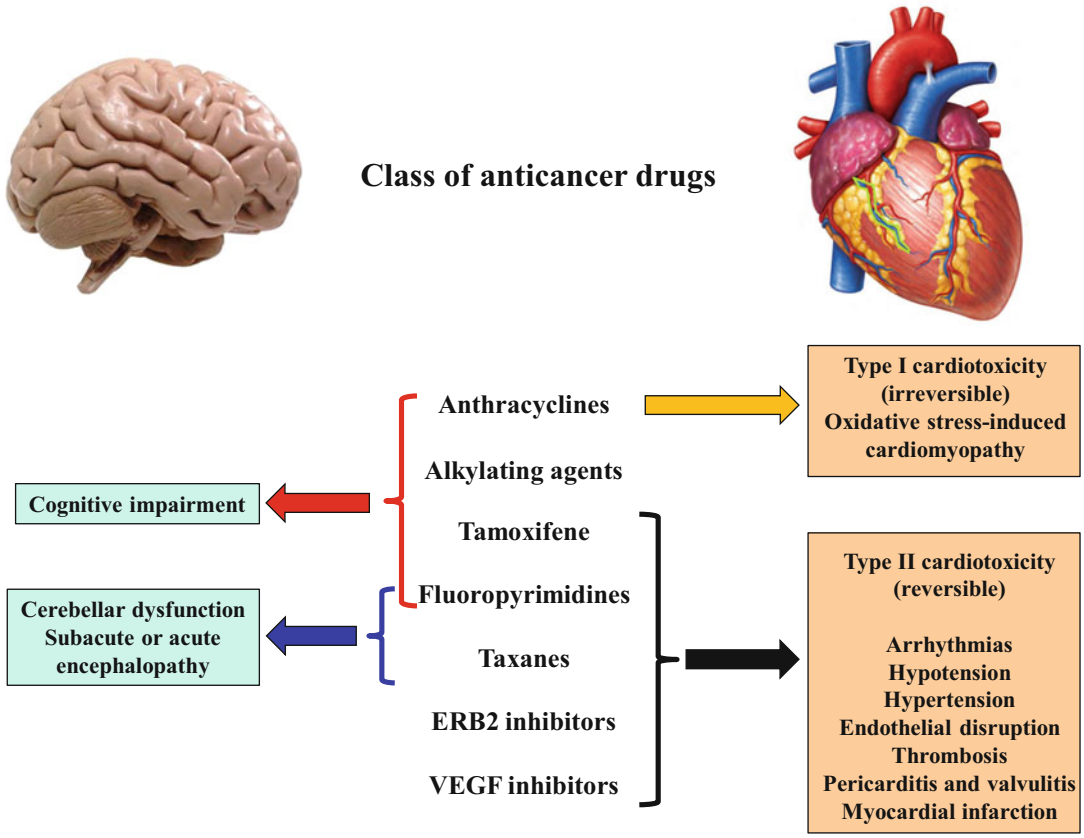

Fig. 1 Main cardiovascular and central nervous system toxicity of antineoplastic drugs currently administered in breast cancer patients

dysfunction, with absence of ultrastructural alterations (Fig. 1). This difference depends on dissimilar mechanisms. Then, although recent therapeutic strategies appear endowed with less severe cardiovascular toxic effects, attention must be paid in their application. Oncologists should consider the potential of the anticancer therapy addressed to the patient, informing her on reasonable expectations of benefits and side effects. In younger patients with high risk of cancer relapse, the possible occurrence of cardiotoxicity should be accepted in comparison with improvements in survival. A major attention is needed in patients with specific risk factors. In particular, genetic assessment of clinical risk factors and molecular and imaging techniques are necessary to recognize those patients at high risk of developing chemotherapy-related cardiovascular toxicity. At the same time, cardiac monitoring, in terms of biomarker assessment as well as functional and myocardial strain indices, plays a pivotal role in preventing heart failure. Innovative and improved combination chemotherapeutic regimens, as well as cardioprotective agents, also need to be appropriately developed in order to mitigate or limit unwanted effects [6, 9–13].

Chemotherapy-Induced Cardiotoxicity in Breast Cancer

Traditional drugs, such as anthracyclines, taxanes, and fluoropyrimidines, are very effective pharmacological agents endowed with a widely used antineoplastic spectrum in the treatment of breast cancer. However, in spite of their potent

anticancer activity, these agents induce severe side effects, including life-threatening cardiotoxic disorders. Even if new agents have been successfully introduced in anticancer therapy, these old drugs still represent important reference tools in chemotherapeutic protocols when treating cancer patients. Although the novel tyrosine kinase inhibitors revealed remarkably effective as anticancer drugs with less severe side effects, cardiotoxicity remains the main concern, especially in combination therapies, where unexpected reactions can occur [14].

Traditional Anticancer Drugs

Anthracyclines

Anthracyclines represent an old group of anticancer drugs, mainly including doxorubicin and epirubicin. They are natural compounds which were derived in the 1950s from rhodomycin B and isolated from the actinomyces *Streptomyces peucetius*, showing also antibacterial activity. At present, thanks to their efficacy on survival in lymphomas and different solid cancers, in particular breast cancer, they are still a major component of antitumor drug regimens. Indeed, anthracycline-based antitumor protocols significantly decrease breast cancer mortality. However, this class of drugs, apart from severe cardiotoxicity, can also cause alopecia and leukemia [15]. Menopause and hypertension represent risk factors for anthracycline-induced cardiac impairment. Accordingly, in experimental studies, spontaneously hypertensive or ovariectomized rats were shown to exhibit an increased incidence and severity of doxorubicin-induced cardiotoxicity [16].

The antitumor activity of anthracyclines is due to different mechanisms which can be, at least in part, responsible for cardiotoxicity, as well as interaction with the DNA gyrase and topoisomerase II (alpha and beta), allowing anthracyclines to intercalate DNA, with consequent double-stranded chromosomal DNA breaks which inhibit transcription and replication, with cell cycle arrest; modulation of signal transduction pathways involved in cell growth inhibition; production of both reactive oxygen species (ROS) and reactive nitrogen species (RNS); oxidative stress-induced apoptosis; intracellular calcium dysregulation; increased expression of endothelin-1 and its receptor, with vasoconstrictive effects; extracellular matrix remodeling, with increased production of matrix metalloproteinases-2 and metalloproteinases-9; and ceramide accumulation. At the same time, doxorubicin is able to induce cyclooxygenase-2 (COX-2) activity, with cardioprotective effects. Then, co-administration of COX-2 inhibitors aggravates doxorubicin-induced myocardial apoptosis [13, 15, 17, 18].

Since the 1960s dose-dependent anthracycline-induced severe cardiotoxicity is well-known. In particular, cumulative doses exceeding 550 mg/m^2 for doxorubicin and 950 mg/m^2 for epirubicin have been associated with an enhanced incidence of heart failure [13, 19, 20].

Anthracyclines are just regarded as the representative member of drugs able to induce early onset type I cardiotoxicity, with dose-dependent severe and irreversible cardiomyopathy, leading to heart failure. Recent observations indicate that some complications can occur independently on the dose regimen, suggesting that there is not a safe dose [6].

Apart from a reversible inflammation, with pericarditis and myocarditis, cardiomyopathy remains the principal severe toxic effect induced by anthracyclines. This specific cardiomyopathy seems to depend on the interaction with both types of topoisomerase II. While the alpha form is observed in rapidly dividing cells, as it occurs in tumor cells, and accounts for the anticancer activity of anthracyclines, the interaction with the beta form present in cardiomyocytes triggers the activation of DNA repair. In particular, the induction of protein p53 can also lead to suppression of genes involved in organelle biogenesis, with consequent abnormal mitochondria. At the same time, the process of autophagy deputed to removal of altered organelles is also impaired. Taken together, these events lead to an increased number of dysfunctional mitochondria in cardiomyocytes. In addition to this, thanks to their high affinity for the mitochondrial phospholipid cardiolipin, anthracyclines accumulate in myocardial cell mitochondria, where they reduce oxidative phosphorylation, with ROS generation, leading to

endomyocardial interstitial fibrosis and vacuolation. Additional mechanisms include direct toxic effects on cardiac progenitor cells with reduced repair potential after injury; degradation of ultrastructural proteins including titin and dystrophin; oxidative stress through the chelation of free intracellular iron and formation of anthracycline-iron complexes; and alteration of cellular and mitochondrial calcium homeostasis [5, 13, 15, 21].

Besides the heart, doxorubicin is able to accumulate also in the spleen, kidney, and large intestine. However, experimental studies in rats showed that the pretreatment with reserpine or the calcium antagonist nicardipine is able to reduce the accumulation of doxorubicin in these organs, but not in the heart, where the typical red-orange fluorescence of the drug is high in both atrium and ventricle. This finding might be attributable to the formation of the main metabolite adriamycinol which is more hydrophilic than doxorubicin and cannot easily cross membranes in cardiomyocytes, where it exerts its selective toxicity [22, 23].

Additional mechanisms include the loss of iron homeostasis and the calcium overload. The latter would be responsible for increased calpain proteolytic activity, with cellular changes and sarcomere disruption, leading to sarcopenia, impairment of cardiomyocyte energy, and redox balance. Anthracyclines may also affect mitogen-activated protein kinase (MAPK) pathway via ROS- and calcium-dependent mechanisms and cardiac progenitor cells, these effects deserving to be well characterized [13].

Anthracycline cardiotoxicity mainly consists of dilated myocardiopathy with progressive heart dysfunction, pericarditis, arrhythmias, and reduced left ventricle ejection fraction, until heart failure and death. A rare complication in adult patients is represented by mitral regurgitation, as recently reported in a 62-year-old woman affected by breast cancer and treated with six cycles of adjuvant chemotherapy with doxorubicin, cyclophosphamide, and docetaxel, followed by adjuvant anastrozole. This severe dysfunction may be due to an initial local effect of the drug on papillary muscles [24].

Taxanes

The antitumor efficacy of taxanes is due to their ability to act as anti-microtubule agents, then promoting polymerization of tubulin. Accordingly, these agents cause microtubule dysfunction and impair cell division. Members of this class of anticancer drugs mainly include docetaxel and paclitaxel, used in non-small cell lung, ovarian, as well as breast malignancies. Taxane-induced cardiotoxicity is not so frequent and is principally represented by arrhythmias, with mild alterations, such as sinus bradycardia and conduction blocks. Ventricular arrhythmias (tachycardia and fibrillation) and ischemia are very uncommon side effects. The deleterious effects of taxanes can be ascribed to histamine release and cardiac H1 and H2 receptor stimulation. In particular, H2 receptors are involved in reentry depolarization, with consequent ventricular ectopy [13, 25].

Therapeutic protocols containing docetaxel showed to provide excellent results in terms of benefits and survival in breast cancer patients. The addition of bevacizumab to three standard docetaxel-containing adjuvant regimens (doxorubicin plus cyclophosphamide, doxorubicin plus cyclophosphamide, and carboplatin plus trastuzumab) led to a low rate of cardiotoxic events [26]. Similar results were obtained in a phase II, open-label, multicenter pilot study of two docetaxel-based regimens plus bevacizumab for the adjuvant treatment of patients with node-positive or high-risk node-negative breast cancer [27].

Fluoropyrimidines

Fluoropyrimidines are an important class of antimetabolite anticancer agents used for the treatment of several solid tumors, including breast cancer. These drugs were designed as fluorinated uracil-based nucleic acid analogs which irreversibly inhibit thymidylate synthase, a key enzyme in the synthesis of DNA, then inhibiting nucleic acid synthesis and function. The most important representative of this class of fluorinated chemotherapeutic agents is the synthetic 5-fluorouracil (5-FU) which is administered intravenously to be converted into three main active metabolites. The more recent prodrug oral capecitabine

undergoes a sequential enzymatic reaction to be transformed into 5-FU, after a rapid and almost complete gastrointestinal absorption [28].

Cardiotoxicity is an important side effect of cytostatic fluoropyrimidines, with angina pectoris, arrhythmias, palpitation, hypotension, hypertension, malaise, and dyspnea, until life-threatening damages, including myocardial infarction and sudden cardiac death. Electrocardiographic findings show transmural myocardial ischemia, with ST segment elevation [29–32]. Different mechanisms are involved in 5-FU cardiovascular toxicity: vascular endothelial damage followed by coagulation and thrombosis; ischemia secondary to coronary artery spasm; direct toxicity on the myocardium; and thrombosis due to altered rheological factors [33].

Fluoropyrimidines induce irreversible disruption of the endothelial sheet, sometimes leading to thrombus formation [34], extensive cytolysis, and cell detachment, with denudation of the underlying internal elastic lamina, platelet aggregation, fibrin formation, and areas of contracted vessel walls with contracted endothelial cells [33], as well as coronary spasm or microspasm with pain, but no or little changes in functional tests [35, 36]. In animal models several changes were observed, including hemorrhagic infarction, interstitial fibrosis, and inflammatory reaction in the myocardium, including perivascular involvement, pericarditis, and valvulitis, these effects being due to induction of apoptosis, increased oxidative stress, lipid peroxidation with altered antioxidant defense, depletion of high-energy phosphate compounds and accumulation of citrate in the myocardium, and increased oxygen consumption [33, 37]. In a 23-year-old patient, the endomyocardial biopsy evidenced the proliferation of the sarcoplasmic reticulum with marked vacuolization [38], similar to what found with doxorubicin cardiotoxicity [23].

The effects of 5-FU were examined in in vitro primary cell cultures of human cardiomyocytes and human umbilical vein endothelial cells, showing the occurrence of rupture of mitochondrial cristae and dilatation of the cisternae of the endoplasmic reticulum, leading to reduced growth and survival and autophagy activation, as confirmed by the presence of several autophagic vacuoles [39].

Some cardiovascular side effects have been interpreted as allergic reactions, because of the hapten-like properties due to the low molecular weight of fluoropyrimidines. These unwanted events, including allergic angina and myocardial infarction, deal with all kinds of hypersensitivity reactions and were named Kounis syndrome, that is, the concurrence of acute coronary syndromes with the release of inflammatory mediators, such as histamine, arachidonic acid products, platelet-activating factor, and a variety of cytokines and chemokines. Accordingly, the term "cardiovascular toxicity," referred to dose-dependent side effects, should be more correctly replaced by "cardiovascular hypersensitivity," referred to dose-independent side effects [40].

Targeted Therapies

Tyrosine kinases are enzymes that catalyze the transfer of a phosphate residue from ATP to tyrosine residues in other proteins, with consequent modification of their activity. Their activation seems to participate in cancer initiation and progression. For this reason, tyrosine kinases represent the target of novel anticancer therapies. In particular, two classes of inhibitors of these enzymes have been developed: monoclonal antibodies against receptor tyrosine kinases or their ligands and small-molecule inhibitors, targeting both receptor and non-receptor tyrosine kinases [8].

The more recent and innovative targeted therapies acting at more specific molecular sites, such as the human epidermal growth factor receptor 2 (HER2) and the vascular endothelial growth factor (VEGF), have been regarded as safe adjuvant treatments when administered with concomitant traditional chemo- or radiotherapy, especially with the aim to minimize cardiotoxicity [5, 13].

ERB2 Inhibitors

A new class of anticancer drugs introduced for the treatment of breast cancer is represented by ERB2 inhibitors. The human epidermal growth factor (EGF) receptor family includes ERB1-4 members. These transmembrane receptors, endowed

with tyrosine kinase activity, homodimerize or heterodimerize; then they are trans-phosphorylated to finally trigger intracellular responses. In particular, ERB2 is able to interact spontaneously with other ERB members, independently from specific ligand stimulation, thus leading to the activation of signaling pathways that stimulate tumor growth and survival. This glycoproteic receptor appears overexpressed in about 15–30% of breast cancer cases. For this reason, patients with HERB2-positive tumor have a more aggressive disease, with increased cell growth, differentiation, migration, neo-angiogenesis, and worse prognosis, if not properly treated [5, 13].

Then, ERB2 appeared a promising target to design new therapeutic strategies and a new class of humanized monoclonal antibodies that binds the extracellular domain of HER2 has been developed as adjuvant agents. The first compound to be investigated and approved for its use in 1998 was trastuzumab, which binds the extracellular domain IV of ERB2 and is the most frequently employed in therapy. Other available HERB2 inhibitors include pertuzumab, trastuzumab emtansine (T-DMI), and lapatinib [13, 41].

Trastuzumab alone ameliorates the prognosis of breast cancer and decreases the rate of tumor recurrence. The combination of two HERB2 inhibitors, such as trastuzumab and pertuzumab, also led to impressive improvement in overall survival [42]. However, in 0.6–4.5% of cases, it can also induce early and mild reversible cardiotoxicity. When associated with anthracyclines, the incidence of cardiac events reaches 34%, with severe side effects, until heart failure [42–44]. Trastuzumab-induced reversible cardiotoxicity, pertinent to type II cardiac dysfunction, is dose-independent and is characterized by cardiomyocyte alterations rather than necrosis [13]. The administration of trastuzumab can provoke a decrease in left ventricular ejection fraction, without any clinical symptoms. Indeed, this effect can fluctuate over time during treatment, with a partial recovery [45]. On a few number of patients, trastuzumab was shown to be a safe adjuvant treatment when administered with concomitant radiotherapy, reporting a limited cardiotoxicity [46].

In a case report, a 49-year-old woman affected by metastatic breast cancer developed a cardiogenic shock due to pump failure after 3 months of treatment with trastuzumab which was interrupted. After intensive cardiac care, the patient recovered the left ventricular ejection fraction, and trastuzumab therapy was resumed under accurate cardiac monitoring [47].

In a meta-analysis of clinical trials and cohort studies, the frequency of cardiotoxic effects following trastuzumab administration was evaluated in early and metastatic breast cancer patients up to 3 years after drug initiation, with an occurrence of severe cardiac events of 3% of overall patients. Cardiotoxicity varied according to age, increasing from 2.31% in patients <50 years, to 3.46% in those 50–59 years, to 4.91% in those >60 years of age. Its occurrence was higher in smokers (5.3%), dyslipidemic patients (3.9%), and persons with body mass index >25 (6.5%), diabetes (6.2%), hypertension (5.5%), or positive history of cardiac disease (19.1%). A significant difference was found between the estimated risk factors provided in clinical trials compared with cohort studies, with the frequency of cardiotoxicity being about half in experimental studies with respect to that calculated in observational studies [12]. A more recent retrospective study confirmed that the preexistence of cardiac pathologies increases toxic effects in cancer patients administered with trastuzumab, leading to drug discontinuation. Again, these data underlined the importance of monitoring cardiac risk factors [48].

In some trials, a median follow-up of 12–28 months confirmed that the addition of trastuzumab to standard chemotherapy is associated with an approximate 50% decrease in the risk of breast cancer relapse and an approximate 33% decrease in the risk of death from this tumor. Even though the adjuvant trastuzumab provided beneficial effects, a continued cardiac follow-up is strongly recommended. This is important, also considering that an asymptomatic decrease in cardiac efficiency occurs in patients treated with this anticancer agent, thus underestimating its cardiotoxicity [49]. Indeed, when including both symptomatic and asymptomatic cardiac side effects, the incidence of trastuzumab-induced cardiotoxicity can reach 21.3% [50].

A fixed 600 mg dose of trastuzumab added with a recombinant hyaluronidase, aiming to favor absorption by transiently hydrolyzing the subcutaneous matrix, was also proposed as subcutaneous formulation, showing similar beneficial anticancer effects. This route of administration, alternative to intravenous injection, reduces treatment duration, eliminates the need for an intravenous access, is safe, appears time- and cost-saving, and limits hospital visits [51].

Trastuzumab-induced cardiotoxicity is attributable to the role of the *erbB2* gene which is known to play a pivotal role in the developing embryonic heart. Again, in the adult heart, this gene is essential in regulating the cardiac activity and seems to participate in modifying the myocardial response to stress. Then, HERB2 inhibitors make the heart more susceptible to cardiac stressors, including anthracyclines, with overproduction of reactive oxygen species, this effect being reversible [49, 50].

Furthermore, neuregulin-1 exerts its cardiac protection by acting on HERB2. Then, disruption of neuregulin-1-mediated signaling cascade by trastuzumab would make cardiomyocytes more prone to develop alterations in the presence of stressful stimuli, such as anthracyclines [8, 13]. Indeed, the association of doxorubicin with trastuzumab or paclitaxel in breast cancer patients is deleterious, since the cardiotoxicity of the anthracycline agent is significantly increased through two different mechanisms. More in depth, since trastuzumab downregulates HER2 receptor, it competes for signaling of neuregulin-1 which is an important adaptive response to the cardiac stress induced by several noxious stimuli, including anthracyclines. On the other hand, the taxane agent increases the formation of toxic doxorubicin metabolites, in particular doxorubicinol [52, 53].

Pertuzumab is a humanized monoclonal antibody that targets HERB2. It acts at a different epitope than trastuzumab and prevents the formation of ligand-induced ErbB2 heterodimers. Thanks to the synergistic activity, the association of trastuzumab and pertuzumab with neoadjuvant chemotherapy led to improved anticancer efficacy with complete remission in breast cancer patients, with good tolerability [13, 54, 55].

VEGF Inhibitors

Vascular endothelial growth factor (VEGF) is an important agent that influences the development of blood vessels and acts as a modulator of myocardial function and growth, including the integrity and expansion of coronary vessels. Bevacizumab is a recombinant humanized monoclonal antibody addressed against VEGF receptor, showing benefits in the treatment of many types of tumors, including breast cancer. Not surprisingly, cardiotoxic effects of this agent mainly consist in hypertension, with an incidence ranging from 16% to 47%. However, cardiac ischemia and arterial thromboembolic events were also reported. The activity induced by bevacizumab can be attributed to functional disruption of endothelial cells, which from one hand promotes inhibition of angiogenesis (anticancer activity) and from the other hand impairs nitric oxide production and platelet-endothelial cells interaction (cardiovascular side effects) [8].

The heart is very sensitive to the adverse effects of anti-angiogenic agents, and several mechanisms have been advocated to explain such unwanted events: inhibition of cKit and platelet-derived growth factor receptor (PDGFR); alteration of mitochondrial function; and induction of arterial hypertension. The last side effect, as previously underlined, represents one of the main concerns when using bevacizumab. Arterial hypertension is attributed to inactivation of endothelial nitric oxide synthase, production of vasoconstrictors such as endothelin-1, and capillary rarefaction, leading to vasoconstriction and increased peripheral vascular resistance. In particular, capillary rarefaction depends on the loss of pericytes, due to PDGFR inhibition as well as anti-angiogenenic effect. The bevacizumab-induced hypertension is not reversed by drug discontinuation and appears proportional to the anticancer effect of this agent. Bevacizumab is also responsible for arterial and venous thrombosis, due to the reduction of nitric oxide synthesis and endothelial dysfunction. This effect is more frequent when this drug is associated to other anticancer agents [13].

Small-Molecule Tyrosine Kinase Inhibitors

Lapatinib is an orally active anticancer drug that inhibits tyrosine kinase of epidermal growth

factor receptor. It showed to be effective, with a 0.2% rate of symptomatic congestive heart failure and a 1.4% rate of asymptomatic cardiac events. This safer profile is due to its mechanism of action. Unlike monoclonal antibodies, such as trastuzumab, this small molecule does not induce antibody- and complement-mediated cytotoxicity. Furthermore, lapatinib promotes the cytoprotective AMP-activated protein kinase that induces the ATP production and preserves the function of cardiomyocytes [8].

The multi-kinase inhibitors sorafenib, sunitinib, regorafenib, pazopanib, axitinib, and the most recent vatalanib and nintedanib are non-specific small molecules able to inhibit several tyrosine kinases, leading more frequently to cardiotoxic effects. However, these novel drugs are not used for breast cancer treatment [8, 13].

Endocrine Therapy

Endocrine therapy (ET) represents the treatment reference in estrogen receptor (ER)-positive breast cancer, in both pre- and postmenopausal women. ET includes mainly the selective estrogen receptor modulators (SERMs), aromatase inhibitors (AIs; i.e., anastrozole), and the ovarian function suppression [56].

As a SERM, tamoxifen represents the most used drug in the adjuvant setting, because of its effects on overall survival: the risk of death is reduced annually by 31%, and it is still significant 15 years after diagnosis [57]. From a pharmacodynamic point of view, tamoxifen mainly acts as an antiestrogen molecule on mammary epithelium but as an estrogen-like agonist on the uterus, bone, and cardiovascular system [58].

Tamoxifen and other selective estrogen receptor compounds were shown to reduce plasma levels of cholesterol, homocystine, C-protein, and fibrinogen but to increase serum triglyceride levels. For these actions, it has been believed to possess favorable cardiovascular effects, but this profile is debated, since tamoxifen was also associated with higher rates of venous thromboembolic disease and stroke with respect to the placebo [59].

AIs are an effective endocrine therapy for patients with hormone receptor-positive breast cancer, in early stage as well as in metastatic disease. Unfortunately, the decrease in serum levels of estrogens leads to reduced protective effects of estrogens on the cardiovascular system. Indeed, in comparison with tamoxifen, patients treated with AIs more often develop hyperlipidemia, hypercholesterolemia, and hypertension, which are regarded as risk factors for cardiovascular disease [60, 61].

Chemotherapy Combinations

In general, different chemotherapy combinations have shown superior efficacy in patients affected by primary and metastatic breast cancer. However, cardiotoxicity remains a major unwanted side effect that deserves a particular attention.

Multidrug anticancer regimens containing anthracyclines (such as doxorubicin and cyclophosphamide; cyclophosphamide, doxorubicin, and 5-fluorouracil; 5-fluorouracil, epirubicin, and cyclophosphamide) proved to be highly active in breast cancer patients, in either the adjuvant or neoadjuvant settings, with reduced risk of recurrence and death in comparison with non-anthracycline-containing protocols, the cardiotoxicity being the main concern [62].

In this respect, in order to reduce anthracycline-induced cardiotoxicity, alternative combination therapies without this class of drugs have been evaluated.

In a phase I study, a combined weekly paclitaxel plus cyclophosphamide therapy administered to patients with advanced or recurrent breast cancer showed to be safe and well tolerated [63].

In a phase II study, HERB2-positive metastatic breast cancer patients were administered with weekly paclitaxel (80 mg/m^2) plus trastuzumab (8 mg/kg loading dose followed by 6 mg/kg) and pertuzumab (840 mg loading dose followed by 420 mg) every 3 weeks. This dual anti-HERB2 regimen with trastuzumab and pertuzumab combined with a taxane-based chemotherapy demonstrated an improved overall survival [64]. In line with this, in the CLEOPATRA phase III study, a combination regimen including pertuzumab and trastuzumab with the taxane docetaxel in HERB2-positive metastatic breast cancer patients also

showed improvement in progression-free survival and overall survival [65].

The pioneering adjuvant CMF (oral cyclophosphamide with intravenous methotrexate and 5-FU) regimen, introduced in 1976, has been recently revalued as well-tolerated metronomically delivered adjuvant protocol for early-stage breast cancer [66]. The same conclusion was obtained in a multicenter retrospective analysis that evaluated palliative CMF regimen in metastatic breast cancer patients [67]. A large variety of CMF regimens have been developed in the last decades, in terms of doses, route of administration, and interval time. In the retrospective nonrandomized study by Salek et al. [68], the two most common intravenous regimens have been compared: cyclophosphamide 600 mg/m^2, methotrexate 40 mg/m^2, and 5-FU 600 mg/m^2 administered intravenously on days 1 and 8 every 28 days for six cycles and the same drugs and doses administered on day 1 and repeated at 21-day intervals for six cycles. The first schedule was shown to be more effective, because of improved dose density of treatment.

The meta-analysis study by Ghanbari et al. [69] showed that the anthracycline-based regimens proved to be more effective on tumor-free survival and overall survival curves with respect to CMF regimen, reducing the chance of recurrence and death in breast cancer patients. Again, in a retrospective study, postneoadjuvant CMF did not improve poor outcomes in patients with residual invasive breast cancer after neoadjuvant epirubicin/docetaxel chemotherapy [70].

When combined to trastuzumab in HER2-positive metastatic breast cancer patients, CMF was effective, with an acceptable cardiotoxicity profile, as reported in the EORTC 10995 phase II study [71].

Cardiotoxicity Detection and Management

An accurate consideration of risk factors for developing cardiotoxicity in breast cancer patients is of pivotal importance. Metabolic syndrome already represents a great risk for cardiovascular diseases in non-cancer patients, and then it deserves a particular attention when administering potentially cardiotoxic anticancer drugs. Being overweight and obesity are well-recognized factors influencing the onset of heart failure in general population, and Guenancia et al. [72] showed that they make breast cancer patients more sensitive to the cardiotoxic effects of anthracyclines alone or with trastuzumab. An increased number of breast cancer survivors and an increased aging population lead to important clinical debates, in terms of comorbid illnesses, with particular attention to cardiovascular diseases [8].

Cardiac monitoring is essential when administering antitumor drugs to patients affected by primary and metastatic breast cancer. In particular, the left ventricular systolic function deserves an accurate evaluation before and during anticancer therapy in order to assess a possible decline in cardiac activity.

There is no consensus in the definition of cardiotoxicity, and different parameters have been proposed in the course of time. However, the European Society of Cardiology has recently published a position paper on cancer treatments and cardiovascular toxicity, suggesting the diagnosis of cardiotoxicity with an ejection fraction reduction $>10\%$ for values below normality (53%) [73].

The left ventricular ejection fraction has been assessed by means of equilibrium radionuclide angiocardiography, this technique being independent on left ventricular geometric assumptions or endocardial detection. Its limitations include radiation exposure, difficulty with optimal image acquisition angles, and lack of ability to report on pericardial and valvular disease. This method was replaced by the safer and less expensive two-dimensional echocardiography (ECHO). This imaging approach allows serial monitoring of left ventricular systolic and diastolic function, ventricular wall mechanics, and pericardial and valvular disease. However it lacks the sensitivity to detect early and mild subclinical changes, then underestimating cardiac damage. More in depth, functional parameters examined include diastolic function, evaluated by use of mitral flow with anterograde values of E wave and A wave, tissue

Doppler imaging of septal and lateral mitral annulus, measures of S′ wave (systolic velocity of the mitral ring) and E/E′ ratio, S wave of the right ventricle (cm/s), indexed left atrial volume (mL/m^2), tricuspid annular plane systolic excursion, and pulmonary artery systolic pressure. Contrast-enhanced two-dimensional ECHO improves the assessment of left ventricular volume, left ventricular ejection fraction, thrombus detection, and Doppler measurements. Three-dimensional ECHO adds reliability and reproducibility of volumetric assessment. Coronary disease is evaluated by means of stress ECHO, under exercise or dobutamine administration, as well as computed tomography angiography. Radionuclide ventriculography techniques, such as the multiple-gated acquisition scan, have been also employed to monitor cardiac functions in patients receiving potentially cardiotoxic anticancer agents [6, 8, 9, 49, 64, 74, 75].

However, cardiac deformity changes would precede ventricular dysfunction, then appearing more important for the prevention of cardiotoxicity. For this reason, myocardial strain indices, measured as global longitudinal strain (GLS), have been introduced in the early detection of contractile function changes. They usually include three clips with images of the left ventricle on three apical views, so that all myocardial segments could be well visualized. Indeed, three strain components are generally used to describe left ventricular deformation: longitudinal, circumferential, and radial strain. These myocardial strain indices can be evaluated with speckle-tracking ECHO and acquired by use of automated functional imaging, providing a more sensitive and quantitative assessment of left ventricular systolic function than ejection fraction. These techniques, together with cardiac biomarkers, are useful tools for the cardiac monitoring of patients treated with dual anti-HERB2 therapy [9, 64, 74, 76].

Then, the ejection fraction is not considered a good predictor of cardiotoxicity, because it does not unmask early changes of myocardial contractile function, whereas cardiac deformity evaluated as GLS anticipates the functional changes occurring in patients undergoing anticancer treatment. Nevertheless, the specific cutoff point of that variable which should be used as a predictor of cardiotoxicity is still a matter of debate [9].

Electrocardiography can be useful to evidence conduction alterations, but these data are not specific. Significant prolongation of electrocardiographic-corrected QT interval and an elevation in serum troponin levels were observed in patients with nonmetastatic breast cancer treated with doxorubicin, cyclophosphamide, and paclitaxel infusion [77].

Novel imaging approaches provide early detection of cardiac impairment. These include SPECT and PET techniques and the more recent SPECT-CT and PET-CT which require a molecular probe (radiolabeled substrates) that provides an analytical signal, leading to molecular and metabolic imaging. Magnetic resonance and dynamic magnetic resonance allow high-resolution anatomical images without the risk of radiation [8, 74].

Although rarely used for being considered a high-risk procedure, the endomyocardial biopsy of the right ventricle is regarded as the gold standard to investigate acute anthracycline-induced cardiotoxicity, thanks to its high sensitivity and specificity. Endomyocardial tissue shows typical histopathological changes, including vacuolization of the cytoplasm. Under electron microscopy the common ultrastructural alterations include loss of myofibrils and distention of the sarcoplasmic reticulum and T-tubules [17].

Cardiac serum biomarkers include the evaluation of cardiac-specific isoenzymes of troponins T and I, N-terminal pro-brain natriuretic peptide (NT-proBNP), soluble ST2 (a protein receptor belonging to the toll-like/interleukin-1 superfamily), microRNAs, and adrenomedullin. Troponin release was measured either in cohort studies or in controlled clinical trials. It is due to cardiomyocyte lysis, then depending on severe cardiac damage. However, its half-life is short and multiple blood sample collections are necessary. NT-proBNP is released by left ventricular cardiomyocytes in response to wall stress, and its increase reflects the decline in ejection fraction. Soluble ST2 is a recent biomarker shown to be a good predictor of cardiac death. MicroRNAs (in particular, miR-126-3p, miR-199a-3p, miR-34a-5p, and miR-423-5p) are short nucleotide

sequences involved in proliferation, differentiation, and apoptosis and are released into peripheral blood under normal and pathological conditions, including cellular toxicity. An increase in miR-34a plasma levels has been described after anthracycline chemotherapy [6, 8, 19, 64, 74, 78, 79].

When using drugs that induce the production of ROS and RNS, such as anthracyclines, the evaluation of markers of oxidative and nitrosative stress (myeloperoxidase and nitrotyrosine) and of systemic inflammation (tumor necrosis factor alpha and interleukin-6) may be particularly useful [8].

Cytometric evaluation of circulating endothelial progenitor cells is also recommended. A low number of these cells predict an increased risk for cardiovascular diseases. On the contrary, a high number is counted in the early phase of myocardial infarction [8].

The assessment of genetic polymorphisms of tyrosine kinase activities appears important when exploring the cardiovascular risk in patients administered with targeted therapies. For example, the I655V variant was significantly associated with *ErbB2* overexpression in tumor biopsy samples, indicating a higher risk of cardiotoxicity. The examination of mitochondrial DNA is useful under anthracycline therapy, since these drugs induce mitochondrial damage, with consequent impairment of oxidative phosphorylation. Other potential biomarkers are represented by microRNAs whose overexpression was associated with cardiomyocyte hypertrophic growth [8].

Sun et al. [80] elaborated phenotyping algorithms for cardiotoxicity induced by five first-line breast cancer chemotherapy agents: adotrastuzumab emtansine, trastuzumab, doxorubicin, epirubicin, and pertuzumab. While it is possible to observe that the patient has received chemotherapy and that she developed heart failure, it is not possible to determine whether the heart disease is a direct consequence of the chemotherapy. So, causal inference has been used to ascertain the degree to which chemotherapy contributed to the heart failure. Since the patient may have suffered from heart disease even if she had not received chemotherapy, it is not possible to establish a causal relationship between these two elements. For this reason, the authors distinguished associative phenotypes from causal phenotypes. In particular, three different predictive models have been developed: (1) causal phenotyping algorithm to predict the patient risk of cardiotoxicity as the difference between the heart disease risks with exposure and non-exposure to the drugs; (2) regular predictive model to directly estimate the patient risk of cardiotoxicity based on the available physiological data; and (3) combined predictive model of the previous two models to incorporate the estimated causal effects. Causal phenotyping model is more sensitive in predicting long-term cardiotoxicity, while the regular model built on baseline physiological data is more sensitive toward short-term cardiotoxicity. The combined model successfully utilizes the physiological data to predict short-term cardiotoxicity and the causal effect toward predicting long-term cardiotoxicity.

Cardioprotection in Anticancer Therapy

In an attempt to ameliorate the compliance of the anticancer therapy, two main approaches can be considered: modification of anticancer treatment regimens and cardioprotective strategies. They can be largely implemented to mitigate cardiotoxic effects in breast cancer patients.

Anticancer drug reduction, interruption, and discontinuation or changes in administration schedules represent the immediate and easy way to limit severe adverse effects. Undoubtedly, together with nutritional supplementation and appropriate exercise training, this approach can reduce cardiotoxicity when the damage is reversible, but the efficacy of chemotherapy can be compromised. In this respect, the search for alternative protocols and combination regimens, as previously discussed, appears necessary to improve both efficacy and safety of anticancer regimens [5, 7]. Toxicity of taxanes can be reduced by therapy discontinuation, while corticosteroids and antihistamines may be useful to reduce the occurrence of clinically significant arrhythmias [13].

Changes in doses and time intervals have been also proposed to optimize chemotherapy combinations in metastatic breast cancer (increased dose intensity). In particular, higher dose of chemotherapy per cycle (dose escalation) or interval shortening between cycles (dose-dense) has been compared by Lalisang et al. [81] in a phase II study evaluating two different approaches, epirubicin 110 mg/m^2 combined with paclitaxel 200 mg/m^2 every 21 days and epirubicin 75 mg/m^2 combined with paclitaxel 175 mg/m^2 every 10 days, both supported with granulocyte colony-stimulating factor (G-CSF). The two approaches appeared quite effective, but the dose-dense protocol showed fewer side effects.

The encapsulation of doxorubicin in liposomes (pegylated liposomal doxorubicin) was shown to alter the pharmacokinetic properties of the anticancer drug with reduced cardiotoxicity. Thanks to this formulation, active doxorubicin is directly delivered to the tumor site, and a lesser amount of the drug would reach cardiomyocytes. Furthermore, the slow release of the drug, due to its longer half-life (50–80 h), avoids high peak plasma concentrations [5, 8, 82, 83].

According to the *multiple-hit hypothesis* (Knudson's hypothesis), based on the idea that cancer is due to accumulated mutations, there would be a late onset of cardiotoxicity induced by pharmacological and non-pharmacological chronic injury. Therefore, all strategies favoring cardiac adaptation to different stressors would be beneficial during anticancer drug therapy [13].

Several ways have been followed to reduce cardiovascular toxicity induced by anticancer drugs. A particular attention has been focused on the approaches proposed to limit anthracycline side effects. Doxorubicin-induced cardiac toxicity can be ameliorated to some extent by the concomitant use of antioxidant drugs, such as the iron-chelating agents. The most promising agent is represented by the prodrug dexrazoxane, which turns into its active form in cardiomyocytes, where it also modifies the Top2beta configuration. This effect seems to be determinant for cardioprotection, since dexrazoxane derivatives lacking the capability to affect topoisomerase 2beta configuration showed to be less effective in preventing anthracycline cardiotoxicity [5, 6, 13, 17, 84].

Antagonists of beta-adrenergic receptors are also useful cardioprotective agents. With respect to traditional drugs, such as propranolol and atenolol, merely endowed with beta-blocker activity, more recent and selective molecules, including carvedilol and nebivolol, showing also antioxidant properties, appeared effective in mitigating anthracycline-induced side effects. Furthermore, they reduce myocardial calcium overload and preserve epidermal growth factor signaling [6, 13, 17]. In particular, the selective beta-1-adrenergic receptor antagonist nebivolol showed antioxidant, antiapoptotic, and vasodilator properties mediated by nitric oxide release and proved to prevent anthracycline-induced myocardiopathy [85].

Drugs acting on renin-angiotensin-aldosterone system, including inhibitors of the angiotensin-converting enzyme (ACE) (enalapril and captopril) and antagonists of angiotensin II receptors (candesartan, valsartan, and telmisartan), also revealed effective in reducing the progression of cardiac dysfunction. ACE inhibitors are able to neutralize oxidative damage, reduce interstitial fibrosis, prevent intracellular calcium overload, and ameliorate mitochondrial respiration and cardiomyocyte metabolism. In particular, telmisartan modulates peroxisome proliferator-activated receptor-gamma and inhibits inflammatory molecules. A combination of ACE inhibitors and beta-blockers is beneficial in reducing anthracycline-induced cardiotoxicity [13, 17].

Another promising cardioprotective agent is represented by the flavonoid monoHER. As shown in in vitro and in vivo studies, as well as in patients and animal models, this agent protects against doxorubicin-induced cardiotoxicity, without affecting the anticancer activity of the drug. Also phosphodiesterase 5 inhibitors, including sildenafil, revealed potential NOS-dependent cardioprotective agents. These inhibitors can attenuate cardiomyocyte apoptosis, preserve mitochondrial membrane potential, maintain myofibrillar integrity, and prevent ST-interval prolongation and left ventricular dysfunction, as shown in experimental models. Pretreatment with sildenafil would maintain mitochondrial integrity

by augmenting cellular mechanisms mediated by NO/cyclic GMP, and a combination between sildenafil and doxorubicin would increase the anticancer effect of doxorubicin with an improved cardiac function [17].

Brain Toxicity by Antineoplastic Drugs

Chemotherapy-related neurotoxicity may have harmful effects on either the central or peripheral nervous system, resulting in a wide range of clinical syndromes [86]. In this part of the chapter, we will focus our attention on a peculiar and neglected aspect concerning the rare – but sometimes severe – adverse drug events involving the CNS (Fig. 1). Indeed, neurotoxicity can even lead to the development of a post-chemotherapy clinical syndrome characterized by the subjective experience of cognitive deficits especially in the elderly patients, this condition having being named "chemobrain" [87]. The concept of "chemobrain" has evolved over the past decade and remains a controversial topic in the literature [88], and it is defined as cognitive impairment in the absence of direct involvement of the CNS by systemic tumor, in the context of long-term chemotherapy treatment [89]. The neuronal injury caused by the chemotherapeutic drugs with consequent inadequate repair, abnormal brain remodeling, and changes in the neuroendocrine-immunological axis may be at the basis of the development of cognitive deterioration [90]. Among the proposed hypotheses, it has been suggested that the impairment in the cytokine microenvironment induces persistent epigenetic modulation, which in turn leads to changes in gene expression, alterations in metabolic activity, and neuronal transmission, finally responsible for the cognitive dysfunction [91, 92]. As shown in particular in breast cancer patients, chemotherapy-induced neurotoxic brain injury is mainly associated with an altered global brain network organization in frontal, striatal, and temporal areas [93, 94].

Cognitive changes in breast cancer survivors administered with chemotherapy have been described [95]. Indeed, clinical findings are now supported by a growing number of animal model [96, 97] and neuroimaging [98] studies. The cognitive impairments associated with chemotherapy have been observed up to 2 years after therapy in prospective longitudinal studies [99] and as long as 21 years after treatment in cross-sectional studies [100]. Deficits in both immediate and delayed memory recall, working memory, attention, and processing speed have been reported [101] but with a large intraindividual variability [102–104].

However, many of the studies on this topic have noted subtle but significant cognitive impairment in patients, in comparison with control subjects. Moreover, the level of cognitive dysfunction did not seem to correlate with other psychiatric disease or disorders such anxiety, depression, fatigue, or menopausal symptoms [105, 106]. Patients were more likely to be impaired if they received high-dose regimens in comparison with those treated with standard- or low-dose regimens [107]. In general, there are some important limitations of the performed studies on this subject such as relatively small sample sizes, the presence or absence of concomitant hormonal therapy, variability in the cognitive tests used and the interpretation applied to the data, and, above all, the differences among the chemotherapy regimens [108]. Thus, large, multicenter, prospective studies are needed to clarify this question and determine the contribution of systemic chemotherapy to the cognitive impairment noted in breast cancer patients [109].

Fluoropyrimidines

Neurotoxicity is an uncommon but severe adverse drug reaction of fluoropyrimidine therapy [28]. Its incidence seems to be higher in patients with DPD deficiency [110, 111]. The direct effects on the nervous tissue are probably due to the active metabolites of fluoropyrimidines that can pass through the blood-brain barrier [112]. The most common form of neurotoxicity associated with 5-FU is an acute or subacute pancerebellar syndrome, with an estimated incidence of 2–4% [29]. Indeed, rare cases of cerebellar alterations with ataxia have been described, as well as the

presence of multifocal cerebral leukoencephalopathy, with an outfit of symptoms including dizziness, memory deficits, gait disturbances, and confusion. These ailments are usually reversible upon drug discontinuation and supportive therapy administration [29].

Subacute multifocal leukoencephalopathy has been reported in patients treated with 5-FU in combination with levamisole [112] and in patients treated with capecitabine [113]. From a histopathological point of view, the damages consisted of demyelination of cerebral white matter, similar to those seen in acute multiple sclerosis, with an inflammatory infiltrate of macrophages, reversed by corticosteroid therapy [112].

Systemic administration of 5-FU in mice can cause progressive degenerative impairment of myelin, reflecting combined effects of oligodendrocyte death and a deficit of different progenitor cell populations required for replacement. In fact, 5-FU treatment can cause the loss of myelin basic protein in oligodendrocytes of the corpus callosum, as shown by electron microscopy, with scattered foci of demyelinated axons. The partial or complete loss of myelin sheaths and the presence of myelin vacuolization with degenerating axons (i.e., multi-laminated structures and collapsed centers, altered axonal cytoskeleton and organelles) are possible findings in association with an inflammation and apoptosis of microvasculature endothelial cells [114].

Among the numerous case reports published in the literature of a toxic effect of fluoropyrimidines on CNS, the majority is referred to colorectal cancer female patients [28], showing toxic encephalopathies with seizures, ataxia, mental confusion, alteration of consciousness, and progressive deterioration of neurocognitive function leading to coma. However, in a 56-year-old woman with metastatic breast cancer treated with capecitabine, a marked truncal ataxia was observed, without evidence of cerebellar abnormalities [115]. Moreover, in another 45-year-old woman with metastatic breast cancer, an acute toxic leukoencephalopathy was diagnosed after treatment with capecitabine when presented nausea, headaches, muscle cramps, dysarthria, and swallowing disorders [116].

Optic nerve neuropathy and extrapyramidal syndromes have been described in patients with normal clearance of 5-FU, and acute or subacute cerebellar dysfunction, including visual disturbances and seizures, has been reported in patients receiving a combination therapy of 5-FU with allopurinol [117]. Recently, Winocur and colleagues demonstrated that the combination of 5-FU and methotrexate caused cognitive deficits in mice with significant changes in brain volume, including the hippocampus and frontal lobes [118].

Taxanes

Chemotherapy-induced peripheral neuropathy (CIPN) is a common and disabling side effect of taxanes (i.e., paclitaxel and docetaxel) in breast cancer patients. Indeed, CIPN can interfere with daily function and quality of life, and there are no known preventive approaches [119, 120]. On the contrary, because taxanes cross the blood-brain barrier (BBB) very poorly, and have undetectable cerebrospinal fluid levels after IV injection, the central neurotoxicity has been very uncommon, affecting mainly the visual system [117]. Reports have included transient scintillating scotomas and occasional visual loss. Indeed, a sensation of light flashing across the visual field has been reported by some patients during paclitaxel infusion [117]. Interestingly, in some of those patients, visual evoked potentials resulted abnormal, whereas electroretinograms were intact, suggesting that the optic nerve was the region of injury. However, the visual symptoms resolved in most patients after discontinuation of the taxanes [121].

Generalized seizures and encephalopathy have also been reported in rare cases after paclitaxel administration. Ziske and colleagues observed three patients who presented with acute encephalopathy within 6 h after infusion of paclitaxel at normal doses [122], whereas Muallaoglu and collaborators reported the clinical case of a patient with advanced stage breast carcinoma who developed acute and spontaneous resolving encephalopathy after weekly dose of paclitaxel [123]. In another case of two women with breast cancer treated with paclitaxel, the encephalopathy was

characterized by confusion, word-finding difficulty, behavioral changes, headache, and ataxia. These clinical states resolved spontaneously [124].

Docetaxel is less neurotoxic than paclitaxel and only rarely causes CNS toxicity, such as seizures or encephalopathy [125].

Anthracyclines

During IV infusion, doxorubicin and daunorubicin are not able to penetrate the BBB to any significant degree; central neurotoxicity has not been reported [117]. However, when administered intra-arterially to patients with brain tumors, doxorubicin has caused cerebral infarcts and hemorrhagic necrosis [126]. Accidental intrathecal injection of anthracyclines in pediatric patients can lead to acute and fatal myelopathy and encephalopathy [127].

Recently, new findings seem to suggest a key role of anthracyclines, in particular doxorubicin, in the onset and development of cognitive impairment in chemotherapy-treated breast cancer patients. In particular, anthracyclines may have greater negative effects than non-anthracycline schedules on particular cognitive domains and brain network connections. Kesler and Blyney retrospectively examined, in an observational study, cognitive and resting state functional MRI data acquired from breast cancer survivors. The anthracycline-treated patients demonstrated significantly lower verbal memory performance as well as lower left precuneus connectivity [128]. Indeed, previous preclinical studies on doxorubicin-treated rats showed a significantly disrupted hippocampal-based memory function and a significant decline in neurogenesis (a decrease of 80–90%) [129]. Moreover, doxorubicin induced cognitive dysfunction through the activation of ERK and AKT signaling pathways in hippocampal neurons, decreasing significantly the locomotor activity and impairing working and spatial memory in female rats [130]. Furthermore, doxorubicin produced a significant inhibition of dopamine system activity in the hippocampus of rats that could lead to the disturbances of the cognitive functions, whereas the same drug did not significantly affect other monoaminergic transmitters such as noradrenaline and serotonin [131]. Recently, Liao and co-workers found that the administration of doxorubicin caused a dysregulation of neuregulin-1/ErbB signaling in the hippocampus of rats, indicating the potential involvement of the NRG1/ErbB pathway in the doxorubicin-induced nervous system dysfunction [132]. Of note, the observed decreased cognitive function in rats after doxorubicin treatment, along with deficits in levels of neurogenesis in the hippocampus, associated with an increase in apoptosis, was attenuated by low-intensity exercise that could assist in preventing cognitive dysfunction during or after chemotherapy in breast cancer patients [89]. Moreover, the neuroprotective potential of catechin, a tea polyphenol, has been recently proposed in order to reduce the oxidative stress, acetylcholine esterase activity, and the neuroinflammation in the hippocampus and cerebral cortex in doxorubicin-induced toxicity in vivo models [133].

Alkylating Agents

Cyclophosphamide is an antineoplastic drug that belongs to the alkylating agents class and requires activation in the liver to its metabolites 4-OH-cyclophosphamide and phosphoramide mustard. These metabolites form DNA cross-links both between and within DNA strands at guanine N-7 positions, causing the cancer cell apoptosis [134]. Central neurotoxicity is very uncommon, but during high-dose IV infusions, the patients could suffer a mild, reversible encephalopathy with dizziness, blurred vision, and confusion [117].

Similar to doxorubicin, also cyclophosphamide has been recently involved in clinical research about the cognitive dysfunctions in chemotherapy-treated breast cancer patients. Indeed, Ramalho and collaborators showed that there was a significantly increased risk of incident cognitive impairment among patients with schemes including doxorubicin and cyclophosphamide [135]. Moreover, combination regiments, including cyclophosphamide, epirubicin, and 5-FU, had a negative effect on cognition [136].

A clinically relevant preclinical mouse model showed that high doses of cyclophosphamide chemotherapy caused a decline in delayed spatial memories [137]. Cyclophosphamide, as well as doxorubicin, affected cognitive function and impacted synaptic plasticity/aging molecules in the hippocampus of female rats [130], impairing cognitive ability and disrupting hippocampal neurogenesis [129]. In female rats, other data clearly showed learning and memory impairment following the classic combination of cyclophosphamide, methotrexate, and 5-FU (CMF) administration with a decreased hippocampal cell proliferation, suggesting negative consequences of chemotherapy on the self-renewal potential of neural progenitor cells in the hippocampus [90]. Interestingly, also 26 breast cancer patients treated with adjuvant CMF chemotherapy revealed, at the EEG registration, longer reaction times (although not significantly different) than the control group [138]. Finally, Schagen and colleagues found that in 39 breast carcinoma patients treated with adjuvant CMF chemotherapy, there was a significant higher risk of late cognitive impairment than breast carcinoma patients not treated with chemotherapy [139].

Ifosfamide is an alkylating agent structurally similar to cyclophosphamide that is used for treatment of many solid and hematopoietic tumors [140], known to frequently cause CNS toxicity [125]. Central neurotoxicity occurs in 20–40% of all patients who receive high-dose IV ifosfamide treatment, including symptoms such as delirium, mutism, visual hallucinations, seizures, and aphasia [117, 125]. Treatment with benzodiazepines or methylene blue, either before or after the onset of symptoms, could control this reversible encephalopathy [125].

Endocrine Therapy

A recent meta-analysis reviewed the neuropsychological scores of 1,822 breast cancer patients receiving endocrine therapy (ET), i.e., tamoxifen and aromatase inhibitors (AIs), versus a control group (i.e., either non-cancer controls or breast cancer controls not treated with ET) in the first 6 months to 3 years of initiation. The authors found a significative worse performance of ET patients in verbal learning/memory tests, but they did not identify a direct link with ET duration, and neither did they find diversities between tamoxifen and AIs [141]. However, there are numerous small-sized studies that seem to suggest that tamoxifen could cause cognitive impairments in breast cancer patients. Indeed, Chen and coworkers [142] were able to detect impairment of the attention network and deficit in executive function performance in 43 premenopausal women with breast cancer exposed to 20 mg/day tamoxifen, whereas Boele and collaborators [143] found lower scores in verbal memory among 20 tamoxifen postmenopausal users.

Moreover, Palmer and colleagues showed that 20 premenopausal women taking tamoxifen have lower neuropsychological scores, compared to age-matched healthy controls. In particular, the immediate and delayed visual memory, verbal fluency, immediate verbal memory, visuospatial ability, and processing speed were affected [144]. A different set of neuropsychological domains were affected in a study by Lejbak and collaborators [145]. The authors compared 28 women administered with ET (with no difference between tamoxifen and AIs users) with healthy postmenopausal women. Their analysis demonstrated significant differences on measures of complex visuomotor attention, letter fluency, and speeded manual dexterity in treated patients. Finally, Eberling and co-workers [146] used positron emission tomography to evaluate metabolic activity in different brain regions in ten chemotherapy-naïve breast cancer patients taking tamoxifen, comparing them with matched controls. Interestingly, they reported lower frontal lobe glucose metabolism and smaller hippocampal volumes in tamoxifen users, as well as lower scores in semantic memory tests. Notwithstanding the low number of patients enrolled, Collins and colleagues [147] found that tamoxifen and anastrozole both had an impact on cognitive decline after 6 months of initiation but the latter having a more pronounced effect.

On the other hand, there are numerous studies that did not find any relationship between ET (in

particular tamoxifen) and cognitive impairments of breast cancer patients. A cohort study by Sun and colleagues [148] investigated data extracted from a national registry of 24,197 women diagnosed with breast cancer. These authors found that patients who used tamoxifen had a 17% lower risk of being diagnosed with dementia compared to controls and that this risk was further decreased after a therapy longer than 5 years. Another cohort study by Ording and collaborators [149] including 16,419 patients with breast cancer did not retrieve any association between ET and neither dementia nor cognitive impairment. Moreover, Jenkins and co-workers [150] found a null association between anastrozole and cognitive impairment compared to placebo at baseline, 6 months and 24 months of follow-up.

There are evidences that the effect of tamoxifen may act as an agonist on CNS, showing neuroprotective properties [151] and improving memory performance on estrogen-deprived animal models. There are also other preclinical studies that suggested a protective effect by tamoxifen on frontal and hippocampal brain regions, as well as spatial and contextual memory [152], and on the neurological damages induced by cerebral ischemia [153].

Conclusion

The cardiovascular and neuropsychiatric toxicities remain important severe adverse drug reactions in the therapeutic management of breast cancer patients. Although recent therapeutic strategies appear endowed with less severe cardiovascular toxic effects, attention must be paid in their use. Oncologists should focus their efforts to the potential cardiovascular risks of all the anticancer therapies, informing patients on reasonable expectations of benefits and side effects. For these reasons, it is particularly important to develop cardioprotective strategies, improving the quality of life of patients. To date, among the central neurotoxicities described by antineoplastic drugs in breast cancer patients, the cognitive impairment is the most investigated. The link between chemotherapy and cognitive dysfunction has been proven whereas for ET is still controversial. New data are emerging from clinical trials, observational studies, and meta-analysis, but there are numerous difficulties to retrieve the proper clinical research methods to deeply investigate this particular clinical issue. Indeed, numerous factors such as the administration of combined different chemotherapeutic drugs, the menopausal status, and the use of different neuropsychological tests frustrate our ability to determine the exact contribution of single drugs to cognitive impairment. A strong effort by the scientific community will be needed in order to overcome these drawbacks of the research dealing with cognitive deterioration. Future studies on available and upcoming drugs will need to include proper cognitive evaluation scales and an adequate number of participants.

References

1. Melchor L, Benitez J. The complex genetic landscape of familial breast cancer. Hum Genet. 2013;132:845–63.
2. Hackshaw AK, Paul EA. Breast self-examination and death from breast cancer: a meta-analysis. Br J Cancer. 2003;88:1047–53.
3. American Institute of Ultrasound in Medicine. AIUM practice guideline for the performance of a breast ultrasound examination. J Ultrasound Med. 2009;28:105–9.
4. Hellquist BN, Duffy SW, Abdsaleh S, Björneld L, Bordás P, Tabár L, Viták B, Zackrisson S, Nyström L, Jonsson H. Effectiveness of population-based service screening with mammography for women ages 40 to 49 years: evaluation of the Swedish Mammography Screening in Young Women (SCRY) cohort. Cancer. 2011;117(4):714–22.
5. Caron J, Nohria A. Cardiac toxicity from breast cancer treatment: can we avoid this? Curr Oncol Rep. 2018;20(8):61.
6. Dong J, Chen H. Cardiotoxicity of anticancer therapeutics. Front Cardiovasc Med. 2018;5:9.
7. Gavila J, Seguí MÁ, Calvo L, López T, Alonso JJ, Farto M, Sánchez-de la Rosa R. Evaluation and management of chemotherapy-induced cardiotoxicity in breast cancer: a Delphi study. Clin Transl Oncol. 2017;19(1):91–104.
8. Zambelli A, Della Porta MG, Eleuteri E, De Giuli L, Catalano O, Tondini C, Riccardi A. Predicting and preventing cardiotoxicity in the era of breast cancer targeted therapies. Novel molecular tools for clinical issues. Breast. 2011;20(2):176–83.

9. Gripp EA, Oliveira GE, Feijó LA, Garcia MI, Xavier SS, Sousa AS. Global longitudinal strain accuracy for cardiotoxicity prediction in a cohort of breast cancer patients during anthracycline and/or trastuzumab treatment. Arq Bras Cardiol. 2018;110(2):140–50.
10. Hawkes EA, Okines AF, Plummer C, Cunningham D. Cardiotoxicity in patients treated with bevacizumab is potentially reversible. J Clin Oncol. 2011;29(18): e560–2.
11. Jain D, Russell RR, Schwartz RG, Panjrath GS, Aronow W. Cardiac complications of cancer therapy: pathophysiology, identification, prevention, treatment, and future directions. Curr Cardiol Rep. 2017;19:36.
12. Mantarro S, Rossi M, Bonifazi M, D'Amico R, Blandizzi C, La Vecchia C, Negri E, Moja L. Risk of severe cardiotoxicity following treatment with trastuzumab: a meta-analysis of randomized and cohort studies of 29,000 women with breast cancer. Intern Emerg Med. 2016;11(1):123–40.
13. Tocchetti CG, Cadeddu C, Di Lisi D, Femminò S, Madonna R, Mele D, Monte I, Novo G, Penna C, Pepe A, Spallarossa P, Varricchi G, Zito C, Pagliaro P, Mercuro G. From molecular mechanisms to clinical management of antineoplastic drug-induced cardiovascular toxicity: a translational overview. Antioxid Redox Signal. 2019;30(18):2110–53.
14. Martel S, Maurer C, Lambertini M, Pondé N, De Azambuja E. Breast cancer treatment-induced cardiotoxicity. Expert Opin Drug Saf. 2017;16 (9):1021–38.
15. Jasra S, Anampa J. Anthracycline use for early stage breast cancer in the modern era: a review. Curr Treat Options in Oncol. 2018;19(6):30.
16. Pokrzywinski KL, Biel TG, Rosen ET, Bonanno JL, Aryal B, Mascia F, Moshkelani D, Mog S, Rao VA. Doxorubicin-induced cardiotoxicity is suppressed by estrous-staged treatment and exogenous 17β-estradiol in female tumor-bearing spontaneously hypertensive rats. Biol Sex Differ. 2018;9(1):25.
17. Octavia Y, Tocchetti CG, Gabrielson KL, Janssens S, Crijns HJ, Moens AL. Doxorubicin-induced cardiomyopathy: from molecular mechanisms to therapeutic strategies. J Mol Cell Cardiol. 2012;52(6):1213–25.
18. Singal PK, Deally CM, Weinberg LE. Subcellular effects of adriamycin in the heart: a concise review. J Mol Cell Cardiol. 1987;19(8):817–28.
19. de Vries Schultink AHM, Boekhout AH, Gietema JA, Burylo AM, Dorlo TPC, van Hasselt JGC, Schellens JHM, Huitema ADR. Pharmacodynamic modeling of cardiac biomarkers in breast cancer patients treated with anthracycline and trastuzumab regimens. J Pharmacokinet Pharmacodyn. 2018;45(3):431–42.
20. Ryberg M, Nielsen D, Cortese G, Nielsen G, Skovsgaard T, Andersen PK. New insight into epirubicin cardiac toxicity: competing risks analysis of 1097 breast cancer patients. J Natl Cancer Inst. 2008;100(15):1058–67.
21. Geisberg CA, Sawyer DB. Mechanisms of anthracycline cardiotoxicity and strategies to decrease cardiac damage. Curr Hypertens Rep. 2010;12 (6):404–10.
22. Pellegrini A, Soldani P, Breschi MC, Paparelli A. Effects of reserpine and calcium antagonists pre-treatment on doxorubucin storage in various organs of young and senescent rats. In Vivo. 1991;5(2):171–4.
23. Soldani P, Pellegrini A, Breschi MC, Natale G, Paparelli A. Doxorubicin storage in myocardial tissue of reserpine- and nicardipine-pretreated rats. Anticancer Res. 1991;11:2123–4.
24. Liu X, Zhu Y, Lin X, Fang L, Yan X. Mitral regurgitation after anthracycline-based chemotherapy in an adult patient with breast cancer: a case report. Medicine (Baltimore). 2017;96(49):e9004.
25. Rowinsky EK, Eisenhauer EA, Chaudhry V, Arbuck SG, Donehower RC. Clinical toxicities encountered with paclitaxel (Taxol). Semin Oncol. 1993;20:1–15.
26. Yardley DA, Hart L, Waterhouse D, Whorf R, Drosick DR, Murphy P, Badarinath S, Daniel BR, Childs BH, Burris H. Addition of bevacizumab to three docetaxel regimens as adjuvant therapy for early stage breast cancer. Breast Cancer Res Treat. 2013;142(3):655–65.
27. Hurvitz SA, Bosserman LD, Chan D, Hagenstad CT, Kass FC, Smith FP, Rodriguez GI, Childs BH, Slamon DJ. Cardiac safety results from a phase II, open-label, multicenter, pilot study of two docetaxel-based regimens plus bevacizumab for the adjuvant treatment of subjects with node-positive or high-risk node-negative breast cancer. Springerplus. 2014;3:244.
28. Natale G, Di Paolo A, Bocci G. Dermatological, cardiovascular and neurological morphohistopathological effects of fluoropyrimidine-based chemotherapy in humans. Clin Cancer Drugs. 2017;4:104–11.
29. Endo A, Yoshida Y, Nakashima R, Takahashi N, Tanabe K. Capecitabine induces both cardiomyopathy and multifocal cerebral leukoencephalopathy. Int Heart J. 2013;54(6):417–20.
30. Karakulak UN, Aladağ E, Maharjan N, Övünç K. Capecitabine-induced coronary artery vasospasm in a patient who previously experienced a similar episode with fluorouracil therapy. Turk Kardiyol Dern Ars. 2016;44(1):71–4.
31. Molteni LP, Rampinelli I, Cergnul M, Scaglietti U, Paino AM, Noonan DM, Bucci EO, Gottardi O, Albini A. Capecitabine in breast cancer: the issue of cardiotoxicity during fluoropyrimidine treatment. Breast J. 2010;16(Suppl 1):S45–8.
32. Shah NR, Shah A, Rather A. Ventricular fibrillation as a likely consequence of capecitabine-induced coronary vasospasm. J Oncol Pharm Pract. 2011;18 (1):132–5.
33. Polk A, Vistisen K, Vaage-Nilsen M, Nielsen DL. A systematic review of the pathophysiology of 5-fluorouracil-induced cardiotoxicity. BMC Pharmacol Toxicol. 2014;15:47.
34. Cwikiel M, Zhang B, Eskilsson J, Wieslander JB, Albertsson M. The influence of 5-fluorouracil on the

endothelium in small arteries. An electron microscopic study in rabbits. Scanning Microsc. 1995;9(2):561–76.
35. Henry D, Rudzik F, Butts A, Mathew A. Capecitabine-induced coronary vasospasm. Case Rep Oncol. 2016;9(3):629–32.
36. Kosmas C, Kallistratos MS, Kopterides P, Syrios J, Skopelitis H, Mylonakis N, Karabelis A, Tsavaris N. Cardiotoxicity of fluoropyrimidines in different schedules of administration: a prospective study. J Cancer Res Clin Oncol. 2008;134(1):75–82.
37. Layoun ME, Wickramasinghe CD, Peralta MV, Yang EH. Fluoropyrimidine-induced cardiotoxicity: manifestations, mechanisms, and management. Curr Oncol Rep. 2016;18(6):35.
38. Kuropkat C, Griem K, Clark J, Rodriguez ER, Hutchinson J, Taylor SG. Severe cardiotoxicity during 5-fluorouracil chemotherapy: a case and literature report. Am J Clin Oncol. 1999;22(5):466–70.
39. Focaccetti C, Bruno A, Magnani E, Bartolini D, Principi E, Dallaglio K, Bucci EO, Finzi G, Sessa F, Noonan DM, Albini A. Effects of 5-fluorouracil on morphology, cell cycle, proliferation, apoptosis, autophagy and ROS production in endothelial cells and cardiomyocytes. PLoS One. 2015;10(2):e0115686.
40. Kounis NG, Tsigkas GG, Almpanis G, Mazarakis A. Kounis syndrome is likely culprit of coronary vasospasm induced by capecitabine. J Oncol Pharm Pract. 2012;18(2):316–8.
41. Constantinidou A, Smith I. Is there a case for anti-HER2 therapy without chemotherapy in early breast cancer? Breast. 2011;20(Suppl 3):S158–61.
42. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, Fleming T, Eiermann W, Wolter J, Pegram M, Baselga J, Norton L. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med. 2001;344(11):783–92.
43. Martín M, Esteva FJ, Alba E, Khandheria B, Pérez-Isla L, García-Sáenz JA, Márquez A, Sengupta P, Zamorano J. Minimizing cardiotoxicity while optimizing treatment efficacy with trastuzumab: review and expert recommendations. Oncologist. 2009;14(1):1–11.
44. Perez EA, Rodeheffer R. Clinical cardiac tolerability of trastuzumab. J Clin Oncol. 2004;22(2):322–9.
45. Jacquinot Q, Paget-Bailly S, Fumoleau P, Romieu G, Pierga JY, Espié M, Lortholary A, Nabholtz JM, Mercier CF, Pauporté I, Henriques J, Pivot X. Fluctuation of the left ventricular ejection fraction in patients with HER2-positive early breast cancer treated by 12months of adjuvant trastuzumab. Breast. 2018;41:1–7.
46. Bonzano E, Guenzi M, Corvò R. Cardiotoxicity assessment after different adjuvant hypofractionated radiotherapy concurrently associated with trastuzumab in early breast cancer. In Vivo. 2018;32(4):879–82.
47. Minichillo S, Gallelli I, Barbieri E, Cubelli M, Rubino D, Quercia S, Dall'Olio M, Rapezzi C, Zamagni C. Trastuzumab resumption after extremely severe cardiotoxicity in metastatic breast cancer patient: a case report. BMC Cancer. 2017;17(1):722.
48. Moilanen T, Jokimäki A, Tenhunen O, Koivunen JP. Trastuzumab-induced cardiotoxicity and its risk factors in real-world setting of breast cancer patients. J Cancer Res Clin Oncol. 2018;144(8):1613–21.
49. Telli ML, Hunt SA, Carlson RW, Guardino AE. Trastuzumab-related cardiotoxicity: calling into question the concept of reversibility. J Clin Oncol. 2007;25(23):3525–33.
50. Tang GH, Acuna SA, Sevick L, Yan AT, Brezden-Masley C. Incidence and identification of risk factors for trastuzumab-induced cardiotoxicity in breast cancer patients: an audit of a single "real-world" setting. Med Oncol. 2017;34(9):154.
51. Pinto AC, Ades F, de Azambuja E, Piccart-Gebhart M. Trastuzumab for patients with HER2 positive breast cancer: delivery, duration and combination therapies. Breast. 2013;22(Suppl 2):S152–5.
52. An J, Sheikh MS. Toxicology of trastuzumab: an insight into mechanisms of cardiotoxicity. Curr Cancer Drug Targets. 2019;19(5):400–7.
53. Gianni L, Salvatorelli E, Minotti G. Anthracycline cardiotoxicity in breast cancer patients: synergism with trastuzumab and taxanes. Cardiovasc Toxicol. 2007;7(2):67–71.
54. Fasching PA, Hartkopf AD, Gass P, Häberle L, Akpolat-Basci L, Hein A, Volz B, Taran FA, Nabieva N, Pott B, Overkamp F, Einarson H, Hadji P, Tesch H, Ettl J, Lüftner D, Wallwiener M, Müller V, Janni W, Fehm TN, Schneeweiss A, Untch M, Pott D, Lux MP, Geyer T, Liedtke C, Seeger H, Wetzig S, Hartmann A, Schulz-Wendtland R, Belleville E, Wallwiener D, Beckmann MW, Brucker SY, Kolberg HC. Efficacy of neoadjuvant pertuzumab in addition to chemotherapy and trastuzumab in routine clinical treatment of patients with primary breast cancer: a multicentric analysis. Breast Cancer Res Treat. 2018;173:319–28, in press
55. Spring L, Niemierko A, Haddad S, Yuen M, Comander A, Reynolds K, Shin J, Bahn A, Brachtel E, Specht M, Smith BL, Taghian A, Jimenez R, Peppercorn J, Isakoff SJ, Moy B, Bardia A. Effectiveness and tolerability of neoadjuvant pertuzumab-containing regimens for HER2-positive localized breast cancer. Breast Cancer Res Treat. 2018;172:733–40, in press
56. Senkus E, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rutgers E, Zackrisson S, Cardoso F, Committee EG. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26(Suppl 5):v8–30.
57. Lumachi F, Luisetto G, Basso SM, Basso U, Brunello A, Camozzi V. Endocrine therapy of breast cancer. Curr Med Chem. 2011;18(4):513–22.
58. Shagufta, Ahmad I. Tamoxifen a pioneering drug: an update on the therapeutic potential of tamoxifen derivatives. Eur J Med Chem. 2018;143:515–31.
59. Bird BR, Swain SM. Cardiac toxicity in breast cancer survivors: review of potential cardiac problems. Clin Cancer Res. 2008;14(1):14–24.

60. Foglietta J, Inno A, de Iuliis F, Sini V, Duranti S, Turazza M, Tarantini L, Gori S. Cardiotoxicity of aromatase inhibitors in breast cancer patients. Clin Breast Cancer. 2017;17(1):11–7.
61. Khosrow-Khavar F, Filion KB, Al-Qurashi S, Torabi N, Bouganim N, Suissa S, Azoulay L. Cardiotoxicity of aromatase inhibitors and tamoxifen in postmenopausal women with breast cancer: a systematic review and meta-analysis of randomized controlled trials. Ann Oncol. 2017;28(3):487–96.
62. Early Breast Cancer Trialists' Collaborative Group. Polychemotherapy for early breast cancer: an overview of the randomized trials. Lancet. 1998;352:930–42.
63. Masuda N, Nakayama T, Yamamura J, Kamigaki S, Taguchi T, Hatta M, Sakamoto J. Phase I study of combination therapy with weekly paclitaxel and cyclophosphamide for advanced or recurrent breast cancer. Cancer Chemother Pharmacol. 2010;66(1):89–94.
64. Yu AF, Manrique C, Pun S, Liu JE, Mara E, Fleisher M, Patil S, Jones LW, Steingart RM, Hudis CA, Dang CT. Cardiac safety of paclitaxel plus trastuzumab and pertuzumab in patients with HER2-positive metastatic breast cancer. Oncologist. 2016;21(4):418–24.
65. Swain SM, Ewer MS, Cortés J, Amadori D, Miles D, Knott A, Clark E, Benyunes MC, Ross G, Baselga J. Cardiac tolerability of pertuzumab plus trastuzumab plus docetaxel in patients with HER2-positive metastatic breast cancer in CLEOPATRA: a randomized, double-blind, placebo-controlled phase III study. Oncologist. 2013;18(3):257–64.
66. Cho E, Schwemm AK, Rubinstein LM, Stevenson PA, Gooley TA, Ellis GK, Specht JM, Livingston RB, Linden HM, Gadi VK. Adjuvant metronomic CMF in a contemporary breast cancer cohort: what's old is new. Clin Breast Cancer. 2015;15(5):e277–85.
67. Park JH, Im SA, Byun JM, Kim KH, Kim JS, Choi IS, Kim HJ, Lee KH, Kim TY, Han SW, Oh DY, Kim TY. Cyclophosphamide, methotrexate, and 5-fluorouracil as palliative treatment for heavily pretreated patients with metastatic breast cancer: a multicenter retrospective analysis. J Breast Cancer. 2017;20(4):347–55.
68. Salek R, Bayatmokhtari N, Homaei Shandiz F, ShahidSales S. The results of chemotherapy with two variants of intravenous CMF in patients with early stage breast carcinoma; Does dose density matter? Breast J. 2016;22(6):623–9.
69. Ghanbari S, Ayatollahi SM, Zare N. Comparing role of two chemotherapy regimens, CMF and anthracycline-based, on Breast Cancer Survival in the Eastern Mediterranean Region and Asia by multivariate mixed effects models: a meta-analysis. Asian Pac J Cancer Prev. 2015;16(14):5655–61.
70. Promberger R, Dubsky P, Mittlböck M, Ott J, Singer C, Seemann R, Exner R, Panhofer P, Steger G, Bergen E, Gnant M, Jakesz R, Bago-Horvath Z, Rudas M, Bartsch R. Postoperative CMF does not ameliorate poor outcomes in women with residual invasive breast cancer after neoadjuvant epirubicin/docetaxel chemotherapy. Clin Breast Cancer. 2015;15(6):505–11.
71. Tryfonidis K, Marreaud S, Khaled H, De Valk B, Vermorken J, Welnicka-Jaskiewicz M, Aalders K, Bartlett JMS, Biganzoli L, Bogaerts J, Cameron D, EORTC- Breast Cancer Group. Cardiac safety, efficacy, and correlation of serial serum HER2-extracellular domain shed antigen measurement with the outcome of the combined trastuzumab plus CMF in women with HER2-positive metastatic breast cancer: results from the EORTC 10995 phase II study. Breast Cancer Res Treat. 2017;163(3):507–15.
72. Guenancia C, Lefebvre A, Cardinale D, Yu AF, Ladoire S, Ghiringhelli F, Zeller M, Rochette L, Cottin Y, Vergely C. Obesity as a risk factor for anthracyclines and trastuzumab cardiotoxicity in breast cancer: a systematic review and meta-analysis. J Clin Oncol. 2016;34(26):3157–65.
73. Zamorano JL, Lancellotti P, Rodriguez Muñoz D, Aboyans V, Asteggiano R, Galderisi M, Habib G, Lenihan DJ, Lip GYH, Lyon AR, Lopez Fernandez T, Mohty D, Piepoli MF, Tamargo J, Torbicki A, Suter TM, ESC Scientific Document Group. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: the task force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). Eur Heart J. 2016;37(36):2768–801.
74. Garg V, Vorobiof G. Echocardiography and alternative cardiac imaging strategies for long-term cardiotoxicity surveillance of cancer survivors treated with chemotherapy and/or radiation exposure. Curr Oncol Rep. 2016;18(8):52.
75. Gulati G, Zhang KW, Scherrer-Crosbie M, Ky B. Cancer and cardiovascular disease: the use of novel echocardiography measures to predict subsequent cardiotoxicity in breast cancer treated with anthracyclines and trastuzumab. Curr Heart Fail Rep. 2014;11(4):366–73.
76. Nicolazzi MA, Carnicelli A, Fuorlo M, Scaldaferri A, Masetti R, Landolfi R, Favuzzi AMR. Anthracycline and trastuzumab-induced cardiotoxicity in breast cancer. Eur Rev Med Pharmacol Sci. 2018;22(7):2175–85.
77. Veronese P, Hachul DT, Scanavacca MI, Hajjar LA, Wu TC, Sacilotto L, Veronese C, Darrieux FCDC. Effects of anthracycline, cyclophosphamide and taxane chemotherapy on QTc measurements in patients with breast cancer. PLoS One. 2018;13(5):e0196763.
78. Cardinale D, Ciceri F, Latini R, Franzosi MG, Sandri MT, Civelli M, Cucchi G, Menatti E, Mangiavacchi M, Cavina R, Barbieri E, Gori S, Colombo A, Curigliano G, Salvatici M, Rizzo A, Ghisoni F, Bianchi A, Falci C, Aquilina M, Rocca A, Monopoli A, Milandri C, Rossetti G, Bregni M, Sicuro M, Malossi A, Nassiacos D, Verusio C, Giordano M, Staszewsky L, Barlera S, Nicolis EB, Magnoli M, Masson S, Cipolla CM, ICOS-ONE Study

Investigators. Anthracycline-induced cardiotoxicity: a multicenter randomised trial comparing two strategies for guiding prevention with enalapril: the International CardioOncology Society-one trial. Eur J Cancer. 2018;94:126–37.
79. Frères P, Bouznad N, Servais L, Josse C, Wenric S, Poncin A, Thiry J, Moonen M, Oury C, Lancellotti P, Bours V, Jerusalem G. Variations of circulating cardiac biomarkers during and after anthracycline-containing chemotherapy in breast cancer patients. BMC Cancer. 2018;18(1):102.
80. Sun D, Simon GJ, Skube S, Blaes AH, Melton GB, Zhang R. Causal phenotyping for susceptibility to cardiotoxicity from antineoplastic breast cancer medications. AMIA Ann Symp Proc. 2018;2017:1655–64.
81. Lalisang RI, Erdkamp FL, Rodenburg CJ, Knibbeler-van Rossum CT, Nortier JW, van Bochove A, Slee PH, Voest EE, Wils JA, Wals J, Loosveld OJ, Smals AE, Blijham GH, Tjan-Heijnen VC, Schouten HC. Epirubicin and paclitaxel with G-CSF support in first line metastatic breast cancer: a randomized phase II study of dose-dense and dose-escalated chemotherapy. Breast Cancer Res Treat. 2011;128(2):437–45.
82. Gil-Gil MJ, Bellet M, Morales S, Ojeda B, Manso L, Mesia C, Garcia-Martínez E, Martinez-Jáñez N, Melé M, Llombart A, Pernas S, Villagrasa P, Blasco C, Baselga J. Pegylated liposomal doxorubicin plus cyclophosphamide followed by paclitaxel as primary chemotherapy in elderly or cardiotoxicity-prone patients with high-risk breast cancer: results of the phase II CAPRICE study. Breast Cancer Res Treat. 2015;151(3):597–606.
83. Leonardi V, Palmisano V, Pepe A, Usset A, Manuguerra G, Savio G, DE Bella MT, Laudani A, Alù M, Cusimano MP, Scianna C, Giresi A, Agostara B. Weekly pegylated liposomal doxorubicin and paclitaxel in patients with metastatic breast carcinoma: a phase II study. Oncol Lett. 2010;1(4):749–53.
84. Venturini M, Michelotti A, Del Mastro L, Gallo L, Carnino F, Garrone O, Tibaldi C, Molea N, Bellina RC, Pronzato P, et al. Multicenter randomized controlled clinical trial to evaluate cardioprotection of dexrazoxane versus no cardioprotection in women receiving epirubicin chemotherapy for advanced breast cancer. J Clin Oncol. 1996;14(12):3112–20.
85. Cochera F, Dinca D, Bordejevic DA, Citu IM, Mavrea AM, Andor M, Trofenciuc M, Tomescu MC. Nebivolol effect on doxorubicin-induced cardiotoxicity in breast cancer. Cancer Manag Res. 2018;10:2071–81.
86. Taillibert S. Is systemic anti-cancer therapy neurotoxic? Does chemo brain exist? And should we rename it? Adv Exp Med Biol. 2010;678:86–95.
87. Lange M, Rigal O, Clarisse B, Giffard B, Sevin E, Barillet M, Eustache F, Joly F. Cognitive dysfunctions in elderly cancer patients: a new challenge for oncologists. Cancer Treat Rev. 2014;40(6):810–7.
88. Lange M, Joly F. How to identify and manage cognitive dysfunction after breast cancer treatment. J Oncol Pract. 2017;13(12):784–90.
89. Park HS, Kim CJ, Kwak HB, No MH, Heo JW, Kim TW. Physical exercise prevents cognitive impairment by enhancing hippocampal neuroplasticity and mitochondrial function in doxorubicin-induced chemobrain. Neuropharmacology. 2018;133:451–61.
90. Briones TL, Woods J. Chemotherapy-induced cognitive impairment is associated with decreases in cell proliferation and histone modifications. BMC Neurosci. 2011;12:124.
91. Wang XM, Walitt B, Saligan L, Tiwari AF, Cheung CW, Zhang ZJ. Chemobrain: a critical review and causal hypothesis of link between cytokines and epigenetic reprogramming associated with chemotherapy. Cytokine. 2015;72(1):86–96.
92. Henneghan AM, Palesh O, Harrison M, Kesler SR. Identifying cytokine predictors of cognitive functioning in breast cancer survivors up to 10years post chemotherapy using machine learning. J Neuroimmunol. 2018;320:38–47.
93. Bruno J, Hosseini SM, Kesler S. Altered resting state functional brain network topology in chemotherapy-treated breast cancer survivors. Neurobiol Dis. 2012;48(3):329–38.
94. Kesler SR. Default mode network as a potential biomarker of chemotherapy-related brain injury. Neurobiol Aging. 2014;35(Suppl 2):S11–9.
95. Ahles TA, Saykin AJ. Breast cancer chemotherapy-related cognitive dysfunction. Clin Breast Cancer. 2002;3(Suppl 3):S84–90.
96. Seigers R, Schagen SB, Beerling W, Boogerd W, van Tellingen O, van Dam FS, Koolhaas JM, Buwalda B. Long-lasting suppression of hippocampal cell proliferation and impaired cognitive performance by methotrexate in the rat. Behav Brain Res. 2008;186(2):168–75.
97. Seigers R, Schagen SB, Coppens CM, van der Most PJ, van Dam FS, Koolhaas JM, Buwalda B. Methotrexate decreases hippocampal cell proliferation and induces memory deficits in rats. Behav Brain Res. 2009;201(2):279–84.
98. Pomykala KL, de Ruiter MB, Deprez S, McDonald BC, Silverman DH. Integrating imaging findings in evaluating the post-chemotherapy brain. Brain Imaging Behav. 2013;7(4):436–52.
99. Fan HG, Houede-Tchen N, Yi QL, Chemerynsky I, Downie FP, Sabate K, Tannock IF. Fatigue, menopausal symptoms, and cognitive function in women after adjuvant chemotherapy for breast cancer: 1- and 2-year follow-up of a prospective controlled study. J Clin Oncol. 2005;23(31):8025–32.
100. Koppelmans V, Breteler MM, Boogerd W, Seynaeve C, Schagen SB. Late effects of adjuvant chemotherapy for adult onset non-CNS cancer; cognitive impairment, brain structure and risk of dementia. Crit Rev Oncol Hematol. 2013;88(1):87–101.
101. Edelstein K, Bernstein LJ. Cognitive dysfunction after chemotherapy for breast cancer. J Int Neuropsychol Soc. 2014;20(4):351–6.
102. Bernstein LJ, McCreath GA, Komeylian Z, Rich JB. Cognitive impairment in breast cancer survivors

treated with chemotherapy depends on control group type and cognitive domains assessed: a multilevel meta-analysis. Neurosci Biobehav Rev. 2017;83: 417–28.
103. Yao C, Bernstein LJ, Rich JB. Executive functioning impairment in women treated with chemotherapy for breast cancer: a systematic review. Breast Cancer Res Treat. 2017;166(1):15–28.
104. Yao C, Rich JB, Tannock IF, Seruga B, Tirona K, Bernstein LJ. Pretreatment differences in intraindividual variability in reaction time between women diagnosed with breast cancer and healthy controls. J Int Neuropsychol Soc. 2016;22(5):530–9.
105. Klemp JR, Myers JS, Fabian CJ, Kimler BF, Khan QJ, Sereika SM, Stanton AL. Cognitive functioning and quality of life following chemotherapy in pre- and peri-menopausal women with breast cancer. Support Care Cancer. 2018;26(2):575–83.
106. Vega JN, Dumas J, Newhouse PA. Self-reported chemotherapy-related cognitive impairment compared with cognitive complaints following menopause. Psychooncology. 2018;27(9):2198–205.
107. Lange M, Heutte N, Noal S, Rigal O, Kurtz JE, Levy C, Allouache D, Rieux C, Lefel J, Clarisse B, Leconte A, Veyret C, Barthelemy P, Longato N, Tron L, Castel H, Eustache F, Giffard B, Joly F. Cognitive changes after adjuvant treatment in older adults with early-stage breast cancer. Oncologist. 2018;24:62–8, in press
108. Joly F, Giffard B, Rigal O, De Ruiter MB, Small BJ, Dubois M, LeFel J, Schagen SB, Ahles TA, Wefel JS, Vardy JL, Pancre V, Lange M, Castel H. Impact of cancer and its treatments on cognitive function: advances in Research From the Paris International Cognition and Cancer Task Force Symposium and Update since 2012. J Pain Symptom Manag. 2015;50(6):830–41.
109. Hurria A, Lachs M. Is cognitive dysfunction a complication of adjuvant chemotherapy in the older patient with breast cancer? Breast Cancer Res Treat. 2007;103(3):259–68.
110. Dean L. Capecitabine therapy and DPYD genotype. In: Pratt V, McLeod H, Rubinstein W, Dean L, Malheiro A, editors. Medical genetics summaries. Bethesda: National Center for Biotechnology Information; 2012.
111. Shehata N, Pater A, Tang SC. Prolonged severe 5-fluorouracil-associated neurotoxicity in a patient with dihydropyrimidine dehydrogenase deficiency. Cancer Investig. 1999;17(3):201–5.
112. Formica V, Leary A, Cunningham D, Chua YJ. 5-fluorouracil can cross brain-blood barrier and cause encephalopathy: should we expect the same from capecitabine? A case report on capecitabine-induced central neurotoxicity progressing to coma. Cancer Chemother Pharmacol. 2006;58(2):276–8.
113. Videnovic A, Semenov I, Chua-Adajar R, Baddi L, Blumenthal DT, Beck AC, Simuni T, Futterer S, Gradishar W, Tellez C, Raizer JJ. Capecitabine-induced multifocal leukoencephalopathy: a report of five cases. Neurology. 2005;65(11):1792–4; discussion 1685
114. Han R, Yang YM, Dietrich J, Luebke A, Mayer-Proschel M, Noble M. Systemic 5-fluorouracil treatment causes a syndrome of delayed myelin destruction in the central nervous system. J Biol. 2008;7(4):12.
115. Mukesh M, Murray P. Cerebellar toxicity with capecitabine in a patient with metastatic breast cancer. Clin Oncol (R Coll Radiol). 2008;20(5):382–3.
116. Obadia M, Leclercq D, Wasserman J, Galanaud D, Dormont D, Sahli-Amor M, Psimaras D, Pyatigorskaya N, Law-Ye B. Capecitabine-induced acute toxic leukoencephalopathy. Neurotoxicology. 2017;62:1–5.
117. Verstappen CC, Heimans JJ, Hoekman K, Postma TJ. Neurotoxic complications of chemotherapy in patients with cancer: clinical signs and optimal management. Drugs. 2003;63(15):1549–63.
118. Winocur G, Berman H, Nguyen M, Binns MA, Henkelman M, van Eede M, Piquette-Miller M, Sekeres MJ, Wojtowicz JM, Yu J, Zhang H, Tannock IF. Neurobiological mechanisms of chemotherapy-induced cognitive impairment in a transgenic model of breast cancer. Neuroscience. 2018;369:51–65.
119. Hershman DL, Unger JM, Crew KD, Till C, Greenlee H, Minasian LM, Moinpour CM, Lew DL, Fehrenbacher L, Wade JL 3rd, Wong SF, Fisch MJ, Lynn Henry N, Albain KS. Two-year trends of taxane-induced neuropathy in women enrolled in a randomized trial of Acetyl-L-Carnitine (SWOG S0715). J Natl Cancer Inst. 2018;110(6):669–76.
120. Zirpoli GR, McCann SE, Sucheston-Campbell LE, Hershman DL, Ciupak G, Davis W, Unger JM, Moore HCF, Stewart JA, Isaacs C, Hobday TJ, Salim M, Hortobagyi GN, Gralow JR, Budd GT, Albain KS, Ambrosone CB. Supplement use and chemotherapy-induced peripheral neuropathy in a cooperative group trial (S0221): the DELCaP study. J Natl Cancer Inst. 2017;109(12):djx098.
121. Capri G, Munzone E, Tarenzi E, Fulfaro F, Gianni L, Caraceni A, Martini C, Scaioli V. Optic nerve disturbances: a new form of paclitaxel neurotoxicity. J Natl Cancer Inst. 1994;86(14):1099–101.
122. Ziske CG, Schottker B, Gorschluter M, Mey U, Kleinschmidt R, Schlegel U, Sauerbruch T, Schmidt-Wolf IG. Acute transient encephalopathy after paclitaxel infusion: report of three cases. Ann Oncol. 2002;13(4):629–31.
123. Muallaoglu S, Kocer M, Guler N. Acute transient encephalopathy after weekly paclitaxel infusion. Med Oncol. 2012;29(2):1297–9.
124. Perry JR, Warner E. Transient encephalopathy after paclitaxel (Taxol) infusion. Neurology. 1996;46(6): 1596–9.
125. Soffietti R, Trevisan E, Ruda R. Neurologic complications of chemotherapy and other newer and experimental approaches. Handb Clin Neurol. 2014;121:1199–218.

126. Doolittle ND, Peereboom DM, Christoforidis GA, Hall WA, Palmieri D, Brock PR, Campbell KC, Dickey DT, Muldoon LL, O'Neill BP, Peterson DR, Pollock B, Soussain C, Smith Q, Tyson RM, Neuwelt EA. Delivery of chemotherapy and antibodies across the blood-brain barrier and the role of chemoprotection, in primary and metastatic brain tumors: report of the Eleventh Annual Blood-Brain Barrier Consortium meeting. J Neuro-Oncol. 2007;81(1):81–91.
127. Mortensen ME, Cecalupo AJ, Lo WD, Egorin MJ, Batley R. Inadvertent intrathecal injection of daunorubicin with fatal outcome. Med Pediatr Oncol. 1992;20(3):249–53.
128. Kesler SR, Blayney DW. Neurotoxic effects of anthracycline- vs nonanthracycline-based chemotherapy on cognition in breast cancer survivors. JAMA Oncol. 2016;2(2):185–92.
129. Christie LA, Acharya MM, Parihar VK, Nguyen A, Martirosian V, Limoli CL. Impaired cognitive function and hippocampal neurogenesis following cancer chemotherapy. Clin Cancer Res. 2012;18 (7):1954–65.
130. Salas-Ramirez KY, Bagnall C, Frias L, Abdali SA, Ahles TA, Hubbard K. Doxorubicin and cyclophosphamide induce cognitive dysfunction and activate the ERK and AKT signaling pathways. Behav Brain Res. 2015;292:133–41.
131. Antkiewicz-Michaluk L, Krzemieniecki K, Romanska I, Michaluk J, Krygowska-Wajs A. Acute treatment with doxorubicin induced neurochemical impairment of the function of dopamine system in rat brain structures. Pharmacol Rep. 2016;68(3):627–30.
132. Liao D, Guo Y, Xiang D, Dang R, Xu P, Cai H, Cao L, Jiang P. Dysregulation of Neuregulin-1/ErbB signaling in the hippocampus of rats after administration of doxorubicin. Drug Des Devel Ther. 2018;12:231–9.
133. Cheruku SP, Ramalingayya GV, Chamallamudi MR, Biswas S, Nandakumar K, Nampoothiri M, Gourishetti K, Kumar N. Catechin ameliorates doxorubicin-induced neuronal cytotoxicity in in vitro and episodic memory deficit in in vivo in Wistar rats. Cytotechnology. 2018;70(1):245–59.
134. Ejlertsen B. Adjuvant chemotherapy in early breast cancer. Dan Med J. 2016;63(5):pii:B5222.
135. Ramalho M, Fontes F, Ruano L, Pereira S, Lunet N. Cognitive impairment in the first year after breast cancer diagnosis: a prospective cohort study. Breast. 2017;32:173–8.
136. Cerulla N, Arcusa A, Navarro JB, Garolera M, Enero C, Chico G, Fernandez-Morales L. Role of taxanes in chemotherapy-related cognitive impairment: a prospective longitudinal study. Breast Cancer Res Treat. 2017;164(1):179–87.
137. Janelsins MC, Heckler CE, Thompson BD, Gross RA, Opanashuk LA, Cory-Slechta DA. A clinically relevant dose of cyclophosphamide chemotherapy impairs memory performance on the delayed spatial alternation task that is sustained over time as mice age. Neurotoxicology. 2016;56:287–93.
138. Kreukels BP, Schagen SB, Ridderinkhof KR, Boogerd W, Hamburger HL, van Dam FS. Electrophysiological correlates of information processing in breast-cancer patients treated with adjuvant chemotherapy. Breast Cancer Res Treat. 2005;94(1):53–61.
139. Schagen SB, van Dam FS, Muller MJ, Boogerd W, Lindeboom J, Bruning PF. Cognitive deficits after postoperative adjuvant chemotherapy for breast carcinoma. Cancer. 1999;85(3):640–50.
140. Dechant KL, Brogden RN, Pilkington T, Faulds D. Ifosfamide/mesna. A review of its antineoplastic activity, pharmacokinetic properties and therapeutic efficacy in cancer. Drugs. 1991;42(3):428–67.
141. Underwood EA, Rochon PA, Moineddin R, Lee PE, Wu W, Pritchard KI, Tierney MC. Cognitive sequelae of endocrine therapy in women treated for breast cancer: a meta-analysis. Breast Cancer Res Treat. 2018;168(2):299–310.
142. Chen X, Li J, Zhang J, He X, Zhu C, Zhang L, Hu X, Wang K. Impairment of the executive attention network in premenopausal women with hormone receptor-positive breast cancer treated with tamoxifen. Psychoneuroendocrinology. 2017;75:116–23.
143. Boele FW, Schilder CM, de Roode ML, Deijen JB, Schagen SB. Cognitive functioning during long-term tamoxifen treatment in postmenopausal women with breast cancer. Menopause. 2015;22(1): 17–25.
144. Palmer JL, Trotter T, Joy AA, Carlson LE. Cognitive effects of Tamoxifen in pre-menopausal women with breast cancer compared to healthy controls. J Cancer Surviv Res Pract. 2008;2(4):275–82.
145. Lejbak L, Vrbancic M, Crossley M. Endocrine therapy is associated with low performance on some estrogen-sensitive cognitive tasks in postmenopausal women with breast cancer. J Clin Exp Neuropsychol. 2010;32(8):836–46.
146. Eberling JL, Wu C, Tong-Turnbeaugh R, Jagust WJ. Estrogen- and tamoxifen-associated effects on brain structure and function. NeuroImage. 2004;21(1): 364–71.
147. Collins B, Mackenzie J, Stewart A, Bielajew C, Verma S. Cognitive effects of hormonal therapy in early stage breast cancer patients: a prospective study. Psycho-Oncology. 2009;18(8):811–21.
148. Sun LM, Chen HJ, Liang JA, Kao CH. Long-term use of tamoxifen reduces the risk of dementia: a nationwide population-based cohort study. QJM. 2016;109(2): 103–9.
149. Ording AG, Jensen AB, Cronin-Fenton D, Pedersen L, Sorensen HT, Lash TL. Null association between tamoxifen use and dementia in Danish breast cancer patients. Cancer Epidemiol Biomark Prev. 2013;22 (5):993–6.
150. Jenkins VA, Ambroisine LM, Atkins L, Cuzick J, Howell A, Fallowfield LJ. Effects of anastrozole on cognitive performance in postmenopausal women: a randomised, double-blind chemoprevention trial (IBIS II). Lancet Oncol. 2008;9(10):953–61.

151. Moreira PI, Custodio JB, Oliveira CR, Santos MS. Brain mitochondrial injury induced by oxidative stress-related events is prevented by tamoxifen. Neuropharmacology. 2005;48(3):435–47.
152. Pandey D, Banerjee S, Basu M, Mishra N. Memory enhancement by Tamoxifen on amyloidosis mouse model. Horm Behav. 2016;79:70–3.
153. Wakade C, Khan MM, De Sevilla LM, Zhang QG, Mahesh VB, Brann DW. Tamoxifen neuroprotection in cerebral ischemia involves attenuation of kinase activation and superoxide production and potentiation of mitochondrial superoxide dismutase. Endocrinology. 2008;149(1):367–79.

Part IX

Drugs of Abuse and Cardiovascular Function

Alcohol and Cardiovascular Function

49

Maria Margherita Rando, Luisa Sestito, Antonio Mirijello, and Giovanni Addolorato

Contents

Abstract

The effects of alcohol consumption vary considerably and depend on the concentration and dose, together with various other factors, such as nutritional status, gender, and ethnicity. The present chapter analyzes the main medical consequences related to alcohol consumption on cardiovascular system. Low-to-moderate ethanol consumption has been linked to a reduced cardiovascular risk, with a J-shaped or U-shaped dose-response curve. However, alcohol intake has been associated with several cardiovascular diseases, such as hypertension, cardiomyopathy, coronary artery disease, and stroke. In particular, chronic alcohol consumption induces several alterations in the cardiovascular system, including low-grade systemic inflammation, hyperuricemia, dyslipidemia, hyperhomocysteinemia, increased oxidative stress with enhanced lipid peroxidation, impaired glucose tolerance with insulin resistance, endothelial dysfunction, arterial hypertension, and alcoholic cardiomyopathy. From a clinical point of view, all the mentioned mechanisms are able to modify the pathophysiology of atherosclerosis. In sum, although several studies have described a J-shaped or U-shaped curve to describe the

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*,
https://doi.org/10.1007/978-3-030-28008-6_51

relationship between alcohol intake and total and cardiovascular mortality, these studies have been observational and epidemiological in nature. Promoting alcohol for those who do not drink and/or the use of alcohol as a cardioprotective strategy is not recommended.

Keywords

Alcohol · Ethanol · Cardiovascular disease · Atherosclerosis · Alcoholic cardiomyopathy · Coronary heart disease · Peripheral artery disease · Stroke

Introduction

Alcohol is contained in different beverages consumed since ancient times in most countries around the world. In the past, it has been reported that the consumption of low dose of alcohol (1–2 drinks/day in men and 1 drink/day in women) is associated with decreased cardiovascular risk with a J-shaped dose-response curve. In the 1990s, Renaud et al. showed that in France, wine consumption protected from coronary heart disease, despite a high intake of saturated fat, the so-called French paradox [1].

The moderate consumption of alcoholic beverages seems to have a protective effect on arterial stiffness due to different alcohol-related mechanisms, such as increase in high-density lipoprotein cholesterol (HDL-C), decrease in platelet adhesivity to the endothelium, and changes in fibrinogen and fibrinolytic system [2, 3]. However, despite these findings, the consumption of alcohol for therapeutic purposes on cardiovascular risk should not be encouraged due to the potential risk of damage on several organs and apparatus and development of alcohol use disorders (alcohol abuse and alcohol dependence).

Both acute and chronic alcohol consumption may induce toxic effects on different organs, in particular on liver, digestive, nervous, and cardiovascular systems [4]. Alcohol plays a pivotal role on several cardiovascular disorders, such as alcoholic cardiomyopathy, coronary heart disease (CHD), cardiac arrhythmias, peripheral artery disease (PAD), and ischemic and hemorrhagic stroke [1, 5]. Moreover, ethanol promotes the development of arterial hypertension, and it negatively affects lipid profile, glucose metabolism, and systemic inflammation (with a pro-inflammatory effect at high doses), promoting atherosclerosis [2].

In the present chapter, the effects of alcohol on the cardiovascular system will be analyzed, and the most frequent diseases related to alcohol use and abuse will be discussed according to the most recent scientific data (Fig. 1).

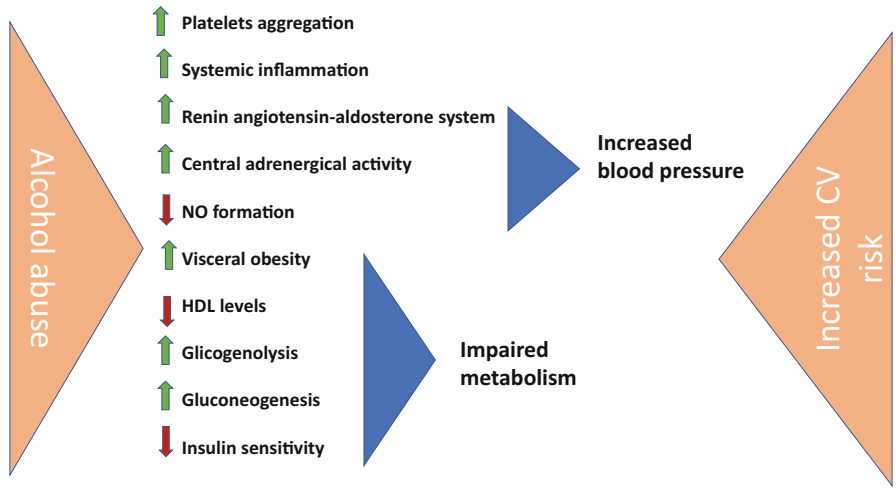

Fig. 1 Mechanisms involved in cardiovascular damage due to alcohol abuse. *CV* cardiovascular, *NO* nitric oxide

Alcohol, Atherosclerosis, and Cardiovascular Risk Factors

Several studies have shown that low-to-moderate alcohol consumption reduces the cardiovascular risk [6–9]. Renaud et al. in 1992 described the "French paradox," which consisted in a reduced incidence of CHD among French population despite a high intake of saturated fat. The explanation of this phenomenon was ascribed to the consumption of wine, as well as to the consumption of similar amount of ethanol consumed in the form of beer and spirits [1]. Despite evidences of the role of alcohol in reducing HDL-C (responsible for transporting cholesterol from arteries to the liver, decreasing accumulation of cholesterol in arterial wall and thus the formation of atherosclerotic plaque), Renaud et al. proposed that a moderate intake of alcohol could inhibit platelet aggregation, thus preventing myocardial infarction.

Subsequently, different studies have shown that the consumption of moderate amount of alcoholic beverages, wine in particular, was associated with cardiovascular benefits. The attention was particularly focused on the role of polyphenols, especially resveratrol (a polyphenol contained in red wine), and their antioxidant and anti-inflammatory effects [10]. However, a prospective cohort study by Semba et al. showed that resveratrol does not associate with inflammatory markers of cardiovascular disease and it does not seem to significantly influence health status and mortality risk [11]. Further studies are needed to verify the impact of resveratrol on cardiovascular risk.

Despite these weak evidences, it should be underlined that chronic alcohol consumption has a negative impact on cardiovascular risk factors (progression of atherosclerosis, arterial damage, and increased cardiovascular mortality) [2]. A prospective cohort study by O'Neill et al. showed that heavy alcohol consumption in men increased arterial stiffness, with consequent reduced responsiveness to pressure variations, thus indicative of both functional and structural vascular adverse changes [12]. Moreover, regular ethanol consumption influences blood pressure in a dose-dependent manner. At low doses (less than 10 gram/day), alcohol has a vasorelaxant effect [2], but at higher doses, alcohol increases blood pressure [11]. Chronic heavy drinking represents one of the most common reversible causes of hypertension [13], and its effect on the development of arterial hypertension is independent of age, smoking, obesity, salt intake, education level, and type of alcoholic beverage [14].

Pathophysiological mechanisms of arterial hypertension due to alcohol abuse are different. The pivotal role seems to be played by oxidative stress and endothelial injury, in addition to vascular responsiveness. It seems that alcohol sensitizes vascular reactivity to α-adrenoceptor agonists in aorta and in segments of superior mesenteric artery. Furthermore, ethanol reduces endothelial nitric oxide (NO) formation. A further mechanism involved is the activation of the renin-angiotensin-aldosterone (RAA) system and the increased central adrenergic activity. Moreover, long-term exposure to alcohol affects baroreflex activity through the control of heart rate [15]. Recently, genetic polymorphisms of aldehyde dehydrogenase 2 (ALDH2) have been related to alcoholic hypertension. ALDH2 is an enzyme involved in ethanol metabolism, turning acetaldehyde into acetate; the presence of a mutant or inactive ALDH2*2 gene increased the risk of hypertension through accumulation of acetaldehyde [16]. Finally, it should be underlined that blood pressure control usually improves with abstinence from alcoholic beverages [2].

Ethanol is also involved in glucose metabolism. Low-to-moderate drinking inhibits gluconeogenesis and glycogenolysis, and it improves insulin sensitivity, while heavy drinking eliminates these effects. With this regard, ethanol consumption induces β-cell dysfunction mediated by oxidative stress, and it is responsible of increased insulin resistance [17, 18]. Furthermore, ethanol acts by regulating appetite peptides such as ghrelin and leptin [18]. Ghrelin is an orexigenic peptide that has a proliferative and protective role on β-cells; it stimulates insulin secretion in response of high circulating glucose levels. This peptide is also able to reduce endogenous glucose production [18]. Leptin is an anorexigenic peptide

able to suppress the production of ghrelin increasing insulin secretion and glucose utilization; leptin has a role in diabetogenic imbalance, leading to beta-cell dysfunction, insulin resistance, obesity, and impairment of liver function in glucose metabolism [18, 19]. Chronic alcohol abuse deregulates ghrelin and leptin systems, in favor this latter, and it leads to impaired insulin secretion, increased endogenous glucose production, and increased insulin resistance.

An additional mechanism involved in impaired glucose metabolism is the effect of alcohol on brain-derived neurotrophic factor (BDNF). BDNF is a neurotrophin expressed especially in the nervous system. It has a role in regulating neuronal survival, differentiation, synaptic plasticity, cognitive function, and memory [18]. People with type 2 diabetes have low levels of BDNF that seems to correlate with severity of insulin resistance [18]. Nakagawa et al. demonstrated that BDNF plays a role in regulating glucose metabolism, reducing food intake, and lowering blood glucose in the obese diabetic mice [20]. They also studied the effect of BDNF on normoglycemic mice with impaired glucose tolerance, demonstrating that BDNF administration improves insulin resistance [20]. Chronic alcohol exposure decreases BDNF levels leading to impaired glucose metabolism. However, the exact mechanism of BDNF in the pathophysiology of type 2 diabetes after ethanol intake needs to be further investigated.

Alcohol plays also a role in visceral obesity. A review by Bendsen et al. shows an association between beer consumption and abdominal adiposity in men [21].

Moreover, ethanol affects systemic inflammation. At low doses, alcohol has an anti-inflammatory effect. At high doses, it has a pro-inflammatory role, affecting levels of inflammasomes, interleukins, cytokines, tumor necrosis factor, C-reactive protein, NADPH activation, and lipid peroxidation, with increased oxidative stress, glutathione and superoxide dismutase (SOD) depletion, endothelial dysfunction, increase of endothelial nitric oxide synthase expression, and monocyte adhesion to the endothelium [2, 22, 23]. As known, inflammation has a fundamental role in the pathogenesis of atherosclerosis, mediating all stages of this disease from initiation through progression and thrombotic complications [21].

All these factors contribute to increase cardiovascular risk in chronic alcohol abuse.

Alcohol and Coronary Heart Disease

Several studies have shown that moderate alcohol intake reduces the risk of new-onset coronary heart disease (CHD), angina, myocardial infarction, and cardiovascular mortality [5, 24–27]. The role of different alcoholic beverages on CHD risk has been examined, but the benefits of components other than ethanol, such as antioxidants, have not been proved [2, 10, 11].

A meta-analysis by Costanzo et al. described a J-shaped association between wine consumption and vascular risk and between beer consumption and vascular risk [28]. Moreover Rebecca et al. recently showed that the type of alcoholic beverages (beer, wine, or liquor) did not influence CHD risk. Therefore, the benefits of alcoholic beverages on vascular risk may derive from ethanol and not from other components, such as polyphenols found in red wine [29].

As previously mentioned, the mechanisms involved in the decrease of CHD risk by low-to-moderate ethanol consumption are multiple, in particular increase in HDL-C and apolipoprotein A-I, decrease in LDL cholesterol, increased adiponectin, reduced gluconeogenesis, decrease in platelet agreeability, changes in fibrinogen and fibrinolysis system, and a decrease in inflammatory system responses [30–32].

Recently, Xu et al. showed that Chinese stable CHD patients with ALDH 2 mutated genotype were vulnerable to coronary artery lesions and had lower levels of HDL-C with respect to ALDH 2 wild genotype [3]. Moreover, low-to-moderate alcohol intake was protective for multi-vessel coronary artery lesion in ALDH2 wild genotype group [3].

The beneficial effect of alcohol on coronary risk disappears at higher doses [28, 33, 34]. Besides quantity of ethanol consumed (low to moderate vs. high), also drinking patterns seem to impact on CHD. Rehm et al. showed that

irregular heavy drinking increases the risk of coronary artery disease via unfavorable impacts on blood lipids and effects on clotting, increasing the risk of thrombosis [35].

Alcohol and Peripheral Artery Disease

Peripheral artery disease (PAD) is the manifestation of atherosclerosis on lower extremities, mainly caused by the interaction of cited cardiovascular risk factors (aging, smoking, diabetes mellitus, dyslipidemia, hypertension, obesity, etc.) on arteries. PAD typically produces intermittent claudication with pain while walking or at rest.

The "PREDIMED Study" [36] demonstrated that a healthy lifestyle is associated with a substantially reduced risk of PAD. Thus, adherence to a Mediterranean diet (MedDiet), including moderate alcohol intake other than to a regular physical activity, normal weight (BMI < 25), and nonsmoking must be encouraged. However, although some studies showed that low-to-moderate alcohol consumption is associated to a reduced risk of PAD [37], data on the effects of chronic intake of large amount of alcohol on PAD are lacking. A retrospective population-based cohort study comparing patients with alcohol intoxication, age, and gender matched with patients without alcohol intoxication investigated the relation between high level of alcohol and atherosclerosis in lower extremities. Patients with alcohol intoxication had a significantly higher cumulative incidence rate of PAD than those without alcohol intoxication. Increased risk has been shown in both men and women [37]. Thus, alcohol intoxication, besides complications of alcohol abuse, should be also considered a major risk factor of PAD. Further studies are needed to evaluate the quantitative effect of alcohol use on PAD.

Alcohol and Stroke

A recent meta-analysis by Zhan and co-workers summarized evidences regarding alcohol consumption and risk of stroke [38]. According to these results, a low alcohol intake is associated with a reduced risk of stroke morbidity and mortality, while heavy alcohol intake is associated with an increased risk of total stroke [38].

A recent study by Costa and co-workers analyzed the relationship between alcohol intake and the risk of intracerebral hemorrhage (ICH). Participants were stratified into excessive drinkers (>45 g of alcohol), light-to-moderate drinkers, or nondrinkers: among white people aged 55 years and older, high alcohol intake was found to exert a causal effect on this cerebrovascular event, with a prominent role in the vascular pathologies underlying deep ICH [39].

Alcohol and Heart: Cardiac Arrhythmias

The toxic effect of alcohol on the heart is influenced by genetic, ethnic, and behavioral factors. Toxicity mostly targets myocytes, highly sensitive to ethanol. The damage is dose dependent, and it can be reversible with abstinence. In some cases, irreversible structural damage develops with cell death by apoptosis and development of fibrosis [2].

The most frequent acute toxic effect of ethanol on the heart is represented by arrhythmias. A positive association between episodic binge drinking (consumption >5 drinks per occasion) and onset of atrial fibrillation has been described in literature [12]. On this connection, heavy alcohol consumption is associated with atrial extrasystoles and atrial fibrillation, common manifestations of the so-called holiday heart syndrome. Even ventricular extrasystoles and ventricular tachycardia (that may result in sudden death) can be associated with alcohol abuse [40].

The arrhythmogenic effect of ethanol seems to be due to alterations in calcium homeostasis, in mitochondrial functions, and in contractile proteins leading to impaired myocardial function. Other mechanisms involved are prolongation of conduction times, of QT interval, and of myocyte refractory periods in the setting of increased sympathetic activity during alcohol withdrawal syndrome and of electrolytic imbalance (such as hypokalemia and hypomagnesaemia) that often accompanies heavy drinking. These conditions act altering transmembrane potentials [41].

Moreover, alcohol use disorder (AUD) is often associated with other substance use disorders or psychiatric comorbidities; these conditions expose patients to QT-prolonging therapies such as tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), and antipsychotic drugs, leading to a major risk of sudden cardiac death [40].

However, it should be underlined that acute arrhythmogenic effect of ethanol is infrequent in individuals with normal heart function and it is often associated with a structural myocardial damage, representing a clinical manifestation of alcoholic dilated cardiomyopathy [2, 40].

Alcohol and Heart: Alcoholic Cardiomyopathy

Chronic exposure of the heart to high doses of alcohol can result in alcoholic cardiomyopathy (AC), a disease characterized by dilation and impaired contraction of one or both myocardial ventricles in the presence of normal or reduced ventricular wall thickness [4].

According to epidemiological data, alcoholic cardiomyopathy is one of the main causes of non-ischemic dilated cardiomyopathy in Western countries [41]; an excessive alcohol intake is evidenced in almost half of cases of this cardiac disease [42]. Although several studies have tried to estimate the exact prevalence of AC, available data are not conclusive [2]. The reported prevalence of alcoholic cardiomyopathy in patients treated in alcohol addiction unit is between 21% and 32% [43, 44]. The diagnosis of AC can be performed in the presence of a history of chronic alcohol abuse after the exclusion of other causes of dilated non-ischemic cardiomyopathies [4, 12].

The effect of ethanol on ventricular function is dose dependent, even if the exact quantity and duration of alcohol consumption to induce cardiac damage are still unknown. There is no agreement on the quantity and duration of alcohol abuse to produce AC. However, according to the majority of the literature, 80 grams/day for at least 5 years represents a reliable cut-off [1].

However, because of different genetic, ethnic, and behavioral factors, not all the heavy drinkers will develop AC. HLA-B8, alleles of the alcohol dehydrogenase, and nongenetic factors, such as thiamine deficiency and exposure to other cardiotoxic substances (e.g., cocaine, previously utilized beer additives like cobalt and arsenic), are involved [45]. There is no difference in the prevalence of AC in males and females [46].

Evidences of alcohol-induced toxicity to myocardial cell have been reported [47] both in binge drinkers and in chronic alcohol abuse. In acute consumption, alcohol has been shown to promote myocardial inflammation, detectable by the raising in serum troponin concentration [48]. In chronic consumption, alcohol seems to produce alterations in myocytes as hypertrophy, apoptosis and necrosis, and intracellular structure dysfunction, modification of contractile proteins and calcium homeostasis, mitochondrial degeneration, and fibrosis [49]. Moreover, alcohol metabolites (acetaldehyde and ethyl esters) promote oxidative damage and lipid peroxidation causing the alteration of excitation-contraction sequence [29, 47, 50]. Thus, alcohol leads to the reduction of myofibrillar proteins and the expression of different isoforms of myosin that results in depressed cardiac contraction [51]. As a consequence, the decrease in cardiac output and the dilatation of the left ventricle ensue from the long-term activation of compensatory mechanisms (hyperactivation of sympathetic nervous system, RAA system, cytokines, and natriuretic peptide), resulting in increased preload and the hypertrophy of normal myocytes [52].

The natural history of AC is not completely understood for the scarcity of evidences and because of the few studies available [4, 42]. There are also uncertainties regarding the clinical progression of the disease and the prognosis. It is known that end-stage AC is characterized by left ventricle dilatation and systolic dysfunction but, if ventricular dilatation and ejection fraction impairment are preceded or not by hypertrophy and diastolic dysfunction, has not been completely clarified [4]. Diastolic dysfunction has been proposed as an early manifestation of AC [2]. Even systolic dysfunction (reduction in left ventricular

ejection) can be found in a subclinical stage, and it seems to involve about 13% of heavy alcohol drinkers [2]. Clinical manifestations of AC appear at end stage when the damage is advanced. Signs and symptoms are those of congestive heart failure, and they are correlated to reduced cardiac output: dyspnea, orthopnea, bilateral peripheral edema, fatigue, oliguria, and nycturia. At physical examination, jugular vein distension, tachyarrhythmia, and third and/or fourth tone can be present. Moreover, it should be underlined that AC can be accompanied by alcoholic liver disease (ALD) and neurological disorders typical of AUD patients.

Regarding the diagnosis of AC, no specific clinical, instrumental, or histological features have been identified. AC remains a diagnosis of exclusion in the presence of a positive patient history of alcohol intake/abuse. Heavy drinking should be accurately evaluated and confirmed by biomarkers of alcohol abuse (gamma-glutamyltranspeptidase, mean corpuscular volume, carbohydrate-deficient transferrin, and ethyl glucuronide) and by the consultation of an alcohol addiction specialist [53]. ECG is not specific; it can show ST segment and/or T-wave alterations and any arrhythmias secondary to cardiac dilatation. Chest X-ray can document cardiomegaly, pulmonary congestion, and pleural effusion. Echocardiography can help to identify hypertrophy, dilatation, and systolic and diastolic dysfunction at early stage, and it can exclude other causes of heart failure, such as other diagnostic tools like magnetic resonance (MR) and biopsy.

The cornerstone of the treatment of AC is total alcohol abstinence or, at least, a significant reduction of alcohol consumption [2, 54]. Thus, the correct identification and treatment of AUD in the context of an alcohol addiction unit are of primary importance, even for the possibility to manage pharmacotherapies (i.e., anti-craving drugs) [55, 56]. Moreover, as recommended by the ESC Guidelines, patients have to receive a specific treatment for heart failure (i.e., beta-blockers, ace inhibitors, angiotensin receptor antagonists, diuretics, angiotensin receptor-neprilysin inhibitor (ARNI)) [57]. In case of persistent severe ventricular dysfunction, even with a maximally optimized therapy, an ICD implant and heart transplantation could be considered [57].

Currently, new strategies are being evaluated for the treatment of AC. In course of study, there are inhibitors of pathways involved in myocyte hypertrophy and cell loss (myostatin, sirtuins, caspase, etc.), drugs for the control of cardiac fibrosis (miRNAs, TGF-β, relaxin, etc.), drugs for the control of oxidative damage (cardiomyokines, leptin, ghrelin, etc.), and treatments direct to myocyte regeneration and repair (telocytes and stem cells [4, 58]).

Prognosis of AC has not been completely defined because of lack of evidences. Generally, AC patients show a better prognosis and a longer transplantation-free survival than patients affected by idiopathic dilated cardiomyopathy [42]. The presence of atrial fibrillation, QRS duration >120 ms, and lack of beta-blocker therapy seem to represent independent predictors of mortality [42]. Moreover, the long-term prognosis seems to be influenced also by the course of AUD; in fact worsening of systolic function is directly related to the amount and to the duration of alcohol consumption [4]. However, although total alcohol abstinence represents the gold standard in the treatment of AC, data of a correlation between reduction of alcohol intake and cardiac improvement are still lacking [4].

Conclusion

Data on the potential benefits of low-to-moderate alcohol intake on cardiovascular risk are at present still debated and controversial. At present, promoting alcohol consumption for those not drinking or the use of alcohol as a cardioprotective strategy is not recommended for the risk of organ damage and of alcohol misuse.

Acknowledgment

We wish to thank Mariangela Antonelli, Tommaso Dionisi, Daniele Ferrarese, Carolina Mosoni, Claudia Tarli, Alberto Tosoni and Gabriele Vassallo for their cooperation in the literature review useful to finalize the present chapter.

References

1. Renaud S, de Lorgeril M. Wine, alcohol, platelets, and the French paradox for coronary heart disease. Lancet. 1992;339(8808):1523–6.
2. Fernández-Solà J. Cardiovascular risks and benefits of moderate and heavy alcohol consumption. Nat Rev Cardiol. 2015;12(10):576–87.
3. Xu L, Zhao G, Wang J, et al. Impact of genetic variation in aldehyde dehydrogenase 2 and alcohol consumption on coronary artery lesions in Chinese patients with stable coronary artery disease. Int Heart J. 2018;59:689–94.
4. Mirijello A, Tarli C, Vassallo GA, et al. Alcoholic cardiomyopathy: what is known and what is not known. Eur J Intern Med. 2017;43:1–5.
5. Ricci C, Wood A, Muller D, Gunter MJ, Agudo A, Boeing H, et al. Alcohol intake in relation to non-fatal and fatal coronary heart disease and stroke: EPIC-CVD case-cohort study. BMJ. 2018;361:k934.
6. Thun MJ, Peto R, Lopez AD, et al. Alcohol consumption and mortality among middle-aged and elderly U.S. adults. N Engl J Med. 1997;337:1705–14.
7. Renaud SC, Gueguen R, Schenker J, d'Houtaud A. Alcohol and mortality in middle-aged men from eastern France. Epidemiology. 1998;9:184–8.
8. Waskiewicz A, Sygnowska E, Drygas W. Relationship between alcohol consumption and cardiovascular mortality – the Warsaw Pol-MONICA project. Kardiol Pol. 2004;60:552–62. discussion 563
9. Ronksley P, Brien S, Turner B, Mukamal K, Ghali W. Association of alcohol consumption with selected cardiovascular disease outcomes: a systematic review and meta-analysis – with comments. BMJ. 2011;342:d671.
10. Biagi M, Bertelli AAE. Wine, alcohol and pills: what future for the French paradox? Life Sci. 2015;131:19–22.
11. Semba RD, Ferrucci L, Bartali B, et al. Resveratrol levels and all-cause mortality in older community-dwelling adults. JAMA Intern Med. 2014;174 (7):1077–84.
12. O'Neill D, Britton A, Brunner EJ, Bell S. Twenty-five-year alcohol consumption trajectories and their association with arterial aging: a prospective cohort study. J Am Heart Assoc. 2017;6(2): pii: e005288.
13. O'Keefe EL, Di Nicolantonio JJ, O'Keefe JH, Lavie CJ. Alcohol and CV health: Jekyll and Hyde J-curves. Prog Cardiovasc Dis. 2018;61:68–75.
14. Katsiki N, Tziomalos K, Mikhailidis DP. Alcohol and the cardiovascular system: a double-edged sword. Curr Pharm Des. 2014;20:6276–88.
15. Crestani CC, Lopes da Silva A, Scopinho AA, Ruginsk SG, Uchoa ET, FMA C, et al. Cardiovascular alterations at different stages of hypertension development during ethanol consumption: time-course of vascular and autonomic changes. Toxicol Appl Pharmacol. 2014;280(2):245–55.
16. Hu N, Zhang Y, Nair S, Culver BW, Ren J. Contribution of ALDH2 polymorphism to alcoholism-associated hypertension. Recent Pat Endocr Metab Immune Drug Discov. 2014;8:180–5.
17. Pietraszek A, Gregersen S, Hermansen K. Alcohol and type 2 diabetes. A review. Nutr Metab Cardiovasc Dis. 2010;20:366–75.
18. Kim S-J, Kim D-J. Alcoholism and diabetes mellitus. Diabetes Metab J. 2012;36(2):108–15.
19. Addolorato G, Capristo E, Greco AV, Stefanini GF, Gasbarrini G. Influence of chronic alcohol abuse on body weight and energy metabolism: is excess ethanol consumption a risk factor for obesity or malnutrition? J Intern Med. 1998;244(5):387–95.
20. Nakagawa T, Tsuchida A, Itakura Y, Nonomura T, Ono M, Hirota F, et al. Brain-derived neurotrophic factor regulates glucose metabolism by modulating energy balance in diabetic mice. Diabetes. 2000;49:436–44.
21. Bendsen NT, Christensen R, Bartels EM, Kok FJ, Sierksma A, Raben A, et al. Is beer consumption related to measures of abdominal and general obesity? A systematic review and meta-analysis. Nutr Rev. 2013;71:67–87.
22. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. Circulation. 2002;105:1135–43.
23. Obad A, Peeran A, Little JI, Haddad GE, Tarzami ST. Alcohol-mediated organ damages: heart and brain. Front Pharmacol. 2018;9:81.
24. Wells S, Broad J, Jackson R. Alcohol consumption and its contribution to the burden of coronary heart disease in middle-aged and older New Zealanders: a population-based case-control study. N Z Med J. 2004;117: U793.
25. Camargo CA, Stampfer MJ, Glynn RJ, Grodstein F, Gaziano JM, Manson JE, et al. Moderate alcohol consumption and risk for angina pectoris or myocardial infarction in U.S. male physicians. Ann Intern Med. 1997;126(5):372–5.
26. Mukamal KJ, Chiuve SE, Rimm EB. Alcohol consumption and risk for coronary heart disease in men with healthy lifestyles. Arch Intern Med. 2006;166(19):2145–50.
27. Song RJ, Nguyen X-MT, Quaden R, Ho Y-L, Justice AC, Gagnon DR, et al. Alcohol consumption and risk of coronary artery disease (from the Million Veteran Program). Am J Cardiol. 2018;121(10):1162–8.
28. Costanzo S, Di Castelnuovo A, Donati MB, Iacoviello L, de Gaetano G. Wine, beer or spirit drinking in relation to fatal and non-fatal cardiovascular events: a meta-analysis. Eur J Epidemiol. 2011;26(11):833–50.
29. Department of Agriculture Dietary Guidelines Recommendation. In: https://health.gov/dietaryguidelines/2015/resources/2015-2020_Dietary_Guidelines.pdf.
30. Demrow HS, Slane PR, Folts JD. Administration of wine and grape juice inhibits in vivo platelet activity and thrombosis in stenosed canine coronary arteries. Circulation. 1995;91(4):1182–8.
31. Miceli M, Alberti L, Bennardini F, Di Simplicio P, Seghieri G, Rao GHR, et al. Effect of low doses of ethanol on platelet function in long-life abstainers and moderate-wine drinkers. Life Sci. 2003;73(12): 1557–66.

32. Brien SE, Ronksley PE, Turner BJ, Mukamal KJ, Ghali WA. Effect of alcohol consumption on biological markers associated with risk of coronary heart disease: systematic review and meta-analysis of interventional studies. BMJ. 2011;342:d636.
33. Kloner RA, Rezkalla SH. To drink or not to drink? That is the question. Circulation. 2007;116:1306–17.
34. Foerster M. Alcohol drinking and cardiovascular risk in a population with high mean alcohol consumption. Am J Cardiol. 2009;103:361–8.
35. Rehm J, Roerecke M. Cardiovascular effects of alcohol consumption. Trends Cardiovasc Med. 2017;27(8):534–8.
36. Ros E, Martínez-González MA, Estruch R, Salas-Salvadó J, Fitó M, Martínez JA, et al. Mediterranean diet and cardiovascular health: teachings of the PREDIMED study. Adv Nutr. 2014;5(3):330S–6S.
37. Huang JY, Chen WK, Lin CL, Lai CY, Kao CH, Yang TY. Increased risk of peripheral arterial disease in patients with alcohol intoxication: a population-based retrospective cohort study. Alcohol. 2017;65:25–30.
38. Zhang C, Qin YY, Chen Q, Jiang H, Chen XZ, Xu CL, et al. Alcohol intake and risk of stroke: a dose-response meta-analysis of prospective studies. Int J Cardiol. 2014;174(3):669–77.
39. Costa P, Grassi M, Iacoviello L, Zedde M, Marcheselli S, Silvestrelli G, et al. Alcohol intake and the risk of intracerebral hemorrhage in the elderly: the MUCH-Italy. Multicenter Study on Cerebral Haemorrhage in Italy (MUCH-Italy) Investigators. Neurology. 2018;91(3):e227–35.
40. George A, Figueredo VM. Alcohol and arrhythmias: a comprehensive review. J Cardiovasc Med. 2010;11:221–8.
41. Guzzo-Merello G, Cobo-Marcos M, Gallego-Delgado M, Garcia-Pavia P. Alcoholic cardiomyopathy. World J Cardiol. 2014;6(8):771–81.
42. Guzzo-Merello G, Segovia J, Dominguez F, Cobo-Marcos M, Gomez-Bueno M, Avellana P, et al. Natural history and prognostic factors in alcoholic cardiomyopathy. JACC Heart Fail. 2015;3(1):78–86.
43. Regan TJ. Alcohol and the cardiovascular system. JAMA. 1990;264(3):377–81.
44. Urbano-Marquez A, Estruch R, Navarro-Lopez F, Grau JM, Mont L, Rubin E. The effects of alcoholism on skeletal and cardiac muscle. N Engl J Med. 1989;320:409–15.
45. Maisch B. Alcoholic cardiomyopathy: the result of dosage and individual predisposition. Herz. 2016;41(6):484–93.
46. Fernández-Solà J, Estruch R, Nicolás JM, Paré JC, Sacanella E, Antúnez E, et al. Comparison of alcoholic cardiomyopathy in women versus men. Am J Cardiol. 1997;80(4):481–5.
47. Klatsky AL. Alcohol and cardiovascular diseases: where do we stand today? J Intern Med. 2015;278(3):238–50.
48. Waszkiewicz N, Szulc A, Zwierz K. Binge drinking-induced subtle myocardial injury. Alcohol Clin Exp Res. 2013;37(8):1261–3.
49. Beckemeier ME, Bora PS. Fatty acid ethyl esters: potentially toxic products of myocardial ethanol metabolism. J Mol Cell Cardiol. 1998;30(11):2487–94.
50. Ren J, Wold LE. Mechanisms of alcoholic heart disease. Ther Adv Cardiovasc Dis. 2008;2(6):497–506.
51. Mahmoud S, Beauchesne LM, Davis DR, Glover C. Acute reversible left ventricular dysfunction secondary to alcohol. Can J Cardiol. 2007;23(6):475–7.
52. Laonigro I, Correale M, Di Biase M, Altomare E. Alcohol abuse and heart failure. Eur J Heart Fail. 2009;11(5):453–62.
53. Fernández-Solà J, Nicolás JM, Paré JC, Sacanella E, Fatjó F, Cofán M, et al. Diastolic function impairment in alcoholics. Alcohol Clin Exp Res. 2000;24(12):1830–5.
54. Voskoboinik A, Prabhu S, Ling LH, Kalman JM, Kistler PM. Alcohol and atrial fibrillation: a sobering review. J Am Coll Cardiol. 2016;68(23):2567–76.
55. Addolorato G, Mirijello A, Barrio P, Gual A. Treatment of alcohol use disorders in patients with alcoholic liver disease. J Hepatol. 2016;65(3):618–30.
56. Addolorato G, Abenavoli L, Leggio L, Gasbarrini G. How many cravings? Pharmacological aspects of craving treatment in alcohol addiction: a review. Neuropsychobiology. 2005;51(2):59–66.
57. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016;37(27):2129–200.
58. Fernández-Solà J, Planavila PA. New treatment strategies for alcohol-induced heart damage. Int J Mol Sci. 2016;17(10):1651.

Nicotine and Cardiovascular Function

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Cristiano Ialongo, Diletta Sabatini, and Maria Caterina Grassi

Contents

Abstract

Nicotine is a natural alkaloid of tobacco leaves that specifically interacts with a acetiylcholinergic receptor (AChR) population which is therefore pharmacologically identified as nicotinic (nAChR). By virtue of that, nicotine is able to affect the function of those tissues expressing nAChR, particularly the brain, where it develops substance dependence, and the heart. Effects on the heart depend on multiple mechanisms of action involving regulatory centers in the brainstem that control the sympathetic outflow, although most of the effects on heart rate and blood pressure depend upon the direct ganglionic stimulation leading to the release of catecholamines in blood by adrenal glands. Nonetheless, nicotine is able to interact directly with ion channels of cardiomyocytes involved in the development of the action potential, as well as with inflammatory cells involved in cardiac fibrosis and remodeling. Understanding its multiple intimate relationships with human physiology is necessary in order to develop effective pharmacological strategies based on the use of partial agonists aimed at contrasting addiction, thereby preventing nicotine toxicity.

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*,
https://doi.org/10.1007/978-3-030-28008-6_52

Keywords

Nicotine · Nicotinic agonists · Blood pressure · Heart rate · Cardiovascular diseases · Hypertension · Atrial fibrillation · Tobacco smoking · Smoking cessation

Introduction

Nicotine is an addictive alkaloid with highly toxic effects on the cardiovascular system that are independent from the hazardous by-products of tobacco smoking. In this chapter it will be introduced the epidemiology of nicotine spreading and abuse and its relationship with cigarette smoking. Afterward it will be presented the essential pharmacology of the substance, giving relevance to molecular aspects of metabolism and biological variability that are responsible for both addictive and toxicological effects. Then, to highlight the way nicotine interact in the heart-brain connection, it will be reviewed the central mechanism of action whereby nicotine directly affects blood pressure and heart rate. Besides, it will be discussed the direct cardiac toxicity of nicotine and its importance concerning the use of electronic cigarettes, finally introducing the nicotinic partial agonists and reviewing their cardiovascular safety in smoking cessation pharmacotherapy.

Epidemiology of Nicotine and the Role in Tobacco Dependence

Nicotine is among the most used substances of abuse in the world, able to induce addiction and responsible for disturbance in homeostasis and cell integrity of many tissues [1]. In its spreading among populations, nicotine is tightly related with tobacco consumption mostly in the form of cigarette smoking, with estimated 1.1 billion smokers worldwide [2]. Indeed, if we consider that 6.5 trillion cigarettes are yearly sold and that there are about 10 mg of nicotine per cigarette on average, by a simple calculation, we can find that 65,000 tons of substance at least is sold on the market [2, 3].

Because of the close connection existing between the addictive power of nicotine and tobacco smoking, it is almost impossible, if not scarcely practical, to keep separated scholastically the real hazard of nicotine exposure [4]. In many western countries, smoking remains a highly prevailing habit with steady incidence regardless of smoking-cessation sensitizing campaigns and smoking ban policies [2]. Therefore, although cigarette smoking is the recognized leading cause of preventable death in developed countries, and the gain in life expectancy and quality owing to quitting has been widely demonstrated, prevalence of smoking has just reduced by 23.5–20.7% worldwide [2, 5].

Nicotine addiction is considered a "chronic relapsing disease" according to the 5th edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) [6]. Actually, because it is a natural repellent for leaf-eating insects, nicotine is naturally selected as active compound on neuronal cells where it specifically interacts with the nicotine-sensitive subpopulation of the acetylcholine receptor (nAChR) [3]. Binding of the nicotine to the nAChR causes the opening of its pentameric structure that acts as ligand-gated ion channel, with the generation of an inward ionic current of cations, sodium, and calcium depending on the specific subtype that depolarizes the cell [7]. Afterward, the opening of voltage-dependent calcium channels leads to a local increase in calcium level at the presynaptic active zone which triggers neurotransmitters release stored in the synaptic vesicles via the activation of the synaptotagmins [8]. Nicotinic stimulation leads to release of a variety of neurotransmitters, of which dopamine is the major agent responsible for the neurobiological mechanism underlying addiction [1, 9]. The mechanism involves the mesolimbic area, the corpus striatum, and the frontal cortex, but dopaminergic neurons in the ventral tegmental area of the midbrain and in the shell of the nucleus accumbens are those critical to promote self-administration (reinforcing effect) [1].

Psycho-affective effects induced by nicotine include pleasure, reduction of stress and anxiety, as well as enhanced concentration and reaction time [1, 10]. As a consequence, smoking cessation

produces a typical withdrawal syndrome that comprises somatic and cognitive components [9]. Since the inhalation way is a highly efficient and a fast route of substance delivery to the brain, smoking allows a fine titration of the substance which facilitates the building up of conditioned behavior in the so-called tobacco addiction cycle [1].

Because of the highly addictive power of nicotine and easiness in its environmental pollution, vulnerability to this substance of abuse turns out to be insidious and therefore should raise awareness [11]. In fact, inhalation of airborne nicotine (so-called secondhand smoke, SHS) is a passive exposure way with the potential to evoke the same neurobiological activation as direct smoking [12]. Hence, SHS can promote nicotine addiction especially in adolescents, conditioning their future habits and health in adulthood, and the education system indeed should be the mainstay in preventing the nicotine addiction avoiding physical as well as cultural contact with tobacco and smoking [13–15]. Nonetheless universities, which are a place of culture but also of greater exposure to SHS, should take their part in incepting the anti-smoking and nicotine-free habit especially in those who committed to a medical career and have a factual impact in the promotion of personal and public health [16–18]. Besides environment, biological variability plays a pivotal role in the individual vulnerability to nicotine addiction, so that genetics of nAChR and hepatic cytochromes harboring nicotine biotransformation has shown the importance of inherited receptor sensitivity toward nicotine and disposition efficiency of the substance [1, 19]. These very same loci are also involved in susceptibility toward tobacco smoking-associated diseases which are linked with nicotine addiction, for instance, lung cancer, chronic obstructive pulmonary disease, and periphery artery disease [20, 21]. Nonetheless, the actual risk related to nicotine addiction also goes beyond the indirect immediate exposure, as the tobacco combustion produces persistent chemical compounds that contaminate the environment, household surfaces, and fabrics, thus leading to the so-called thirdhand smoke (THS) exposure [22]. What we have seen so far shows that the interaction between individuals and nicotine is indeed far more complex phenomenon than it may be though regardless of the personal involvement with this substance. Thus, in order to face such complexity, it is likely that it will prevail in the future the approach where biological systems rather than single genes function and polymorphisms will provide the means to explain the way nicotine can affect individual physiology time by time (Fig. 1) [23, 24].

By a toxicological and medical perspective, nicotine is a remarkable actor in the interplay between the heart (withal circulation) and brain, for it can interact with both of them either directly (pharmacologically) or indirectly (biochemically as well as metabolically) [4]. Therefore, cardiovascular safety of this substance is a major concern in healthcare, as well as that of nAChR partial agonists (varenicline, cytisine, and dianicline) that have selective interaction in

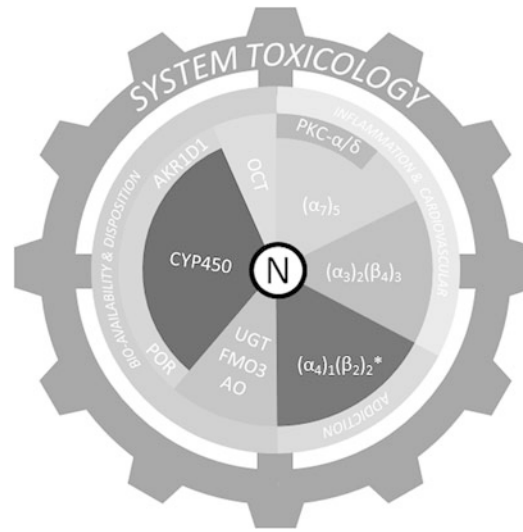

Fig. 1 The "clockwork" of system toxicology of nicotine. In this schematic representation, it is outlined how nicotine is at the center of a complex system of multiple interactions like the coiled spring triggering the cogwheel that drives the clockwork mechanism; N, nicotine; OCT, organic cation transporter; CYP450, cytochrome P450; UGT, uridine-diphosphate glucuronosyl transferase; FMO3, flavin-containing monooxygenase 3; POR, cytochrome P450 oxidoreductase; AKR1D1, aldo-keto reductase 1D1; $(\alpha7)_5/(\alpha3)_2(\beta4)_3/(\alpha4)_1(\beta2)_2*$, nicotinic acetylcholine receptor subtypes; PKC-α/δ, protein kinase C alpha and delta

this connection (mostly with brain and psycho-affective features) and are mainstays for breaking nicotine addiction [25].

Essential Chemistry and Pharmacology of Nicotine

Nicotine is the major alkaloid in tobacco leaves for it accounts up to 95% of the total alkaloids content [26]. Chemically, it is a tertiary amine with stereo-isomers (S)-nicotine (or L-nicotine) and (R)-nicotine (or D-nicotine), of which the former is the pharmacologically more active and abundant in green leaves [3]. It is a weak dibasic base (pKa 8.0), and thus its ionization state is dependent upon the pH of the physiological milieu. Three major routes are commonly encountered in nicotine administration: (a) inhalation, the most frequent one due to the prevalence of tobacco smoking habit, (b) oral, and (c) trans-dermic.

In the inhalation way, the ionized nicotine in the acidic cigarette smoke (pH 5.5–6.0) is passively absorbed after it has turned in the non-ionized form at the level of alveoli and smaller airways. That depends upon the combined action of the neutral air-surface alveolar liquid (pH 6.8–7.1), the deposition of alkaline particulate matter (tar droplets), and the huge diffusion surface [3]. In the oral way, absorption happens mostly at the level of the small intestine where pH is alkaline, allowing 20–40% bioavailable substance compared to inhalation route [27]. By contrast, topic administration is an effective route that is widely exploited in nicotinic replacement therapy allowing steady but complete absorption and comfortable self-management of substance administration [3]. Notably, although massive absorption via the buccal mucosa or the gastro-intestinal tract is possible only with alkaline-buffered formulations, the broad availability of commercial-concentrated nicotine solutions intended for the use with electronic cigarette (e-cigarette) devices has made of it a concern especially in the pediatric setting [28, 29].

In plasma, most of the nicotine in a dose is ionized (≈70%) and minimally bound to proteins (<5%) so that the apparent volume of distribution (V_d) is as large as 2.6 L/kg body weight [3]. After bolus injection or smoking, nicotine is distributed to the brain within 2 min and to other tissues within 15 min, whereas up to 95% of the dose is eliminated within 2.5 h [30]. The brain (owing to nAChR density), heart, liver, and kidney represent the major binding sites of nicotine during the distribution phase, whereas the body fat and skeletal muscle are the major storage tissues at steady state [3]. Notably, as it rapidly passes through biological barriers like the blood-brain barrier (i.e., reaching the brain in 10–20 s after a single cigarette puff), it also easily crosses the placenta reaching the amniotic fluid and the umbilical cord blood where it can directly interact with the fetal tissues [3]. Moreover, being actively excreted into biological fluids like saliva and the gastric juice, it can be found into the breast milk thus representing a remarkable hazard for newborns as well [3].

Nicotine biotransformation (Fig. 2) involves by almost 80% the hepatic metabolism via two-step conversion to cotinine that is mediated by microsomal cytochrome CYP2A6 and cytoplasmic aldehyde oxidase (AO) [3]. Other minor routes of biotransformation concern the production of desmethyl-nicotine or nornicotine (<1%), nicotine 1′-*N*-oxide (4–7%), and nicotine *N*-glucuronide (3–5%) that is formed via the uridine-diphosphate glucuronosyl transferase (UGT) UGT2B10 (high affinity) and UGT1A4 (low affinity) [3, 31, 32]. Notably, cotinine itself is a substrate of CYP2A6 with a pharmacokinetic elimination half-life ($t_{1/2}$) of about 15 h, so just 15% of absorbed nicotine is excreted as unchanged cotinine in urines, otherwise being converted into norcotinine and trans-3′-hydroxycotinine and then conjugated with glucuronic acid via UGT2B17 or cotinine 1′-*N*-oxide [3].

Owing to the pivotal role played by the hepatic cytochrome CYP2A6 in nicotine metabolism, attention must be paid to interaction with drugs and food constituents, as well as the inter-individual-, racial-, and gender-related differences [3]. With respect to interactions, the grapefruit juice is known to inhibit CYP2A6 activity, and as such it can increase nicotine $t_{1/2}$ [3]. Methoxsalen, a drug that is used in photochemotherapy of vitiligo, psoriasis, and cutaneous lymphoma, is

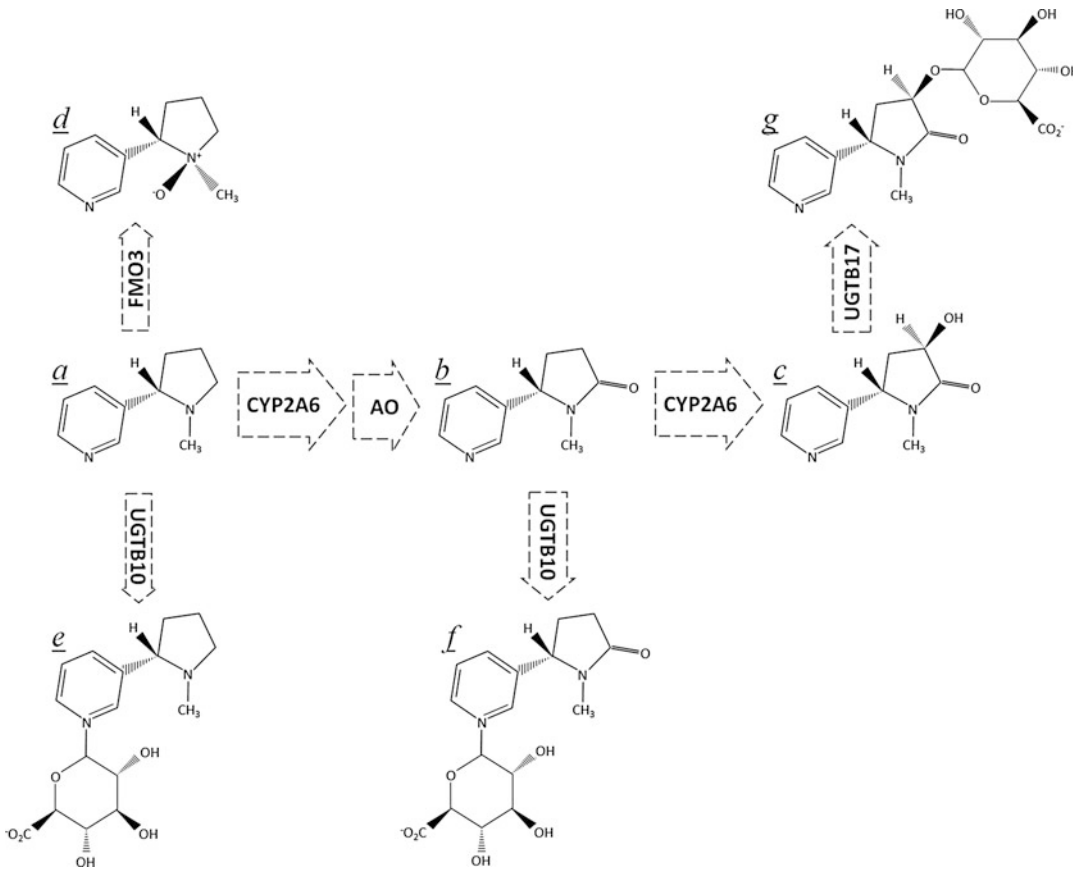

Fig. 2 Nicotine biotransformation. The major metabolic pathway of nicotine (**a**) involves sequential action of cytochrome CYP2A6 and cytosolic aldehyde oxidase (AO) with the production of major metabolite cotinine (**b**) that is further converted by same isoenzyme into trans-3′-hydroxycotinine (**c**). Alternatively, nicotine can be converted to a very minor extent into nicotine 1′-*N*-oxide by the enzyme flavin-containing monooxygenase 3 (FMO3) **(d)**. Finally, while nicotine and cotinine undergo the conjugation via uridine-diphosphate glucuronosyl transferase (UGT) UGT2B10 isoenzyme with formation of nicotine-*N*-glucuronide (**e**) and cotinine-*N*-glucuronide (**f**), the trans-3′-hydroxycotinine is conjugated via UGT2B17 with formation of trans-3′-hydroxycotinine-O-glucuronide (**g**)

another cytochrome inhibitor [31]. Moreover, minor tobacco alkaloids may play a role as either enzyme inhibitors or gene downregulators, although this is not yet fully characterized [3]. On the contrary, typical inducers are represented by drugs as rifampicin and dexamethasone, some anticonvulsants (e.g., barbiturates), and oral contraceptives [3]. Particularly, the effect of oral contraceptives also explains the gender-related difference due to which higher level of estrogens and progesterone induces CYP2A6 activity, so that women have faster metabolism than men that is even higher in same female individuals during estroprogestinic therapy [3]. Genetic polymorphism at CYP2A6 locus is a major determinant of the inter-individual differences because it can account up to 80% of the variation in enzyme activity [33]. Alongside it is possible to find other kind of variants that affect the enzyme expression and in turn the abundancy in the liver tissue, like duplications or deletions of the whole gene, as well as noncoding mutations that alter the gene transcript stability [33]. However, it is known that just few from the very large number of variants documented so far actually determine the biochemical phenotype and thus are of clinical and pharmacological relevance [33, 34]. According to the individual genotype, it is

possible to predict the phenotype of the allele carriers and distinguish them in ultrarapid (>100%), regular (≈100%), intermediate (≤75%), and slow (≤50%) metabolizers according to the trans-3′-hydroxycotinine/cotinine ratio they, respectively, show [35]. Notably, for it greatly affects the level of nicotine exposure, the CYP2A6 polymorphism and in turn the biochemical phenotype are acknowledge to play a role in conditioning the smoking behavior as well as the responsiveness to smoking cessation pharmacotherapy [33, 36]. As a remark, the contribution to variability in biochemical phenotype of those genes directly involved into nicotine metabolism, like UGT, AO, and flavin-containing monooxygenase 3 (FMO3), is ascertained but of unclear relevance in nicotine-related diseases [31, 37–40]. By contrast, there is evidence that other genes like the cytochrome P450 oxidoreductase (POR) and the aldo-keto reductase 1D1 (AKR1D1), which are indirectly involved with CYP2A6, can be of much more interest [33]. For instance, subjects carrying a certain allele of the POR gene have been shown to metabolize nicotine faster regardless of a CYP2A6 genotype predicting regular enzymatic activity [33].

Urinary disposition of nicotine involves both glomerular filtration and tubular secretion, but the net clearance depends on the surrounding pH for it causes the molecule to stay in the ionization state that allows low or high passive resorption via back-diffusion through tubules [3]. Indeed, also in this case, genetic factors are thought to play a role in determining the clearance phenotype of nicotine through the active transporters located at tubular cells, and indeed the organic cation transporter (OCT) family, especially the OCT2 member, seems to be a promising subject of investigation in pharmacotherapy [41, 42].

The Nicotine Stimulatory Effects on the Heart via the Cardiovascular Regulatory Center in the Brain

The nicotine can exert its stimulating activity on heart rate and arterial blood pressure via three potential mechanisms: (a) non-ganglionic on the central regulatory nuclei, (b) ganglionic on the sympathetic transmission, and (c) ganglionic on both the sympathetic terminations and the adrenal glands [43]. To this concern, physiological evidence has shown that cigarette smoking produces a sudden increase in heart rate and arterial blood pressure that is equivalent to the effect provoked by a single nicotine bolus [44]. As far as it has been shown to happen in conjunction with acute rising in plasma catecholamines level, the postganglionic mechanism of action (mechanism "c") is considered to be the prevailing way whereby nicotine exerts its effect on the cardiovascular system [45]. Notwithstanding, for it is mostly in deprotonated form at plasma pH, nicotine can easily permeate the blood-brain barrier reaching the nAChR within the central nervous [3]. As a consequence, the central mechanism of action, that is also responsible for nicotine addiction and smoking behavior, is, of course, a matter of interest for the regulation of the cardiovascular dynamics.

In neurons located within the central nervous system of humans, the pentameric nAChR is mainly present in three subtypes, namely, $(\alpha3)_2(\beta4)_3$, $(\alpha7)_5$, and $(\alpha4)_1(\beta2)_2*$, where "$*$" stands for either $(\alpha4)_2$ or $(\alpha4)_2(\beta2)_1$ or $(\alpha6)_1(\beta3)_1$ [7]. It is remarkable that the nAChR plays a pivotal role as postsynaptic as well as presynaptic receptor, the latter enabling modulation of other neurotransmitters release and the development of excitatory patterns involved in neuronal plasticity [46, 47]. Hence, whereas the $(\alpha4)_1(\beta2)_2*$ subtype is known to mediate the psychoactive effects of nicotine, the $(\alpha3)_2(\beta4)_3$ as well as the $(\alpha7)_5$ is thought to mediate the autonomous effects [48]. To this regard, the homomeric receptor $(\alpha7)_5$ is deemed responsible for the sympathetic downstream following the central stimulation, whereas the heteromeric nAChR plays a role in integrating the regulation of sympathetic and parasympathetic activities and exerting ganglionic stimulation [49, 50].

In the brainstem, the medulla contains two bilateral columns of neurons organized rostrocaudally that harbor the resting and reflexive activity in sympathetic control of vasomotor tone and heart contractility (Fig. 3) [51]. Within this region, the pre-sympathetic barosensitive neurons

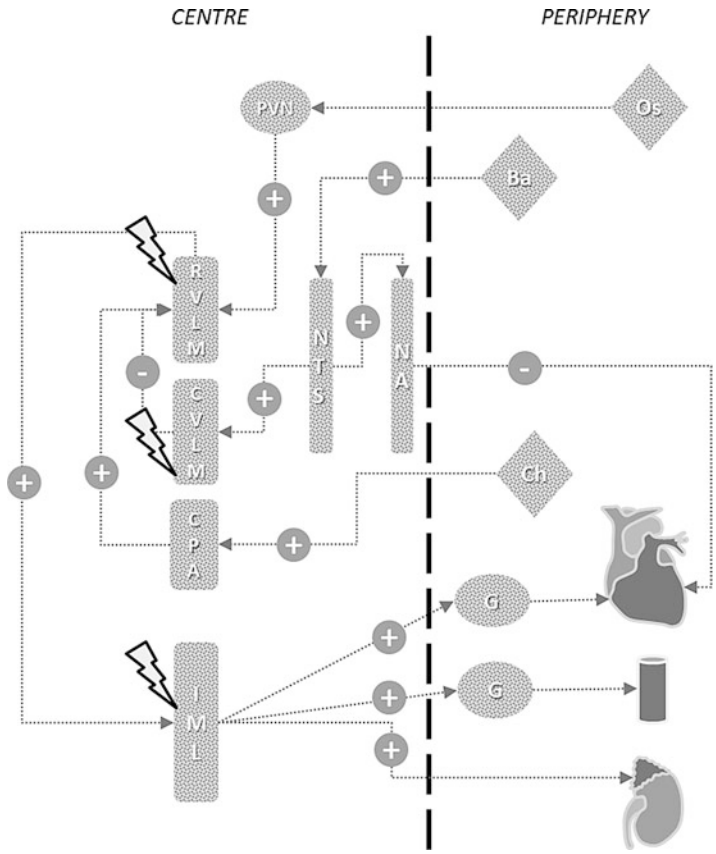

Fig. 3 Central effects of nicotine on cardiovascular system and regulatory mechanisms. The rostral ventrolateral medulla (RVLM) located in the brainstem and the intermediolateral nucleus (IML) within the thoracic spinal cord elicit purely sympathetic effects (hypertension and tachycardia) when directly exposed to nicotine (represented by the bolt in the picture); by contrast, the caudal ventrolateral medulla (CVLM) within the brainstem causes bradycardia repressing the RVLM when exposed to nicotine; in living subjects, the net sympathetic effect which is observed after nicotine bolus injection or cigarette smoking depends on the intervention of baroreceptors (Ba) that are stimulated by the nicotine-hypertensive cure, which act via the nucleus tractus solitarius (NTS) to activate the CVLM and the nucleus ambiguus (NA) to deliver the parasympathetic drive to the heart; in chronic smokers loss of responsiveness by Ba blunts the parasympathetic activation; to this concern, both the chemoreceptors (Ch) acting via the caudal pressor area (CPA) and the periventricular nucleus (PVN) which receives input from the osmoreceptors (Os) may play a role in regulating the tonic RVLM activity

located in the rostral ventrolateral medulla (RVLM) are responsible for tonic discharge activity projecting to preganglionic neurons in the thoracolumbar spinal cord and in turn to sympathetic neurons in the prevertebral and paravertebral sympathetic ganglia and adrenal medulla [51]. The RVLM is stimulated by multiple projections from both center (e.g., the paraventricular nucleus of hypothalamus) and periphery (e.g., baroreceptors via nucleus tractus solitarius), while it is depressed by neurons located in the caudal ventrolateral medulla (CVLM) [51]. Besides, the caudal pressor area (CPA) is another area of relevance that is located further caudally in the brainstem and which is deemed to play a fundamental role in regulating the RVLM tonic activity in response to the chemoreflex [51].

Experimental evidences obtained by animal experiments (rats) have shown that nicotine administration via intrathecal injection at the level of the thoracic spinal cord can elicit a stimulatory effect on blood pressure and heart rate [52, 53]. Similar results have been obtained via

nicotine microinjection into the RVLM with blockade of muscarinic receptors [54]. By contrast, nicotine directly microinjected into the CVLM is able to induce hypotension and bradycardia [48]. Noteworthy, parenteral administration of nicotine via intravenous injection or inhalation of cigarette smoke can produce sudden hypertensive response accompanied by a prolonged tachycardia that has however a delayed onset [55]. In humans, where purely central effect on the cardiovascular system regulation cannot be achieved via direct stimulation of brainstem areas, the effect of nicotine can be only observed as an integrated physiological response. Notwithstanding, central stimulation can be evaluated by measuring the heart rate variability (HRV) for it delivers the balancing dynamics between sympathetic and parasympathetic branches [56]. Actually, acute exposure to nicotine via bolus injection causes transient reduction in HRV of healthy young non-smokers who putatively neither have autonomic compensatory nor receptor adaptive mechanisms [56]. Likewise, same effect can be elicited by acute cigarette smoking in same kind of individuals within 5 min after exposure, with a recovery to basal condition as long as 30 min [57]. However, whether the exposure may cause the parasympathetic response, it is depending on the integrity of baroreflex sensitivity to the hypertensive cue, so that when compromised after chronic cigarette smoking, a dull counteracting bradycardia is observed [56]. Moreover, the loss of sensitivity shown by chemoreceptors after prolonged nicotine stimulation due to the development of tolerance may contribute via the brainstem interconnections, as it shows when smokers and non-smokers are acutely exposed to the substance [58]. Therefore, the prevailing sympathetic effect observed after the nicotine exposure is likely to depend mostly on the lack of integrity of the baroreflex (and chemoreflex as well) and only to a minor extent on the accessibility to central nAChRs determined by the route of administration. Actually, this turns out to be especially true when nicotine is inhaled via cigarette smoking because of the sympathetic stimulatory activity elicited by the cigarette tar through the lung C-fibers [56, 59].

The Direct Effect of Nicotine on the Heart via Ion Channel Interaction, Immune System, and Cell Metabolism

Although direct effects of nicotine on the heart have been ascribed to the catecholamines release via the ganglionic stimulation, there is evidence that the substance can directly interact with A-type ligand-gated ion channels in the cardiomyocytes to modify the cell activity [60]. In particular, nicotine inhibits multiple types of K^+ currents and mostly the transient outward currents (I_{to}) that control the initial repolarization of the myocardium [60]. Indeed, the exposure to the substance induces prolongation in the initial repolarization and subsequent plateau phase, thereby influencing the participation of other currents and membrane transport processes that are elicited by the voltage-time profile of the membrane potential [60]. Nicotine is also effective on the inward rectifier K^+ currents (Kirs) that play a role in stabilizing the resting membrane potential and thereby have been implicated in a number of cardiovascular diseases like arrhythmias and fibrillation [60, 61]. In this regard nicotine exposure can induce electrocardiographic changes and arrhythmias regardless of tobacco exposure by way of possible direct disturbance of cardiac electric activity [62]. Notwithstanding, it is not possible to quantify the actual purely pro-arrhythmic potential of this substance in a real clinical setting because of the overwhelming effect of catecholamines on heart function as well as the tobacco constituents that act alongside nicotine in smoking exposure [63, 64].

Besides, nicotine is involved in a broader mechanism that depends upon the direct heart remodeling effect as well as the hemodynamic stress due to degradation of systemic vasculature which reflects on cardiac function [4]. With respect to heart remodeling, nicotine is able to induce atrial fibrosis by way of an immune-mediated mechanism via the protein kinase C alpha (PKC-α) and delta (PKC-δ) downstream the activation of isoform $(\alpha7)_5$ nAChR located on cardiac fibroblasts [65, 66]. Moreover, nicotine acts per se as chemotactic stimulus to neutrophils, thereby promoting the release of inflammatory cytokines

like the transforming growth factor-β1 (TGF-β1) and the production of reactive oxygen species (ROS) that cause damage to the cell membrane and activate the apoptosis [65]. Hence, nicotine has the capability to induce cardiac remodeling regardless of tobacco exposure as formerly shown by the exposure of atrial tissue slices from non-smokers that showed fibrotic-like profile when cultured in the presence of nicotine base [67]. With respect to the hemodynamic stress to the heart, nicotine is involved in endothelial damage via several mechanisms of action, most of which involve reduced viability and resistance to shear stress [4]. On the one hand, nicotine causes disturbance in the production of nitric oxide (NO) either directly downregulating the endothelial nitric oxide synthase (eNOS) or via the production of ROS that scavenge NO [4, 68]. Thereby, NO-depleted endothelium becomes prone to reduced vasodilation and shows pro-aggregating lumen surface that favors thrombosis despite nicotine is not a platelet-activating factor per se [69, 70]. On the other hand, nicotine that is indeed active on the immune system as we discussed earlier participates to deterioration of the endothelial function promoting the extravasation of neutrophils into the subendothelium and enhancing the leukocyte-endothelial adhesion capacity [4]. Therefore, although the direct effect of nicotine alone must be considered small in the impairment of cardiac function compared to catecholamines and tobacco toxic constituents, it may act a pivotal role in starting up the inflammatory behavior in healthy smokers or triggering smokers with former cardiovascular disease [71].

As far as nicotine is a cardiotoxic substance by way of multiple mechanisms of actions (i.e., on pressor regulatory centers, cardiac ion channel activity, catecholamine release, myocardial remodeling), e-cig can be a deceitful cause of nicotine cardiotoxicity. In fact, regardless of their not superiority in smoking cessation or reduced delivery of harmful products due to heating of liquid filler additives, use of e-cigarettes is steadily increasing worldwide for it is considered a safer way of smoking [72, 73]. However, vaping does not change significantly the pharmacokinetics of the substance compared to a regular cigarette smoking, which means that the acute blood peak of nicotine is not avoided [74, 75]. Indeed healthy non-smoker individuals exposed to e-cigarettes vaping do show acute sympathetic effects which are attributable to nicotine and not to other toxics within the inhaled vapor [59, 76]. Hence, there is evidence to speculate that vaping can deliver as much nicotine as it is necessary to elicit the whole spectrum of effects of which the substance is capable, namely, hypertensive and arrhythmogenic [4, 62]. Of course, this should be a concern not only in adults and elders where there may be a former cardiovascular disorder but also in young smokers, where it could cause a Brugada-like syndrome, and pregnant women, for it could bring systemic and uterine hemodynamic changes resulting in fetal ischemia, respectively [62, 77].

nAChR Partial Agonists in the Heart-Brain Connection

Because of the pivotal role played by the $(\alpha4)_1(\beta2)_2*$ in the nicotine addiction through the control of dopamine release, the nAChR partial agonists cytisine, varenicline, and dianicline are attracting the interest for their role in the pharmacotherapy of smoking cessation [25]. The odds of tobacco quitting and smoking relapse represent major endpoint for evaluating the efficacy of these medications, and to this concern, while cytisine and varenicline have shown favorable outcomes, the newer dianicline has not reached the clinical stage [25]. Of course, since the pharmacotherapy can represent a means to manage and reduce the cardiovascular disease risk factors, the cardiovascular safety of the nAChR partial agonists is of concern especially in those with acute or unstable cardiovascular diseases [78]. Hence, it will be briefly reviewed these substances in light of their participation in the heart-brain connection during pharmacotherapy.

The oldest smoking cessation-aid substance cytisine (Fig. 4) is a natural alkaloid contained in the leaves of European endemic *Cytisus laburnum Linnaeus* (golden rain tree), which was discovered and characterized in the nineteenth century and

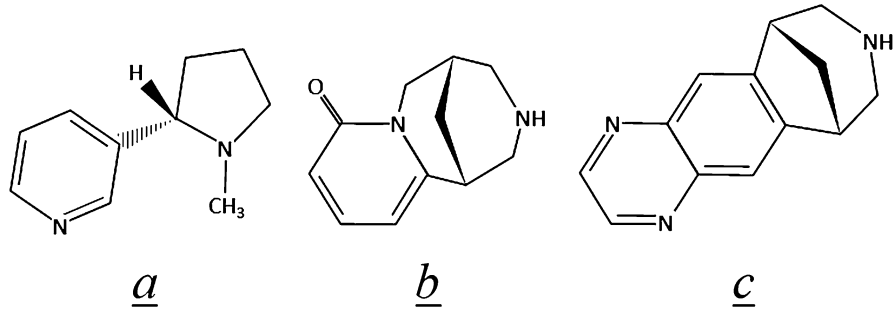

Fig. 4 Nicotine and the nicotinic receptor partial agonists compared. (**a**) The full agonist nicotine; (**b**) the natural partial agonists cytisine; (**c**) the synthetic partial agonists varenicline

later on commercialized since 1964 under the brand name "Tabex®" [79]. It is a weak hydrophilic basis (pKa 7.85) that is rapidly absorbed after oral administration (bioavailability nearly 30% in animals) with blood peak (T_{max}) after 2 h and $t_{1/2}$ 4.8 h [79]. The drug is rapidly distributed to noncentral compartment, and this is deemed to depend on either active or para-cellular transport, but distribution to the brain is <30% of blood level [79]. Remarkably, both high-affinity binding and potency to central nAChRs of the subtype $(\alpha4)_1(\beta2)_2*$ may explain the efficacy of the drug despite low brain permeation, although the full agonist activity at periphery $(\alpha3)_2(\beta4)_3$ subtype may participate in preventing physical abstinence via the stimulation of ganglia [79, 80]. Cytisine, although is a natural alkaloid, undergoes negligible hepatic metabolism, and up to 95% of the substance can be found unchanged in urines, so that potential interactions may arise due to concomitant administration of other substances undergoing extensive renal active excretion/reuptake [79]. Cytisine clinical efficacy has been found to be comparable, if not superior under certain conditions, to varenicline and more cost-effective [81, 82]. By a pharmacodynamic perspective, cytisine is expected to replicate in part the central effect of nicotine, to which was found to be equal in potency when administered via intrathecal injection in rats; notwithstanding, when given parentally, it elicited a faint bradycardia before heart rate increases unlikely to nicotinic agonists [55]. In humans, acute administration at high dosage, twice the therapeutic, of the substance does not seem to affect unfavorably blood pressure, heart rate, and respiratory rate in healthy smokers [79]. This is in agreement with the poor permeation to the brain and the interaction with ganglia, and similarly no cardiovascular unfavorable effects have been found so far in long-term exposure or at least when cytisine was compared with varenicline [25]. Therefore, no cardiovascular significant concern seems arising with the use of this substance.

Varenicline is a cytisine synthetic derivative developed by Pfizer in 1997 that the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) both approved for medical use as tartrate salt since 2006 in the USA (Chantix®) and Europe (Champix®) [83, 84]. Varenicline retains most of the pharmacological properties of its natural precursor although it is much more basic molecule (pKa 9.73) and is distributed to tissues and the brain to a higher degree, so that varenicline V_d is about fourfold of cytisine (415 vs. 115 L, respectively) [79, 85]. Hence, unlikely the precursor, the elimination kinetics is biphasic similarly to nicotine, with $t_{1/2}$ approximating 24 h and 28 h after single and multiple dosing, respectively [85]. In this case as well, the renal function is the major determinant in varenicline disposition since hepatic metabolism is negligible (<5% of the oral dose), and despite the hypothesized participation of active organic cations transporters (OCT) to renal excretion, no remarkable interaction has been shown so far [85]. Pharmacodynamics of this substance shows high selectivity toward the central $(\alpha4)_1(\beta2)_2*$ subtype

of the nAChR with partial agonist activity and potency that seem fairly comparable to cytisine [55, 85]. Besides, it is a low-affinity full agonist at the $(\alpha 7)_5$ subtype and almost twice as potent as cytisine, whereas at $(\alpha 3)_2(\beta 4)_3*$ it shows low-affinity and low-potency full agonist profile [86]. Thereby, owing to the large penetration into the brain and strong interaction with central nAChRs, varenicline is deemed to blunt the dopamine overflow responsible for the reinforcing mechanism much more than cytisine does [25]. On the other hand, this makes varenicline more likely to interact with cardiovascular regulatory centers within the brainstem, and experimental evidence in rats shows that its parental administration produces circulatory and cardiac stimulation as strong as nicotine [55]. Notwithstanding, clinical studies and meta-analyses have given no evidence about pro-hypertensive effect in healthy and non-healthy smokers, suggesting that risk of cardiovascular death and cardiovascular events is unlikely to exceed 0.7% and 5%, respectively [25]. Nevertheless, in 2011 the FDA issued a Drug Safety Communications (updated in 2012) concerning the increased risk of cardiovascular events associated with varenicline pharmacotherapy, so that the cardiovascular safety of this drug remains formally uncertain even if it is likely to be real [87, 88].

Conclusion

Nicotine is an addicting substance with intimate and multiple relationships with human physiology that should be carefully considered and treated regardless of the tobacco exposure. As such nicotine should deserve per se the same public attention as it is usually given to other substances of abuse even though newer and deceitful means of its delivery are distracting the focus from this concern. Of course the deep and complete understanding of its multiple mechanisms of action is necessary to develop and enhance those pharmacological tools by means of which contrasting addiction and reducing the nicotine harmful exposure among people.

References

1. Benowitz NL. Nicotine addiction. N Engl J Med. 2010;362(24):2295–303.
2. World Health Organization (WHO). WHO report on the global tobacco epidemic, 2017: monitoring tobacco use and prevention policies. Geneva; 2017. http://apps.who.int/iris/bitstream/10665/255874/1/9789241512824-eng.pdf?ua=1&ua=1
3. Benowitz NL, Hukkanen J, Jacob P. Nicotine chemistry, metabolism, kinetics and biomarkers. In: Henningfield JE, London ED, Pogun S, editors. Nicotine psychopharmacology. Berlin/Heidelberg: Springer Berlin Heidelberg; 2009. p. 29–60.
4. Benowitz NL, Burbank AD. Cardiovascular toxicity of nicotine: implications for electronic cigarette use. Trends Cardiovasc Med. 2016;26(6):515–23.
5. Jha P, Ramasundarahettige C, Landsman V, Rostron B, Thun M, Anderson RN, et al. 21st-century hazards of smoking and benefits of cessation in the United States. N Engl J Med. 2013;368(4):341–50.
6. American Psychiatric Association (APA). Diagnostic and statistical manual of mental disorders. 5th ed. Arlington: American Psychiatric Publishing; 2013.
7. Dani JA. Neuronal nicotinic acetylcholine receptor structure and function and response to nicotine. Int Rev Neurobiol. 2015;124:3–19.
8. Südhof TC. Calcium control of neurotransmitter release. Cold Spring Harb Perspect Biol. 2012;4(1):a011353-a.
9. Jackson KJ, Muldoon PP, De Biasi M, Damaj MI. New mechanisms and perspectives in nicotine withdrawal. Neuropharmacology. 2015;96(0 0):223–34.
10. Picciotto MR, Lewis AS, van Schalkwyk GI, Mineur YS. Mood and anxiety regulation by nicotinic acetylcholine receptors: a potential pathway to modulate aggression and related behavioral states. Neuropharmacology. 2015;96(Pt B):235–43.
11. La Torre G, Ferketich A, Grassi MC. Tobacco smoking: the evidence from prevention and cessation. Biomed Res Int. 2014;2014:894208.
12. Culbertson CS, Bramen J, Cohen MS, et al. Effect of bupropion treatment on brain activation induced by cigarette-related cues in smokers. Arch Gen Psychiatry. 2011;68(5):505–15.
13. McGrath JJ, Racicot S, Okoli CTC, Hammond SK, O'Loughlin J. Airborne nicotine, secondhand smoke, and precursors to adolescent smoking. Pediatrics. 2018;141(Suppl 1):S63–74.
14. Lessov-Schlaggar CN, Wahlgren DR, Liles S, Ji M, Hughes SC, Winickoff JP, et al. Sensitivity to secondhand smoke exposure predicts future smoking susceptibility. Pediatrics. 2011;128(2):254–62.
15. Centre for Disease Control and Prevention (CDC). Tobacco use prevention through schools. 2015. https://www.cdc.gov/healthyschools/tobacco/index.htm. Accessed July 2018.
16. Wake Forest University Baptist Medical Center. Rates of secondhand smoke exposure high among college

students. 2009. https://www.sciencedaily.com/releases/2009/07/090721091833.htm. Accessed July 2018.
17. Grassi MC, Baraldo M, Chiamulera C, Culasso F, Raupach T. Knowledge about health effects of cigarette smoking and quitting among Italian university students: the importance of teaching nicotine dependence and treatment in the medical curriculum. Biomed Res Int. 2014;2014:321657.
18. Grassi MC, Chiamulera C, Baraldo M, Culasso F, Ferketich AK, Raupach T, et al. Cigarette smoking knowledge and perceptions among students in four Italian medical schools. Nicotine Tob Res. 2012; 14(9):1065–72.
19. Perez-Rubio G, Lopez-Flores LA, Ramirez-Venegas A, Noe-Diaz V, Garcia-Gomez L, Ambrocio-Ortiz E, et al. Genetic polymorphisms in CYP2A6 are associated with a risk of cigarette smoking and predispose to smoking at younger ages. Gene. 2017;628:205–10.
20. Halldén S, Sjögren M, Hedblad B, Engström G, Hamrefors V, Manjer J, et al. Gene variance in the nicotinic receptor cluster (CHRNA5-CHRNA3-CHRNB4) predicts death from cardiopulmonary disease and cancer in smokers. J Intern Med. 2016; 279(4):388–98.
21. Park SL, Murphy SE, Wilkens LR, Stram DO, Hecht SS, Le Marchand L. Association of CYP2A6 activity with lung cancer incidence in smokers: the multiethnic cohort study. PLoS One. 2017;12(5): e0178435.
22. Bahl V, Shim HJ, Jacob P 3rd, Dias K, Schick SF, Talbot P. Thirdhand smoke: chemical dynamics, cytotoxicity, and genotoxicity in outdoor and indoor environments. Toxicol In Vitro. 2016;32:220–31.
23. Thomas PD, Mi H, Swan GE, Lerman C, Benowitz N, Tyndale RF, et al. A systems biology network model for genetic association studies of nicotine addiction and treatment. Pharmacogenet Genomics. 2009;19(7): 538–51.
24. Iskandar AR, Titz B, Sewer A, Leroy P, Schneider T, Zanetti F, et al. Systems toxicology meta-analysis of in vitro assessment studies: biological impact of a candidate modified-risk tobacco product aerosol compared with cigarette smoke on human organotypic cultures of the aerodigestive tract. Toxicol Res. 2017; 6(5):631–53.
25. Cahill K, Lindson-Hawley N, Thomas KH, Fanshawe TR, Lancaster T. Nicotine receptor partial agonists for smoking cessation. Cochrane Database Syst Rev. 2016;(5):Cd006103.
26. Schmeltz I, Hoffmann D. Nitrogen-containing compounds in tobacco and tobacco smoke. Chem Rev. 1977;77(3):295–311.
27. Svensson CK. Clinical pharmacokinetics of nicotine. Clin Pharmacokinet. 1987;12(1):30–40.
28. Gupta S, Gandhi A, Manikonda R. Accidental nicotine liquid ingestion: emerging paediatric problem. Arch Dis Child. 2014;99(12):1149.
29. Centre for Disease Control and Prevention (CDC). New CDC study finds dramatic increase in e-cigarette-related calls to poison centers. 2014. https://www.cdc.gov/media/releases/2014/p0403-e-cigarette-poison.html. Accessed July 2018.
30. Feyerabend C, Ings RM, Russel MA. Nicotine pharmacokinetics and its application to intake from smoking. Br J Clin Pharmacol. 1985;19(2):239–47.
31. Nakajima M, Yokoi T. Interindividual variability in nicotine metabolism: C-oxidation and glucuronidation. Drug Metab Pharmacokinet. 2005;20(4):227–35.
32. Kaivosaari S, Toivonen P, Hesse LM, Koskinen M, Court MH, Finel M. Nicotine glucuronidation and the human UDP-glucuronosyltransferase UGT2B10. Mol Pharmacol. 2007;72(3):761–8.
33. Tanner J-A, Tyndale R. Variation in CYP2A6 activity and personalized medicine. J Pers Med. 2017;7(4):18.
34. PharmGKB. Very important pharmacogene: CYP2A6. https://www.pharmgkb.org/vip/PA166169430. Accessed July 2018.
35. Dempsey D, Tutka P, Jacob P 3rd, Allen F, Schoedel K, Tyndale RF, et al. Nicotine metabolite ratio as an index of cytochrome P450 2A6 metabolic activity. Clin Pharmacol Ther. 2004;76(1):64–72.
36. Schuit E, Panagiotou OA, Munafo MR, Bennett DA, Bergen AW, David SP. Pharmacotherapy for smoking cessation: effects by subgroup defined by genetically informed biomarkers. Cochrane Database Syst Rev. 2017;9:Cd011823.
37. Lessov-Schlaggar CN, Benowitz NL, Jacob P, Swan GE. Genetic influences on individual differences in nicotine glucuronidation. Twin Res Hum Genet. 2009;12(5):507–13.
38. Zhu AZ, Zhou Q, Cox LS, Ahluwalia JS, Benowitz NL, Tyndale RF. Variation in trans-3′-hydroxycotinine glucuronidation does not alter the nicotine metabolite ratio or nicotine intake. PLoS One. 2013;8(8):e70938.
39. Bloom AJ, von Weymarn LB, Martinez M, Bierut LJ, Goate A, Murphy SE. The contribution of common UGT2B10 and CYP2A6 alleles to variation in nicotine glucuronidation among European Americans. Pharmacogenet Genomics. 2013;23(12):706–16.
40. Taghavi T, St Helen G, Benowitz NL, Tyndale RF. Effect of UGT2B10, UGT2B17, FMO3, and OCT2 genetic variation on nicotine and cotinine pharmacokinetics and smoking in African Americans. Pharmacogenet Genomics. 2017;27(4):143–54.
41. Benowitz NL, Lessov-Schlaggar CN, Swan GE. Genetic influences in the variation in renal clearance of nicotine and cotinine. Clin Pharmacol Ther. 2008; 84(2):243–7.
42. Bergen AW, Javitz HS, Krasnow R, Michel M, Nishita D, Conti DV, et al. Organic cation transporter variation and response to smoking cessation therapies. Nicotine Tob Res. 2014;16(12):1638–46.
43. Haass M, Kubler W. Nicotine and sympathetic neurotransmission. Cardiovasc Drugs Ther. 1997;10(6):657–65.
44. Robertson D, Tseng CJ, Appalsamy M. Smoking and mechanisms of cardiovascular control. Am Heart J. 1988;115(1 Pt 2):258–63.

45. Grassi G, Seravalle G, Calhoun DA, Bolla GB, Giannattasio C, Marabini M, et al. Mechanisms responsible for sympathetic activation by cigarette smoking in humans. Circulation. 1994;90(1):248–53.
46. Wonnacott S, Barik J, Dickinson J, Jones IW. Nicotinic receptors modulate transmitter cross talk in the CNS: nicotinic modulation of transmitters. J Mol Neurosci. 2006;30(1–2):137–40.
47. Marchi M, Grilli M. Presynaptic nicotinic receptors modulating neurotransmitter release in the central nervous system: functional interactions with other coexisting receptors. Prog Neurobiol. 2010;92(2): 105–11.
48. Aberger K, Chitravanshi VC, Sapru HN. Cardiovascular responses to microinjections of nicotine into the caudal ventrolateral medulla of the rat. Brain Res. 2001;892(1):138–46.
49. Li YF, LaCroix C, Freeling J. Specific subtypes of nicotinic cholinergic receptors involved in sympathetic and parasympathetic cardiovascular responses. Neurosci Lett. 2009;462(1):20–3.
50. Skok VI. Nicotinic acetylcholine receptors in autonomic ganglia. Auton Neurosci. 2002;97(1):1–11.
51. Ghali MGZ. The brainstem network controlling blood pressure: an important role for pressor sites in the caudal medulla and cervical spinal cord. J Hypertens. 2017;35(10):1938–47.
52. Khan IM, Taylor P, Yaksh TL. Cardiovascular and behavioral responses to nicotinic agents administered intrathecally. J Pharmacol Exp Ther. 1994;270(1): 150–8.
53. Khan IM, Taylor P, Yaksh TL. Stimulatory pathways and sites of action of intrathecally administered nicotinic agents. J Pharmacol Exp Ther. 1994;271(3): 1550–7.
54. Tseng CJ, Appalsamy M, Robertson D, Mosqueda-Garcia R. Effects of nicotine on brain stem mechanisms of cardiovascular control. J Pharmacol Exp Ther. 1993;265(3):1511–8.
55. Jutkiewicz EM, Rice KC, Carroll FI, Woods JH. Patterns of nicotinic receptor antagonism II: cardiovascular effects in rats. Drug Alcohol Depend. 2013; 131(3):284–97.
56. Middlekauff HR, Park J, Moheimani RS. Adverse effects of cigarette and noncigarette smoke exposure on the autonomic nervous system: mechanisms and implications for cardiovascular risk. J Am Coll Cardiol. 2014;64(16):1740–50.
57. Karakaya O, Barutcu I, Kaya D, Esen AM, Saglam M, Melek M, et al. Acute effect of cigarette smoking on heart rate variability. Angiology. 2007;58(5):620–4.
58. Adamopoulos D, van de Borne P, Argacha JF. New insights into the sympathetic, endothelial and coronary effects of nicotine. Clin Exp Pharmacol Physiol. 2008;35(4):458–63.
59. Moheimani RS, Bhetraratana M, Peters KM, Yang BK, Yin F, Gornbein J, et al. Sympathomimetic effects of acute e-cigarette use: role of nicotine and non-nicotine constituents. J Am Heart Assoc. 2017;6(9):e006579.
60. Hanna ST. Nicotine effect on cardiovascular system and ion channels. J Cardiovasc Pharmacol. 2006; 47(3):348–58.
61. Bebarova M, Matejovic P, Svecova O, Kula R, Simurdova M, Simurda J. Nicotine at clinically relevant concentrations affects atrial inward rectifier potassium current sensitive to acetylcholine. Naunyn Schmiedebergs Arch Pharmacol. 2017;390(5):471–81.
62. Bebarova M, Horakova Z, Kula R. Addictive drugs, arrhythmias, and cardiac inward rectifiers. EP Europace. 2017;19(3):346–55.
63. Wang Q, Guo Y, Wu C, Yin L, Li W, Shen H, et al. Smoking as a risk factor for the occurrence of atrial fibrillation in men versus women: a meta-analysis of prospective cohort studies. Heart Lung Circ. 2018; 27(1):58–65.
64. Imtiaz Ahmad M, Mosley CD, O'Neal WT, Judd SE, McClure LA, Howard VJ, et al. Smoking and risk of atrial fibrillation in the REasons for Geographic And Racial Differences in Stroke (REGARDS) study. J Cardiol. 2018;71(2):113–7.
65. Jensen K, Nizamutdinov D, Guerrier M, Afroze S, Dostal D, Glaser S. General mechanisms of nicotine-induced fibrogenesis. FASEB J. 2012;26(12):4778–87.
66. Vang A, Clements RT, Chichger H, Kue N, Allawzi A, O'Connell K, et al. Effect of alpha7 nicotinic acetylcholine receptor activation on cardiac fibroblasts: a mechanism underlying RV fibrosis associated with cigarette smoke exposure. Am J Physiol Lung Cell Mol Physiol. 2017;312(5):L748–59.
67. Goette A, Lendeckel U, Kuchenbecker A, Bukowska A, Peters B, Klein HU, et al. Cigarette smoking induces atrial fibrosis in humans via nicotine. Heart. 2007;93 (9):1056–63.
68. Tonnessen BH, Severson SR, Hurt RD, Miller VM. Modulation of nitric-oxide synthase by nicotine. J Pharmacol Exp Ther. 2000;295(2):601–6.
69. Toda N, Toda H. Nitric oxide-mediated blood flow regulation as affected by smoking and nicotine. Eur J Pharmacol. 2010;649(1–3):1–13.
70. Hom S, Chen L, Wang T, Ghebrehiwet B, Yin W, Rubenstein DA. Platelet activation, adhesion, inflammation, and aggregation potential are altered in the presence of electronic cigarette extracts of variable nicotine concentrations. Platelets. 2016;27(7): 694–702.
71. Messner B, Bernhard D. Smoking and cardiovascular disease: mechanisms of endothelial dysfunction and early atherogenesis. Arterioscler Thromb Vasc Biol. 2014;34(3):509–15.
72. Rodu B, Plurphanswat N. E-cigarette use among US adults: Population Assessment of Tobacco and Health (PATH) study. Nicotine Tob Res. 2018;20(8):940–8.
73. Bullen C, Howe C, Laugesen M, McRobbie H, Parag V, Williman J, et al. Electronic cigarettes for smoking cessation: a randomised controlled trial. Lancet. 2013;382(9905):1629–37.
74. St Helen G, Havel C, Dempsey DA, Jacob P 3rd, Benowitz NL. Nicotine delivery, retention and

pharmacokinetics from various electronic cigarettes. Addiction. 2016;111(3):535–44.
75. Marsot A, Simon N. Nicotine and cotinine levels with electronic cigarette: a review. Int J Toxicol. 2016; 35(2):179–85.
76. Franzen KF, Willig J, Cayo Talavera S, Meusel M. E-cigarettes and cigarettes worsen peripheral and central hemodynamics as well as arterial stiffness: a randomized, double-blinded pilot study. Vasc Med. 2018;23 (5):419–25.
77. Shao XM, Lopez-Valdes HE, Liang J, Feldman JL. Inhaled nicotine equivalent to cigarette smoking disrupts systemic and uterine hemodynamics and induces cardiac arrhythmia in pregnant rats. Sci Rep. 2017; 7(1):16974.
78. Prochaska JJ, Benowitz NL. Smoking cessation and the cardiovascular patient. Curr Opin Cardiol. 2015; 30(5):506–11.
79. Jeong SH, Newcombe D, Sheridan J, Tingle M. Pharmacokinetics of cytisine, an alpha4 beta2 nicotinic receptor partial agonist, in healthy smokers following a single dose. Drug Test Anal. 2015;7(6):475–82.
80. Rollema H, Shrikhande A, Ward KM, Tingley FD, Coe JW, O'Neill BT, et al. Pre-clinical properties of the α4β2 nicotinic acetylcholine receptor partial agonists varenicline, cytisine and dianicline translate to clinical efficacy for nicotine dependence. Br J Pharmacol. 2010;160(2):334–45.
81. Vinnikov D, Tutka P, Brimkulov N, Kolodziejczyk P, Courtney R. Cytisine is an effective smoking cessation medication: more evidence now than ever before. Eur Respir J. 2017;50(Suppl 61).
82. Leaviss J, Sullivan W, Ren S, Everson-Hock E, Stevenson M, Stevens JW, et al. What is the clinical effectiveness and cost-effectiveness of cytisine compared with varenicline for smoking cessation? A systematic review and economic evaluation. Health Technol Assess. 2014;18(33):1–120.
83. US Food and Drug Administration (FDA). Varenicline (Chantix) tablets – drug approval package. 2006. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/021928_s000_ChantixTOC.cfm. Accessed July 2018.
84. European Medicine Agency (EMA). European public assessment report (EPAR) for Champix (varenicline). 2006. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000699/human_med_000696.jsp&mid=WC0b01ac058001d124. Accessed July 2018.
85. Faessel HM, Obach RS, Rollema H, Ravva P, Williams KE, Burstein AH. A review of the clinical pharmacokinetics and pharmacodynamics of varenicline for smoking cessation. Clin Pharmacokinet. 2010;49(12):799–816.
86. Arias HR, Feuerbach D, Targowska-Duda K, Kaczor AA, Poso A, Jozwiak K. Pharmacological and molecular studies on the interaction of varenicline with different nicotinic acetylcholine receptor subtypes. Potential mechanism underlying partial agonism at human α4β2 and α3β4 subtypes. BBA Biomembranes. 2015;1848(2):731–41.
87. US Food and Drug Administration (FDA). FDA Drug Safety Communication: Chantix (varenicline) may increase the risk of certain cardiovascular adverse events in patients with cardiovascular disease. 2011. https://www.fda.gov/Drugs/DrugSafety/ucm259161.htm. Accessed July 2018.
88. US Food and Drug Administration (FDA). FDA Drug Safety Communication: safety review update of Chantix (varenicline) and risk of cardiovascular adverse events. 2012. https://www.fda.gov/Drugs/DrugSafety/ucm330367.htm. Accessed July 2018.

The Impact of Morphine or Methadone Administration on the Heart and Cardiovascular System

51

Flavio Moroni

Contents

Abstract

Opium and morphine have been used for centuries to reduce pain in different clinical conditions including acute heart failure with pulmonary edema or hearth ischemia with infarct. It was soon observed that repeated morphine administration gradually leads to a decrease of the analgesic potency (tolerance) and that, after repeated doses, patients may have difficulties in abandoning morphine or opium use (dependence and withdrawal). Other established morphine side effects such as vomiting, hypotension, respiratory depression, and somnolence suggest careful attention in drug use.

In the last few years, most of the literature outline that morphine should not be used in cases of pulmonary edema because of the risk of increased mortality. In patients with infarct, however, morphine is still considered the analgesic of choice, especially when the ischemic pain is not sensitive to nitrates. It has also been suggested that morphine may activate the ischemic tolerance process, thus reducing the ischemic reperfusion damage.

Another opioid with significant analgesic action is methadone. In 1965, it was clearly demonstrated that methadone was useful in reducing the problems associated with morphine or heroin misuse. A significant number of patients are now chronically treated with the drug in the methadone treatment programs. In the last 20 years, it has been observed that methadone may cause an increase of the QT interval of the ECG and possibly an increased risk of sudden death. Since methadone is a mixture of two stereoisomers (R and S) and since R-methadone has high affinity for opioid receptors while S-methadone is possibly the main responsible for QT elongation, it has been proposed that the racemic form of the drug should be abandoned and

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*,
https://doi.org/10.1007/978-3-030-28008-6_53

substituted with the stereoselective active R-methadone form.

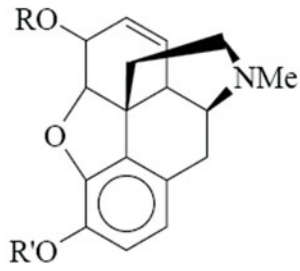
Keywords

Encephalin · Endorphin · Dynorphin · Infarct · Ischemic tolerance · Long QT · Opioid receptors · Potassium channels · Pulmonary edema · Sudden death

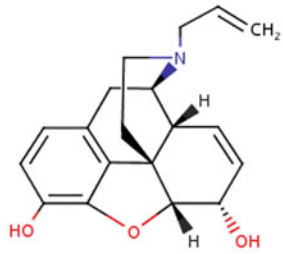
Introduction

Morphine is the main active ingredient found in poppy, a flowering plant (papaver somniferum) of the Papaveroideae subfamily (see Fig. 1). A number of archeological data suggest that the Sumerians started the use of "poppy" for the treatment of painful medical disorders (including heart pain) approximately 3000 years B.C. and that from Sumerian (the actual Iraq) this use spread to most of the other regions of the Old Word. Ancient Egyptian doctors would have their patients eat poppy seeds not only to relieve pain but also for the treatment of diarrhea. The Ebers Papyrus (ca. 1500 B.C.) includes the description of a procedure involving opium (from "opos" the Greek word for juice; opium is indeed the exsiccated juice obtained from poppy flowers) to prevent "excessive crying of children" and to reduce intense pain associated with traumatic or other tissue injuries. Theophrastus, a named Greek physician, described opium use for the relief of chest pain at the beginning of the third century BC. Opium extracts were appreciated not only for medical use but also for religious procedures, possibly because adequate amount of these preparations was able to quietly lead to a "peaceful" death [1, 2]. It was soon observed that repeated administrations of opium cause tolerance (decrease of the expected pharmacological effects), but details of opium abuse and dependence were firstly reported only in the sixteen century by Acosta, a Portuguese physician. In the nineteenth century, Sertürner, a German pharmacist, isolated the main active ingredient present in opium and named it morphine after Morpheus, the god of dreams. Pure morphine, a weak base, became then available as soluble salts (sulfate or hydrochloride) in large quantity, and its medical use rapidly exploded. Codeine, another active ingredient present in opium, was isolated a few years later (see Fig. 1). Unfortunately, repeated morphine administrations caused tolerance, and when the administrations were discontinued, a syndrome characterized by anxiety, pain, sweeting, agitation, and diarrhea emerged (withdrawal syndrome). Both tolerance and withdrawal syndrome were very similar to those obtained with repeated opium use. Excessive morphine doses induced respiratory and cardiovascular depression very similar to those obtained with large opium amount. With the aim of obtaining safer, more efficacious, nonaddicting analgesic agents, numerous scientists attempted to modify morphine structure. In 1898, heroin was synthesized for this purpose and was commercialized by stating that the new compound was more potent than morphine and free from abuse liability (sic!). This was the first of several such claims for novel opioids. Unfortunately, the goal has not been reached. In 1939, meperidine, the first opioid with a structure completely different from that of morphine, was commercialized in Europe. In the same year, methadone, another analgesic agent structurally unrelated to morphine, was synthesized (Fig. 2). In 1942, nalorphine (*N*-allylnormorphine), the first opiate antagonist, was synthesized and carefully characterized. This compound had significant analgesic actions but could also reverse the respiratory depression produced by morphine, and, when administered to morphine-dependent animals chronically, it caused sign and symptoms typical of the withdrawal syndrome (as could be expected by hypothesizing that the molecule had antagonist properties). It is now accepted that nalorphine is an agonist/antagonist of morphine receptors. More selective antagonists were synthesized in the second half of the last century (naloxone and naltrexone) after simple structure-activity studies. Figure 1 shows that both nalorphine and naloxone have an "allyl" group (instead of a methyl as in morphine) linked to the nitrogen.

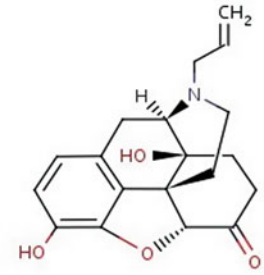
Papaver Somniferum
Poppy



R = R' = H MORPHINE
R = H; R' = Me CODEINE
R = R' = COMe HEROIN

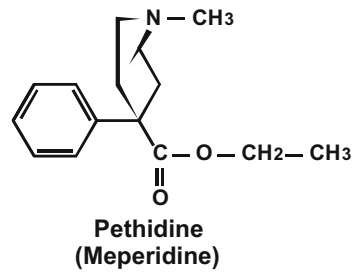


NALORPHINE

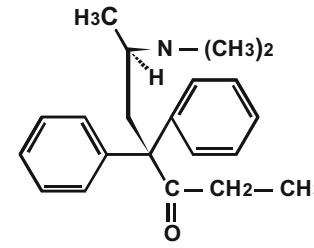


NALOXONE

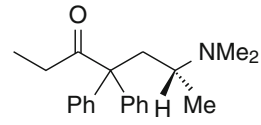
Fig. 1 In the upper left a picture of the poppy flower (*Papaver somniferum*). In the upper right the molecular structure of morphine, codeine, and heroin (potent receptor agonists). In the lower portion of the figure, the first opioid agonist identified, Nalorphine, obtained by substituting the methyl linked to the N with a slightly bigger group (allyl). The presence of the allyl group linked to the nitrogen is present also in Naloxone



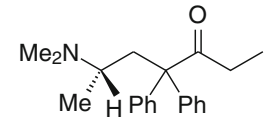
Pethidine
(Meperidine)



Methadone



(*R*)-Methadone
(twice as potent as morphine)



(*S*)-Methadone
(inactive)

Fig. 2 Molecular structure of pethidine, the first opioid agent with a molecular structure completely unrelated to that of morphine. The molecular structure of the two methadone stereoisomers is also reported

It is probably worth to outline that all the molecules contained in opium may be defined opiates; all the other compounds with actions similar to those of opium are usually named opioids. By the mid-1960s, it was becoming clear that the difference in the actions of the numerous opioids then available and used could best be explained assuming the existence of multiple opiate receptors. A conclusive evidence for this concept was provided by Martin [3]. The results of these and other experiments led to the proposal of the existence of at least three receptor types named after the drug used for their characterization: μ (from morphine, MOR), κ (from ketocyclazocine, KOR), and δ (from D-Ala-D-Leu-encephalin, but also because it was abundant in the rat deferens, DOR).

Most (but not all) of the effects of opioid administration in the cardiovascular system are mediated by activation of these receptors. They are Gi/o protein-coupled receptors able to inhibit adenylate cyclase thus reducing cyclic AMP (cAMP) formation, the activation of inwardly rectifying potassium channels and the opening of voltage-dependent calcium channels [4, 5]. The demonstration of the natural existence of different receptors for opioids which were expressed in most mammalian tissues suggested experienced scientists to search for endogenous compounds able to activate them.

In 1975, Kosterlitz and Waterfield observed that brain extracts contained two pentapeptides (Met-encephalin and Leu-encephalin) able to inhibit acetylcholine release from nerves innervating guinea pig ileum [6, 7]. It soon became obvious that the Met-encephalin sequence was also present on the N terminus of another peptide, β-endorphin, a fragment of β-lipotropin that had been isolated several years earlier from pituitary extracts [8, 9]. Like the encephalins, β-endorphin proved to have a high affinity for brain opioid receptors [9–11]. Other peptides, such as dynorphin, a κ-opioid receptor agonist, were subsequently isolated and characterized [12].

Endorphin, encephalin, and dynorphin represent the major endogenous opioid peptides involved in physiology and pathology and are supposed to activate with some selectivity MOR, DOR, and KOR, respectively [13]. The opioid system has multiple actions and may modulate multiple system function by acting both in the brain and periphery, including the myenteric plexus. Focusing on the regulation of the cardiovascular system, we should consider that ORs are localized in different brain areas such as the respiratory and cardiovascular centers of the hypothalamus and brainstem [14, 15] and peripherally in the adrenal medulla and other ganglia of both the sympathetic and parasympathetic branches of the autonomic nervous system [16, 17]. Opioid receptors are also expressed in cardiomyocytes, and the microvasculature [18] and their activation may modulate systemic vascular tone, alter cardiac excitation-contraction coupling, and be involved in the genesis of new cardiomyocytes (Fig. 3) [19, 20].

Exogenous Opioid Administration in Heart Diseases

Therapeutic doses of morphine or other opioids administered to a supine patient have no major effects on blood pressure or cardiac rate and rhythm. However, it is well demonstrated that these agents may cause peripheral vasodilatation, reduce vascular resistance, and attenuate baroreceptor-mediated reflexes [21, 22]. Therefore, when the patient assumes a standing position, orthostatic hypotension and fainting may occur. The arteriolar and venous dilatation induced by morphine may be ascribed to central and peripheral activation of the opioid receptors localized in the autonomic nervous system with reduction of transmitter release. It has also been shown that morphine may increase histamine release thus causing hypotension, flushing, nausea, and vomitus [23]. In spite of these side effects, morphine has been largely used in the past 50 years to reduce pain in patients suffering of at least two common acute clinical situations involving heart function:

1. Pulmonary edema
2. Myocardial infarction

While recent evidence cast doubts on the benefits associated with the administration of

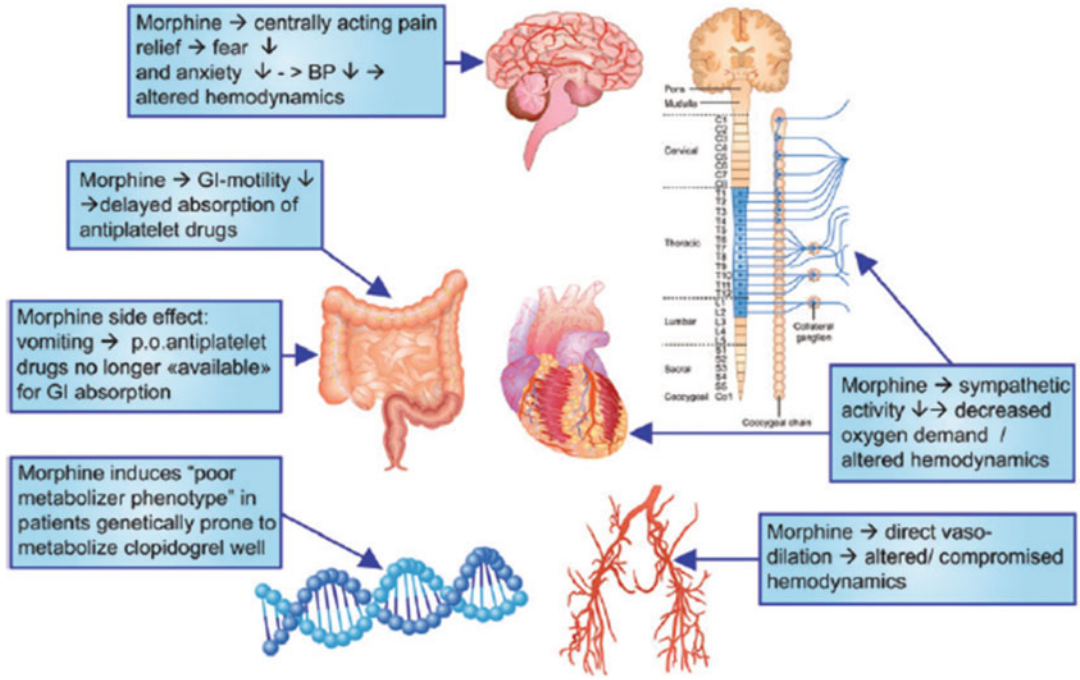


Fig. 3 The multiple sites of morphine actions and the possibility of causing side effects when morphine is administered after an infarct together with the antiplatelet agent clopidogrel. (From Ref. [20])

morphine and other opioids in cases of pulmonary edema, evidence-based medicine confirmed the importance of defeating pain in cases of heart ischemia. Concerning acute hearth failure and pulmonary edema, it is interesting to note that the 13th Edition (1994) of the Harrison's Principle of Internal Medicine (p. 1008) stated that "the first measure of the treatment of pulmonary edema is the i.v. administration of 2–5 mg of morphine sulfate because the drug reduces anxiety, reduces adrenergic vasoconstrictor stimuli to the arteriolar and venous beds and thereby helps to reduce a vicious cycle leading to pulmonary dysfunction." A few years later, the guidelines of the American College of Cardiology Foundation/ American Heart Association do not mention morphine or other opioids in the treatment of pulmonary edema, and a recent review states that the positive effects of morphine in pulmonary edema are not sufficiently documented, while the risks that morphine administration may increase the mortality is real, and therefore the drug should **not** be used in pulmonary edema patients [24].

Contrary to pulmonary edema, a large body of scientific literature support the importance of using morphine or other opioids to reduce pain in angina pectoris and acute myocardial infarction patients [1, 25]. Relief of pain is usually considered of paramount importance not only for humane reasons but also because pain may lead to sympathetic activation that causes vasoconstriction and increases heart workload helping to further deteriorate myocardial ischemic tissue. Thus, despite the lack of rigorous studies designed to assess the effect of morphine administration in patients with acute myocardial ischemia, clinical practice guidelines for managing patients with ST-segment elevation myocardial infarction (STEMI) strongly recommend morphine administration as a routine procedure to reduce pain [26, 27].

These concepts, however, were challenged in 2005, when an observational study performed in a large cohort of patients with non-ST elevation (NSTEMI) myocardial infarction reported that morphine-treated patients had a worse clinical

outcome than controls (patients without morphine administration) [28]. It was also reported, using MRI, that morphine was associated with suboptimal reperfusion after myocardial infarction and primary coronary intervention [29]. A potential explanation of morphine's negative impact on clinical outcome in patients with infarct and coronary intervention may be ascribed to the dose of morphine administered and the subsequent respiratory depression with associated vomitus and possibly vasodilatation. It is also possible that morphine interacts with other drugs required for optimal outcome of these patients. For instance, morphine inhibits gastric emptying, thus reducing the rate of absorption and resulting in decreased peak plasma levels of orally administered antiplatelet drugs. It has been indeed documented that morphine delays clopidogrel (a pro-drug able to inhibit platelet aggregation) absorption and decreases plasma levels of clopidogrel active metabolite [30]. Suboptimal platelet inhibition early after primary stent implantation is associated with thrombotic complications, including stent thrombosis. It has been suggested that intravenous antiplatelet agents such as glycoprotein IIb/IIIa receptor inhibitors should be considered when i.v. morphine is administered to patients with acute infarct and coronary stenting [31]. Even if morphine remains the mainstay analgesic for severe chest pain in acute myocardial infarction, some clinicians now suggest to use morphine only when patient's pain is resistant to nitrates and beta-blockers [32].

An interesting process whereby morphine may reduce hearth damage in patients with an infarct seems to be its ability of mimicking the widely studied phenomenon of "ischemic preconditioning" (or ischemic tolerance), a process attracting the attention of basic scientists involved in studies of both cardio- and neuroprotection.

Opioids and *Ischemic Pre- or Post-conditioning*

Although acute myocardial infarction is a leading cause of morbidity and mortality, the possibility to significantly limit myocardial damage (cardioprotection) during the ischemic and the reperfusion phases of the syndrome remains a largely unrealized therapeutic goal. In order to reduce this damage and to save at least a part of the contractile function after an ischemic event, it is necessary to restore, as soon as possible, the coronary flow (reperfusion). However, in the reperfusion phase, an additional damage of cardiac tissue with a mechanism known as reperfusion injury has been observed in numerous experimental setting. In the clinical settings, the reperfusion damage may limit the potential benefits of coronary flow restoration obtained with coronary bypass surgery, with percutaneous coronary intervention (angioplasty) or with systemic recombinant tissue plasminogen activator (rTPA) administration. It is now well demonstrated that sequences of brief ischemia periods applied before (preconditioning) or after (post-conditioning) the occlusion of a coronary vessel may trigger protective tissue mechanisms that significantly reduce the reperfusion injury. Myocardial preconditioning events are a series of local and systemic processes triggered by transient non-injurious ischemia periods and able to drastically reduce tissue damage caused by I–R injury. Ischemic post-conditioning, on the other hand, describes a similarly potent protection process arising from transient ischemic episodes during the initial minutes of reperfusion following a severe insult. It is now clear that both forms of protection can be induced directly or remotely (i.e., via transient I–R in the heart or an extra-cardiac organ/tissue) and involve common mediators and pro-survival signaling such as protein kinase C (PKC), extracellular signal-regulated kinase (ERK1/2) and Akt/phosphatidylinositol 3-kinase (PI3K), the so-called reperfusion injury salvage kinase (RISK), key mitochondrial targets including the mitochondrial permeability transition pore (mPTP), ATP sensitive potassium channels, and changes in formation or scavenging of reactive oxygen species (ROS). The overall process which is not completely clarified may be defined: **ischemic tolerance**. Since a brief intermittent ischemia applied either before or immediately after the occlusion of a vessel in a remote organ or tissue induces a protective phenotype in a target organ

(e.g., heart and brain) mechanisms implicated have been studied in deep. In fact, while the clinical utility of *preconditioning* is primarily limited to a planned surgical ischemia, *post-conditioning* is highly relevant for the treatment of acute myocardial ischemia, as this efficacious response can be initiated before reperfusion attempts. Unfortunately, while the *pre- and post-conditioning* phenomena have proven effective in experimental models in various species including humans, clinical trial outcomes remain inconclusive, with some studies reporting no change or worsened outcomes [33]. It is important to outline that ischemic tolerance may also be induced by administering opioids and that opioid receptor antagonists (especially those acting on δ or κ receptors) prevent the development of ischemic tolerance induced by pre- or post-conditioning [34]. These observations suggest that intrinsic opioid receptor activity is indispensable in triggering and maintaining the protected state. It has also been suggested that opioid receptor activation may beneficially impact on all major determinants of the I–R damage mechanisms by reducing cell death, arrhythmogenesis, contractile dysfunction, and inflammation [25]. Interestingly, there is evidence that systemic administration of opioid receptor agonists can augment the cardioprotective effects of ischemic conditioning interventions [35]. While there have been relatively few clinical trials of cardioprotection using opioid receptor agonists, the observation of a summative effects of ischemic conditioning stimuli and opioid receptor agonists supports the potential to obtain a robust protection by combining opioid receptor agonists with intrinsic activation of the process using short ischemic stimuli in a remote organ [25].

Methadone and Cardiac Adverse Effects

Methadone was firstly synthetized during World War II in the Hoechst laboratories in Frankfurt, Germany. The research project leading to its discovery was heavily supported by the German government because during the war, it was difficult to import sufficient amount of opium needed for the production of morphine. Methadone has a molecular structure similar to that of pethidine (Dolantin; see Fig. 2), another effective opioid analgesic not related to morphine, prepared in the same laboratory through a relatively simple synthetic procedure not requiring imported chemicals. Methadone's first code name was "amidon," and soon after its synthesis and a brief period of animal testing, it was given to Wehrmacht military doctors for human use. However, probably because of unpleasant side effects due to inadequate dose administration during the first period of human testing, the drug was never used during World War II. After the war, all the German patents with the accompanying experimental observations were requisitioned and brought to the USA, and in 1947 the Council on Pharmacy and Chemistry of the American Medical Association gave to former amidon the generic name of methadone and authorized its medical use. In the same year, Eli Lilly started the commercialization of the compound under the trade name of Dolophine, derived from the Latin dolor (pain) and finis (end). Other pharmaceutical companies also acquired (for one dollar) the rights for methadone production and use for painful conditions. Twenty years later, the use of methadone therapy was proposed for the treatment of heroin addiction [36]. Dole, a psychiatry working in New York, strongly supported the diffusion of this therapeutic strategy because: " . . ..it (methadone), but not any of the other narcotics we tested, had a normalizing rather than narcotic effects on long term administration at a constant dose. . .. A patient who is stabilised on an adequate constant daily dose of methadone is alert, healthy and respond normally to stimuli" [37].

From a pharmacological point of view, methadone can be defined a synthetic μ-opioid receptor agonist. Its pharmacokinetic properties include an elevated oral bioavailability and an average elimination rate that exceed 24 h so that oral once-a-day administration prevents opioid abstinence signs and symptoms in most patients. A significant number of controlled clinical trials have indeed shown that continuous daily methadone use in heroin-addicted patients reduces illicit drug consumption, limits the diffusion of HIV and HCV infections, and reduces mortality rate and criminal activity.

However, it is now widely accepted that methadone maintenance treatments are associated with an increased risk of mortality caused by either acute methadone overdose or sudden unexplained death. It is now well demonstrated that methadone increases the QT interval of the electrocardiogram and possibly the occurrence of polymorphic ventricular tachycardia, or torsades de pointes (TdP) (Fig. 4). This adverse event of common drug use was firstly described in 1990, when Monahan et al. reported that terfenadine (Seldane), a widely used nonsedating antihistamine, was able of prolonging QT interval and causing life-threatening ventricular arrhythmias [38]. Similarly to terfenadine, methadone is able to increase the QT interval of the electrocardiogram and the risk of TdP [39, 40]. The mechanism of this increase has been ascribed to the effects of racemic methadone on myocytes, which represent the vast mass of cardiac tissue, and perform the mechanical

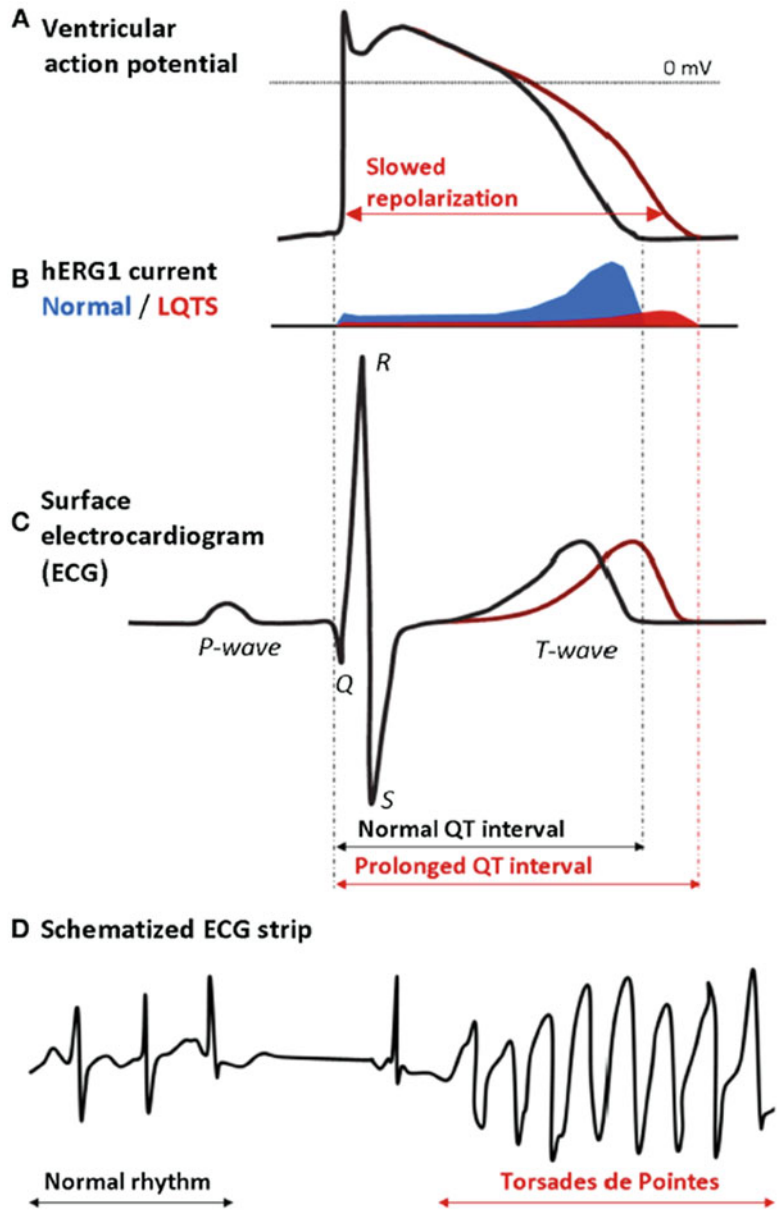


Fig. 4 Ventricular action potentials and related ECG signals: prolonged QT interval is a risk factor for torsades de pointes. (**a**) Normal and prolonged ventricular action potential due to (**b**) reduction of hERG1 currents in LQTS are reflected (**c**) on the ECG recording with lengthening of the QT interval. (**d**) Schematized ECG recording presenting the onset of torsades de pointes in a patient with long QT syndrome. (From Ref. [48])

work of the heart. During the cardiac cycle, an individual myocyte exhibits a nearly100 mV change in electrical voltage from negative to positive during systole "depolarization" and then positive to negative during diastole "repolarization." The time course of this voltage change describes a characteristic shape represented by the ventricular "action potential" (Fig. 4a). Collectively, the aggregate action potentials produce the characteristic tracings of the surface electrocardiogram, and the total duration of ventricular depolarization and repolarization is represented by the QT interval (Fig. 4c). Racemic methadone (10 μM) does modify the conductance of the delayed rectifier potassium channel [41]. This conductance is referred to as IKr, and the protein associated is the human ether-a-go-go (HERG)-related gene channel. Potassium flow through this channel is critical for returning the voltage of the myocyte to its diastolic potential during "repolarization." While other channels also participate in the repolarization process, the hERG-related channel is the most important for determining the action potential duration and hence the QT interval. Unfortunately, the structure of the channel is such that many drugs are capable of entering in and binding to its central pore, thus obstructing K^+ flow. This causes a prolongation of the action potentials and consequently of the QT interval [42, 43]. As previously mentioned, a prolonged repolarization revealed by measuring the QT interval in the electrocardiogram is the basis for a type of polymorphic ventricular tachycardia known as torsades de pointes (TdP, Fig. 4d) [43]. It is now recognized that many structurally unrelated drugs, designed to act on non-cardiac targets, unintentionally block the repolarizing current IKr and increase the QT intervals and the risk of TdP.

The incidence of TdP is fortunately quite rare and not readily observed during clinical trials or postmarketing surveillance. Therefore, in order to reduce the risk of this potentially fatal arrhythmia, it is now accepted to consider QT intervals acceptable surrogate endpoints in order to identify potentially toxic compounds and to reduce the size of clinical trials investigating drug cardiovascular toxicity. In methadone maintenance patients, the administration of relatively large methadone doses significantly increase QT intervals [44].

Methadone is a chiral drug and is commonly administered as a racemic mixture of (R)- and (S)-stereoisomers (see Fig. 2). The (R)-form accounts for most if not all the opioid effects. This has been shown both in vitro with competitive binding experiments (versus labeled *naloxone* in rat brain homogenates) and in vivo in human analgesia testing. On the contrary, whole-cell patch-clamp experiments using HEK293 cells expressing hERG1 showed that (S)-methadone blocks IhERG1 3.5-fold more potently than (R)-methadone (IC50s at 37 °C: 2 and 7 μM, respectively) [41, 45].

Methadone is extensively metabolized by cytochrome P450 isoenzymes; in particular, CYP3A4 and CYP2B6 are the major isoforms involved. CYP2B6 preferentially metabolizes (S)-methadone, and CYP2B6 slow metabolizers have high-plasma concentrations of (S)-methadone and higher frequencies of prolonged QT intervals than controls [41]. Since the proportion of CYP2B6 slow metabolizers in Caucasian and African populations is non-negligible (∼6%), carriers of such polymorphism are at a potentially higher risk for severe cardiac arrhythmias and sudden death while receiving racemic methadone treatment. Since the (S)-enantiomer is thought to be the cardiotoxic form and (R)-methadone is the enantiomer accounting for the desired effects, it has been suggested that the administration of the (R)-form could reduce cardiotoxicity without affecting the therapeutic value of the drug. Availability of (R)-methadone would greatly diminish the clinical concern of methadone administration to CYP2B6 slow metabolizer. A reduction of the overall methadone dose could also reduce the effects the drug may have in patients with long QT syndrome (LQTS), a latent genetic predisposition to have this type of potentially fatal drug side effect [46]. Patients treated with (R)-methadone have indeed a significant reduction of the QT interval values when compared with patients treated with therapeutically equivalent doses of the racemic mixture [47]. It seems therefore obvious that by substituting the racemic drug

with the active stereoisomer, the effects on myocyte repolarization and possibly the incidence of sudden death associated with methadone use will be reduced [48].

References

1. Kerr F, Donald KW. Editorial: analgesia in myocardial infarction. Br Heart J. 1974;36:117–21.
2. Brownstein MJ. A brief history of opiates, opioid peptides, and opioid receptors. Proc Natl Acad Sci U S A. 1993;90:5391–3.
3. Martin WR, Eades CG, Thompson JA, Huppler RE, Gilbert PE. The effects of morphine- and nalorphine-like drugs in the nondependent and morphine-dependent chronic spinal dog. J Pharmacol Exp Ther. 1976;197:517–32.
4. North RA, Tokimasa T. Persistent calcium-sensitive potassium current and the resting properties of guinea-pig myenteric neurons. J Physiol. 1987;386:333–53.
5. North RA, Williams JT, Surprenant A, Christie MJ. Mu and delta receptors belong to a family of receptors that are coupled to potassium channels. Proc Natl Acad Sci U S A. 1987;84:5487–91.
6. Hughes J, Smith TW, Kosterlitz HW, Fothergill LA, Morgan BA, Morris HR. Identification of two related pentapeptides from the brain with potent opiate agonist activity. Nature. 1975;258:577–80.
7. Kosterlitz HW, Taylor DW. The effect of morphine on vagal inhibition of the heart. Br J Pharmacol Chemother. 1959;14:209–14.
8. Bradbury AF, Smyth DG, Snell CR. Biosynthetic origin and receptor conformation of methionine enkephalin. Nature. 1976;260:165–6.
9. Moroni F, Cheney DL, Costa E. beta endorphin inhibits ACh turnover in nuclei of rat brain. Nature. 1977;267:267–8.
10. van Ree JM, de Wied D, Bradbury AF, Hulme EC, Smyth DC, Snell CR. Induction of tolerance to the analgesic action of lipotropin in C-fragment. Nature. 1976;264:792–4.
11. Moroni F, Peralta E, Cheney DL, Costa E. On the regulation of gamma-aminobutyric acid neurons in caudatus, pallidus and nigra: effects of opioids and dopamine agonists. J Pharmacol Exp Ther. 1979;208:190–4.
12. Goldstein A, Tachibana S, Lowney LI, Hunkapiller M, Hood L. Dynorphin-(1-13), an extraordinarily potent opioid peptide. Proc Natl Acad Sci U S A. 1979;76:6666–70.
13. Lord JA, Waterfield AA, Hughes J, Kosterlitz HW. Endogenous opioid peptides: multiple agonists and receptors. Nature. 1977;267:495–9.
14. Goodman RR, Snyder SH, Kuhar MJ, Young WS III. Differentiation of delta and mu opiate receptor localizations by light microscopic autoradiography. Proc Natl Acad Sci U S A. 1980;77:6239–43.
15. May CN, Dashwood MR, Whitehead CJ, Mathias CJ. Differential cardiovascular and respiratory responses to central administration of selective opioid agonists in conscious rabbits: correlation with receptor distribution. Br J Pharmacol. 1989;98:903–13.
16. Wittert G, Hope P, Pyle D. Tissue distribution of opioid receptor gene expression in the rat. Biochem Biophys Res Commun. 1996;218:877–81.
17. Di Giulio AM, Yang HY, Lutold B, Fratta W, Hong J, Costa E. Characterization of enkephalin-like material extracted from sympathetic ganglia. Neuropharmacology. 1978;17:989–92.
18. Ventura C, Spurgeon H, Lakatta EG, Guarnieri C, Capogrossi MC. Kappa and delta opioid receptor stimulation affects cardiac myocyte function and Ca^{2+} release from an intracellular pool in myocytes and neurons. Circ Res. 1992;70:66–81.
19. Holaday JW. Cardiovascular effects of endogenous opiate systems. Annu Rev Pharmacol Toxicol. 1983;23:541–94.
20. Atar D, Agewall S. Morphine in myocardial infarction: balancing on the tight rope. Eur Heart J. 2016;37:253–5.
21. Thomas M, Malmcrona R, Fillmore S, Shillingford J. Haemodynamic effects of morphine in patients with acute myocardial infarction. Br Heart J. 1965;27:863–75.
22. Lal S, Savidge RS, Chhabra GP. Cardiovascular and respiratory effects of morphine and pentazocine in patients with myocardial infarction. Lancet. 1969;1:379–81.
23. Flacke JW, Flacke WE, Bloor BC, Van Etten AP, Kripke BJ. Histamine release by four narcotics: a double-blind study in humans. Anesth Analg. 1987;66:723–30.
24. Ellingsrud C, Agewall S. Morphine in the treatment of acute pulmonary oedema – why? Int J Cardiol. 2016;202:870–3.
25. Headrick JP, See Hoe LE, Du Toit EF, Peart JN. Opioid receptors and cardioprotection – 'opioidergic conditioning' of the heart. Br J Pharmacol. 2015;172:2026–50.
26. Steg PG, James SK, Atar D, Badano LP, Blomstrom-Lundqvist C, Borger MA, Di Mario C, Dickstein K, Ducrocq G, Fernandez-Aviles F, Gershlick AH, Giannuzzi P, Halvorsen S, Huber K, Juni P, Kastrati A, Knuuti J, Lenzen MJ, Mahaffey KW, Valgimigli M, von' t Hof A, Widimsky P, Zahger D. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J. 2012;33:2569–619.
27. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, ALP C, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimský P, ESC Scientific Document Group. 2017 ESC

Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2018;39:119–77.
28. Meine TJ, Roe MT, Chen AY, Patel MR, Washam JB, Ohman EM, Peacock WF, Pollack CV Jr, Gibler WB, Peterson ED. Association of intravenous morphine use and outcomes in acute coronary syndromes: results from the CRUSADE Quality Improvement Initiative. Am Heart J. 2005;149:1043–9.
29. de Waha S, Eitel I, Desch S, Fuernau G, Lurz P, Urban D, Schuler G, Thiele H. Intravenous morphine administration and reperfusion success in ST-elevation myocardial infarction: insights from cardiac magnetic resonance imaging. Clin Res Cardiol. 2015;104:727–34.
30. Hobl EL, Stimpfl T, Ebner J, Schoergenhofer C, Derhaschnig U, Sunder-Plassmann R, Jilma-Stohlawetz P, Mannhalter C, Posch M, Jilma B. Morphine decreases clopidogrel concentrations and effects: a randomized, double-blind, placebo-controlled trial. J Am Coll Cardiol. 2014;63:630–5.
31. Parodi G. Editor's Choice-Chest pain relief in patients with acute myocardial infarction. Eur Heart J Acute Cardiovasc Care. 2016;5:277–81.
32. McCarthy CP, Mullins KV, Sidhu SS, Schulman SP, McEvoy JW. The on- and off-target effects of morphine in acute coronary syndrome: a narrative review. Am Heart J. 2016;176:114–21.
33. Ferdinandy P, Hausenloy DJ, Heusch G, Baxter GF, Schulz R. Interaction of risk factors, comorbidities, and comedications with ischemia/reperfusion injury and cardioprotection by preconditioning, postconditioning, and remote conditioning. Pharmacol Rev. 2014;66:1142–74.
34. Wong GT, Li R, Jiang LL, Irwin MG. Remifentanil post-conditioning attenuates cardiac ischemia-reperfusion injury via kappa or delta opioid receptor activation. Acta Anaesthesiol Scand. 2010;54:510–8.
35. Rentoukas I, Giannopoulos G, Kaoukis A, Kossyvakis C, Raisakis K, Driva M, Panagopoulou V, Tsarouchas K, Vavetsi S, Pyrgakis V, Deftereos S. Cardioprotective role of remote ischemic periconditioning in primary percutaneous coronary intervention: enhancement by opioid action. JACC Cardiovasc Interv. 2010;3:49–55.
36. DOLE VP, NYSWANDER M. A medical treatment for diacetylmorphine (heroin) addiction. A clinical trial with methadone hydrochloride. JAMA. 1965;193:646–50.
37. DOLE VP. Addiction as a public health problem. Alcohol Clin Exp Res. 1991;15:749–52.
38. Monahan BP, Ferguson CL, Killeavy ES, Lloyd BK, Troy J, Cantilena LR Jr. Torsades de pointes occurring in association with terfenadine use. JAMA. 1990;264:2788–90.
39. Krantz MJ, Lewkowiez L, Hays H, Woodroffe MA, Robertson AD, Mehler PS. Torsade de pointes associated with very-high-dose methadone. Ann Intern Med. 2002;137:501–4.
40. Wedam EF, Bigelow GE, Johnson RE, Nuzzo PA, Haigney MC. QT-interval effects of methadone, levomethadyl, and buprenorphine in a randomized trial. Arch Intern Med. 2007;167:2469–75.
41. Eap CB, Crettol S, Rougier JS, Schlapfer J, Sintra GL, Deglon JJ, Besson J, Croquette-Krokar M, Carrupt PA, Abriel H. Stereoselective block of hERG channel by (S)-methadone and QT interval prolongation in CYP2B6 slow metabolizers. Clin Pharmacol Ther. 2007;81:719–28.
42. Wedam EF, Haigney MC. The impact of opioids on cardiac electrophysiology. Curr Cardiol Rev. 2016;12:27–36.
43. Roden DM. Drug-induced prolongation of the QT interval. N Engl J Med. 2004;350:1013–22.
44. Isbister GK, Brown AL, Gill A, Scott AJ, Calver L, Dunlop AJ. QT interval prolongation in opioid agonist treatment: analysis of continuous 12-lead electrocardiogram recordings. Br J Clin Pharmacol. 2017;83:2274–82.
45. Eap CB, Buclin T, Baumann P. Interindividual variability of the clinical pharmacokinetics of methadone: implications for the treatment of opioid dependence. Clin Pharmacokinet. 2002;41:1153–93.
46. Anchersen K, Clausen T, Gossop M, Hansteen V, Waal H. Prevalence and clinical relevance of corrected QT interval prolongation during methadone and buprenorphine treatment: a mortality assessment study. Addiction. 2009;104:993–9.
47. Ansermot N, Albayrak O, Schlapfer J, Crettol S, Croquette-Krokar M, Bourquin M, Deglon JJ, Faouzi M, Scherbaum N, Eap CB. Substitution of (R, S)-methadone by (R)-methadone: impact on QTc interval. Arch Intern Med. 2010;170:529–36.
48. Grilo LS, Carrupt PA, Abriel H. Stereoselective inhibition of the hERG1 potassium channel. Front Pharmacol. 2010;1:137.

Psychostimulants and Cardiovascular Function

52

Emanuela Masini, Silvia Sgambellone, and Cecilia Lanzi

Contents

Abstract

Psychostimulants include a range of substances that encompass cocaine and phenylethylamines, which include amphetamines, some novel amphetamine derivatives, and cannabinoids. This chapter documents the present state of knowledge on the effects of cocaine and cocaethylene, amphetamines, and cannabinoids on heart and brain functions. Cocaine in comparison with the other substances has a particular heart and brain toxicity, exhibiting a variety of prothrombotic effects, hypertension, myocardial infarction, severe arrhythmias, delirium, seizures, intracranial hemorrhage, and serotonin syndrome. Amphetamines and its derivative methamphetamine (METH) are powerful stimulants, while methylenedioxymethamphetamine (MDMA), popularly known as "ecstasy," is a typical entactogenic substance with a pharmacological profile, interpolated between those of typical stimulants, such as amphetamines and hallucinogens. *Cannabis* is the most abused illicit substance with a high incidence of usage in adolescents. The cardiotoxic and neurotoxic

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*,
https://doi.org/10.1007/978-3-030-28008-6_54

effects of *Cannabis* depend on the preparation used. Synthetic cannabinoids (SC), developed to investigate the endogenous cannabinoid system or as potential therapies, have intense psychoactive and toxic effects.

Keywords

Cocaine · Amphetamine · MDMA · Cannabinoids · Cardiac toxicity · Stroke · Seizures · Excited delirium · Cognitive impairment

Introduction

The use of psychostimulants is a worldwide problem with significant regional variation; the number of psychostimulant consumers increased in the last decades, becoming an important public health problem everywhere. Cocaine and amphetamines are the two major psychostimulants used for recreational purposes globally. In 2012, data from the United Nations Office on Drugs and Crime reported 34 million amphetamine users (range 14–53 million) and 17 million cocaine users (range 14–21 million) worldwide. The number of amphetamine users remained stable during the following 6 years, while the cocaine users increased in the same time period by 7% [1]. There is pronounced regional variation in the use of various psychostimulants, with high prevalence rates for amphetamines in North America and Oceania, MDMA in Central Europe, and cocaine in North and South America followed by Central Europe [1]. Psychostimulants are often used in combination with other drugs such as opioids and alcohol, having a substantial toxicological impact on public health. Cocaine is seen as the major public health problem; however two thirds of the burden of stimulant dependence globally is attributed to amphetamines rather than cocaine use. Although cocaine and amphetamine dependence share many features, the two drug classes have important toxicological differences. *Cannabis* is the most commonly used illicit substance in the world. Though it was long considered to be a "soft drug," studies have proven the harmful psychiatric and addictive effects associated with its use. Synthetic cannabinoids (SC) were created for therapeutic and research purposes; however, despite legal efforts to limit their availability, synthetic cannabinoids have become an increasingly common drug of abuse, sold under various street names [2].

This chapter is focused on the effect of cocaine, amphetamines, METH, MDMA, and cannabinoids on heart and brain functions.

Cocaine

Cocaine is a naturally occurring substance found in the leaves of *Erythroxylum coca* plant. This plant is native to northwestern South America. The use of coca has a long tradition in that area, linked to religious and ceremonial purposes. The use of leaves of *Erythroxylum coca* by chewing to overcome fatigue and hunger was first described by Amerigo Vespucci in 1499. In far more recent times, cocaine found a place in therapy as a painkiller and local anesthetic drug and, from the beginning of twentieth century, as a stimulant, psychoactive agent, and recreational drug of abuse. It is commonly available in hydrochloride form, a white, water-soluble powder. It can be used orally or intravenously or by nasal inhalation (snorting). Relatively pure formulations that lack a hydrochloride moiety are presented in crystalline form, freebase, or *crack cocaine* which is used mostly by smoking. Pharmaceutical cocaine preparations are available in some countries and used as a local anesthetic agent blocking voltage-gated sodium channels in the neuronal membranes, inhibiting depolarization, initiation, and conduction of nerve impulses. Cocaine retains an important vasoconstrictive action by inhibiting the local reuptake of norepinephrine [3].

Cocaine, compared to other illicit drugs, poses a particular risk for the cardiovascular and the nervous systems. It may cause hypertension, troubles of rhythm from tachycardia to ventricular arrhythmias, myocardial infarction, stroke, excitation, and delirium resulting in severe functional impairment or sudden death. Causal users, for

environmental and biological risk factors, may progress from recreational consumers to developing a cocaine use disorder, characterized by cognitive impairment with an attention deficit, learning disorder, and memory loss.

Cocaine Blood Concentrations and Pharmacological Actions

Blood cocaine concentrations are responsible for its effects, which are determined by many factors such as the dose and the route of administration, the binding to plasma proteins, and the rate of metabolism. Studies in volunteers who received a known dose of the substance provide precise information of dose and route on blood or serum concentrations, but this does not reflect what occurs in cocaine-abusing patients. Information obtained from blood analysis in patients presenting to the Emergency Departments offers a better picture, but, also, in this case, there are several limitations because the dose assumed is unknown and cocaine is rapidly metabolized. Postmortem studies are susceptible to the same limitations; serum cocaine concentrations exceeding 1 mM have been reported in acute fatal overdoses, although 1 series of 26 cases reported a lower value with a mean concentration of 21 μM in deaths where cocaine was the only drug detected [4].

Cocaine stimulates the sympathetic nervous system by inhibiting the reuptake of norepinephrine, dopamine, and serotonin by interacting with each transporter (NET, DAT, and SERT), which have similar Ki for cocaine, leading to exaggerated, prolonged sympathetic nervous system activity (Fig. 1).

Cocaine also blocks sodium/potassium channels, which induces abnormal, depressed cardiovascular profiles; more over it binds in rat cerebellum with two different neurotransmitter receptors: muscarinic acetylcholine, with a μM Ki, and sigma receptors [5].

In addition to interacting with transporters for neurotransmitters and receptors, cocaine binds to several voltage-gated ion channels in nervous and cardiac tissues; the local anesthetic effect of cocaine doesn't contribute to the effects on the brain, while it is responsible for cocaine's hearth toxicity. In isolated cardiomyocytes, cocaine binds to inactivated state of sodium channels, an

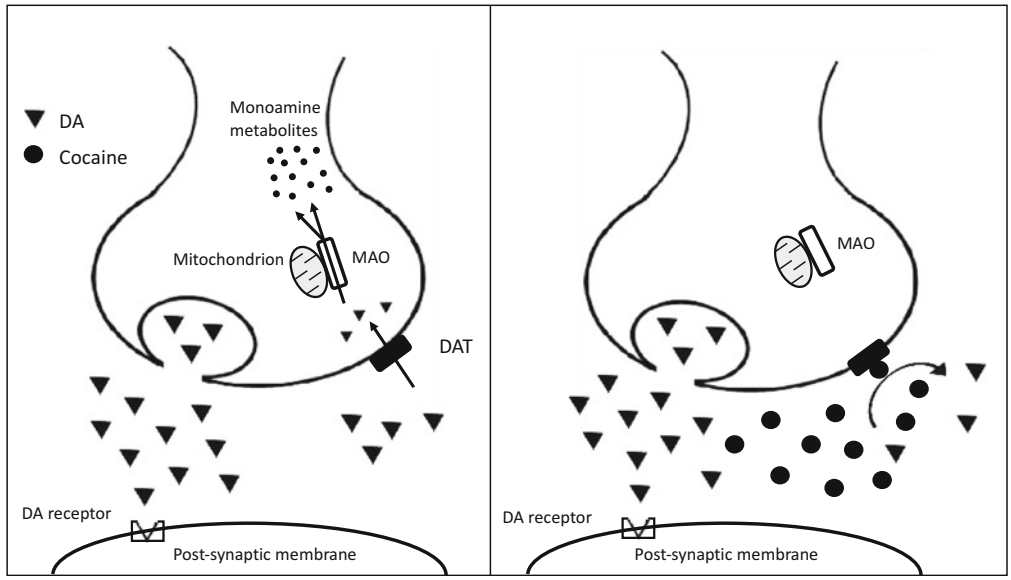

Fig. 1 Pharmacological actions of cocaine on neurotransmission. *DA* dopamine, *DAT* dopamine transporter, *MAO* monoaminoxidase

effect highly dependent on extracellular pH, and increases when the pH decreases under physiological levels, suggesting that changes in plasma pH may modulate cocaine's effect on cardiac conduction [6]. Cocaine also binds and inhibits cardiac potassium rectifier channels prolonging the duration of L-type calcium channels [7].

Two additional cocaine-protein interactions are relevant for its toxicity. Cocaine binds to α_1-acid glycoprotein (A1AG) and to albumin; A1AG has a high affinity for cocaine, while albumin has a much lower affinity. A1AG is present in low concentration, and when cocaine's plasma levels exceed its binding capacity, free cocaine plasma concentration increases and, consequently, increases the toxic effects of cocaine [8].

Effects of Cocaine on the Brain

Cocaine binds directly to few receptors and transporters, but the interaction among these different pathways triggers a cascade of activities which potentiate cocaine toxicity (Table 1).

The inhibition of dopamine transporter (DAT) is responsible for the psychostimulant effects and the recreational use of cocaine. Several studies in monkeys showed that the potency of DAT inhibition, rather than the inhibition of norepinephrine (NET) or serotonin transporter (SERT), is correlated with the behavioral effect of cocaine, supporting the hypothesis that the pharmacological actions of cocaine in the central nervous system (CNS) are mostly due to DAT inhibition [9].

Table 1 Effects of cocaine correlated with the different neurotransmitters

Neurotransmitter	Symptom
Dopamine	Positive Anorexia Hyperactivity Sexual arousal
Serotonin	Hallucinations Vasospasm Hyperthermia
Noradrenaline	Tachycardia Hypertension Vasoconstriction Mydriasis Tremors

Monoamines and particularly dopamine are responsible for the rewarding and psychostimulant properties of cocaine [9], and monoaminergic system has been postulated to be involved in cocaine-induced regulation of adult neurogenesis [10]. Cocaine use can modify several neurotrophic factors that likely regulate learning and memory mechanisms in the brain [11].

Central nervous system symptoms include euphoria, increased self-confidence, and alertness at low doses and aggressiveness, disorientation, and hallucination at high doses (Table 1); cocaine toxicity is enhanced by antidepressants [12].

Long-term use of cocaine can induce a profound dysfunction of monoamine system in the brain causing a condition called *excited delirium* (ED), also known as *agitated delirium*, a condition that presents psychomotor agitation, delirium, and sweating. It may include attempts at violence, unexpected strength, and very high body temperature. Complications include rhabdomyolysis and a high blood potassium concentration that can lead to cardiac arrest [13].

The cellular and neurochemical modifications induced by cocaine abuse during the ED are not completely defined and have been the subject of scientific debate. Abnormalities in D_1, D_2, and D_3 dopamine receptors have been identified, and this hypothesis lies in the fact that hypothalamic dopamine receptors are responsible for thermoregulation. In fact, in case of cocaine-induced ED, alteration of dopamine mesolimbic pathway in the brain is present, resulting in hyperactivity and hyperthermia [14]. Repetitive use of cocaine induces a depletion of dopamine stores, a situation referred as *washout syndrome*, characterized by lethargy, anhedonia, and difficulty in locomotor activity [15].

Cocaine interacts also with non-opioid sigma receptors, which are of two subtypes: sigma-1 and sigma-2. Sigma-1 bind neurosteroids, and conflicting evidences report that sigma receptor ligands decrease the epileptogenic effect of cocaine [15]. Cholinergic M_1 receptors are present in striatal and cortical areas, and, although with a low grade of evidence,

pirenzepine, a M_1 cholinergic receptor antagonist, decreases the lethality of cocaine in the mouse [5].

The toxicity of cocaine can be modified by pharmacological manipulations of several other neurotransmitters, such as GABA and NMDA glutamate systems. GABA is the major inhibitory neurotransmitter in the CNS, and its activity modulates the biochemical and behavioral effects of cocaine. $GABA_A$ agonists decrease the neurotoxicity of cocaine in animal models; benzodiazepines and phenobarbital are widely used in the treatment of cocaine toxicity [16].

Another neurotransmitter implicated in the toxicity of cocaine is glutamate, the major excitatory neurotransmitter in the CNS. Glutamate receptors are the NMDA and the AMPA receptors, and while AMPA receptors contribute little to cocaine toxicity, NMDA receptors are clearly implicated, and NMDA antagonists decrease seizures and lethality induced by cocaine [16].

Cortical excitability, assessed by transcranial magnetic stimulation (TMS) [17], is significantly increased in cocaine-dependent patients than in controls [18], and several studies showed a lower motor cortex excitability in abstinent cocaine-dependent subjects than nondrug-using controls [19], suggesting an adaptation mechanism, which may include changes in the brain GABA and glutamate systems mediated by GABAergic neurotransmission [17].

Some recent studies, realized by means of imaging techniques and morphometric analysis, demonstrated that the *striatum, thalamus*, and subcortical structures are intimately involved in addiction. These structures present morphological and microstructural changes in patients using crack cocaine together with a contraction and gliosis of *nucleus accumbens* (NAc), indicating that cocaine induces a significant remodeling of neurological structure [20], with dysregulation of specific brain circuit involved in learning and memory [21]. The recent emphasis on the impairment of learning process induced by cocaine addiction impacting hippocampal neurogenesis has directed the interest toward the *hippocampus*, the main brain region involved in associative memory [20]. Cocaine use stimulates hippocampal learning systems to form strong memories of cocaine-stimuli associations, evidenced by the facilitation of hippocampal long-term potentiation (LTP) and of glutamatergic transmission by enhancing dopamine signaling [10].

Cardiovascular Toxicity of Cocaine

Cocaine induces several effects on the heart and coronary vasculature including vasospasms, ischemia, myocardial infarction, arrhythmias, and ventricular fibrillation [22]. These actions can be attributed to two prominent effects of cocaine: an increase in sympathetic stimulation to the heart and coronary vasculature and a direct inhibition of cardiac ion channels. The mechanisms that underlie the cardiotoxic effects of cocaine are not well understood and are probably related to a combination of both the sympathomimetic and local anesthetic properties of this drug. Sodium channels play a key role in the electrical excitability of the myocardium and are responsible for the rapid upstroke of the cardiac action potential [23]. Cocaine has long been known to reduce the cardiac Na^+ conductance by promoting the voltage-dependent inactivation of sodium channels [23]. Within the range of concentrations known to cause acute toxicity in humans (1–70 μM) [24], cocaine produces a characteristic voltage- and frequency-dependent inhibition of cardiac Na^+ current in the sinoatrial node in the *myocardium*, stabilizing the channels in an inactivated state and leading to reduced contractility and prolongation of QT interval and QRS complex [25]. These actions induce severe rhythm troubles from ventricular tachycardia to ventricular fibrillation.

Cocaine's effect upon the heart doesn't stop with arrhythmias. Research suggests that cocaine can induce spasms of the coronary arteries that can cause angina pain, even in healthy individuals; cocaine can induce myocardial ischemia and infarction without pathological changes of coronary artery and other risk factors [26]. Cocaine has indirect toxic effects on the heart, through the action of norepinephrine (NE) blocking the reuptake of catecholamine and by binding dopamine and norepinephrine transporters (DAT and NET).

The increased levels of NE at the sympathetic terminals cause an activation of adrenergic receptors with a consequent β_1-receptor activation in the sinoatrial node, increasing heart rate and contractility, and α_1-activation of smooth vascular muscle cells, leading to vasoconstriction and increased blood pressure [26]. Consequently, cocaine users can develop a condition called *silent myocardial ischemia* that may lead to valuable heart muscle cell dying because of oxygen shortage and oxidative stress [27]. Cocaine induces hypertension as both acute spikes in systemic blood pressure as long-term development of persistent hypertension. Acute hypertensive spikes are primarily the result of vasoconstriction mediated by α_1-adrenoceptor stimulation, while persistent hypertension consequent to a chronic use of cocaine is more complex, with direct effects on peripheral vasculature and also on renal blood flow [26]. The most frequent cardiovascular events induced by cocaine use are angina, myocardial infarction, cardiomyopathy, and sudden death. The pathogenesis of myocardial ischemia and infarction is multifactorial and includes increased oxygen demand, vasoconstriction of the coronary arteries, enhanced platelet aggregation, leukocyte migration, and thrombus formation [29]. Coronary vasoconstriction is mostly the result of α-adrenergic receptor stimulation, an effect which is exacerbated by β-blockers; moreover, cocaine induces endothelial production of endothelin and decreased nitric oxide (NO) release, all of which promotes vasoconstriction [28, 29]. Aside from vasoconstriction, cocaine induces the formation of thrombi via enhanced platelet aggregation and activation of plasminogen activator inhibitor [30]. Postmortem studies of chronic cocaine users have shown a progression of atherosclerosis in comparison with the age of the subject due to alteration of endothelial cell barrier with a marked increased expression of adhesion molecules and of permeability of the low-density lipoproteins [29].

Chest pain is certainly the most frequent cocaine-related symptom and accounts for a great number of cocaine-related visits at the Emergency Department. The pain is similar to that experienced in angina especially if it is due to a coronary artery thrombosis and may evolve in a frank myocardial infarction [31]. This symptom is caused by several factors, and it can be dependent on the route of drug use. Cocaine inhalation can induce pneumothorax, while intravenous use causes lung embolism with chest pain and other cardiopulmonary symptoms. Chest pain occurs also several hours after cocaine use when cocaine blood concentrations are very low or undetectable; this is due to cocaine metabolites benzoylecgonine and ecgonine methyl ester [31]. It has shown, in animal models of cocainism, a significant increase in α-natriuretic factor levels and changes in gene expression from α- to β-myosin heavy chains, both factors playing a role in cardiac remodeling [32]. Dilated cardiomyopathy has emerged as a significant long-term problem in cocaine users and accounts for 7% incidence of ventricular dysfunction in long-term cocaine users; however detailed epidemiological studies on cocaine-induced cardiomyopathy are lacking. The clinical presentation of cocaine-induced cardiomyopathy is not distinguished from other forms of cardiomyopathy, and it is a consequence of the persistent and profound hypertension and an increased leukocyte adhesion [29]. Moreover, persistent hypertension is a potent predisposing factor for stroke. Pulmonary hypertension has been described in cocaine users, an effect consequent to pulmonary arterial smooth muscle cell proliferation [32].

When cocaine is assumed with ethanol, cocaethylene, the ethyl ester of benzoylecgonine, is formed in the liver [31] (Fig. 2). Normally, cocaine is metabolized by carboxylesterase to benzoylecgonine and ecgonine, but if ethanol is present during the metabolism of cocaine, part of this substance undergoes transesterification with ethanol rather than undergoing hydrolysis with water, which results in the production of cocaethylene. This metabolite is largely considered a recreational drug with stimulant and euphoriant effects and with a longer duration of action than cocaine. Cocaethylene increases monoaminergic neurotransmission in the brain, inhibiting DAT and NET, and it is more cardiotoxic than cocaine and increases the risk of a cardiac event [31].

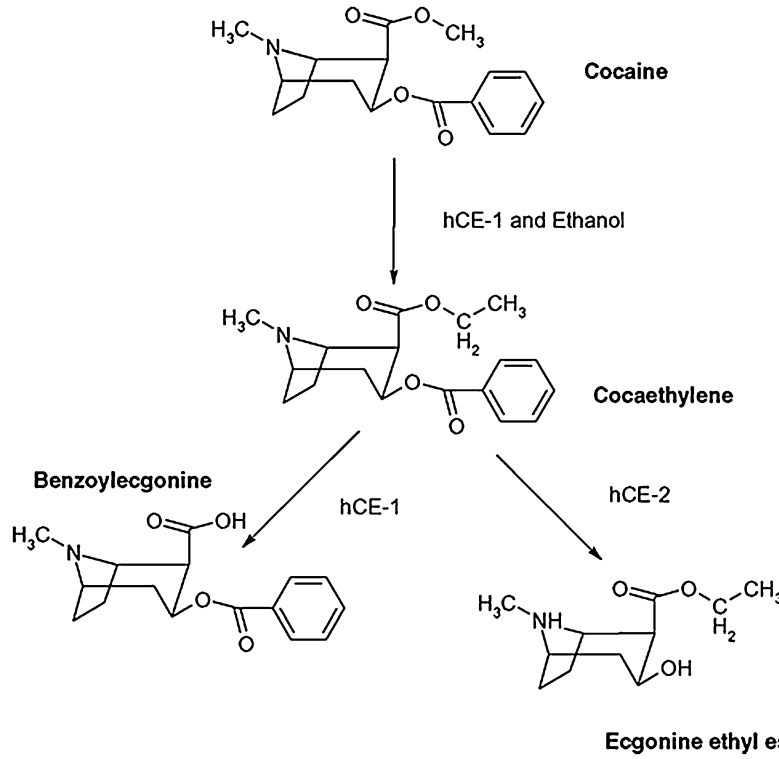

Fig. 2 Cocaine and ethanol lead to the formation of a metabolite known as cocaethylene by esterase (hCE-1/2)

Amphetamines

Amphetamines were discovered over 100 years ago. Since then, it has transformed from a drug that was freely available without prescription as a panacea for a broad range of disorders into a highly restricted therapeutic application to attention deficit hyperactivity disorder (ADHD) and narcolepsy.

As a molecule with a single chiral center, amphetamine exists in two optically active forms, i.e., the dextro- (or *d*-) and levo- (or *l*-) isomers or enantiomers (Fig. 3), but only the *d*-isomer, the more potent, was commercialized under the trade name of Dexedrine® [33].

The cognitive-enhancing properties of amphetamines were quickly recognized, with reports of Benzedrine producing improvements in intelligence tests leading to its widespread use to improve concentration and intellectual performance by academics, students, and medical professionals and the widespread use of "energy pills" by the allied forces in World War II [33].

Amphetamine and its derivative methamphetamine (METH) (Fig. 4), a powerful central nervous system stimulant, exert their pharmacological effects through alterations in the brain's dopaminergic reward circuitry [34].

Amphetamines, including METH, enter dopaminergic presynaptic terminals by acting as substrates for the plasmalemma dopamine transporter (DAT) [35] and elicit the release of vesicular dopamine (DA) stores into the cytosol through an interaction with vesicular monoamine transporter-2 (VMAT2) protein [36] promoting DA release, increasing cytosolic DA concentrations, and inhibiting DA uptake from the cytosol by VMAT2 [37]. As amphetamines inhibit also the activity of the mitochondrial enzyme monoamine oxidase (MAO), elevated concentrations of cytosolic DA are not subjected to metabolism [38]. Enhanced DA release and increased

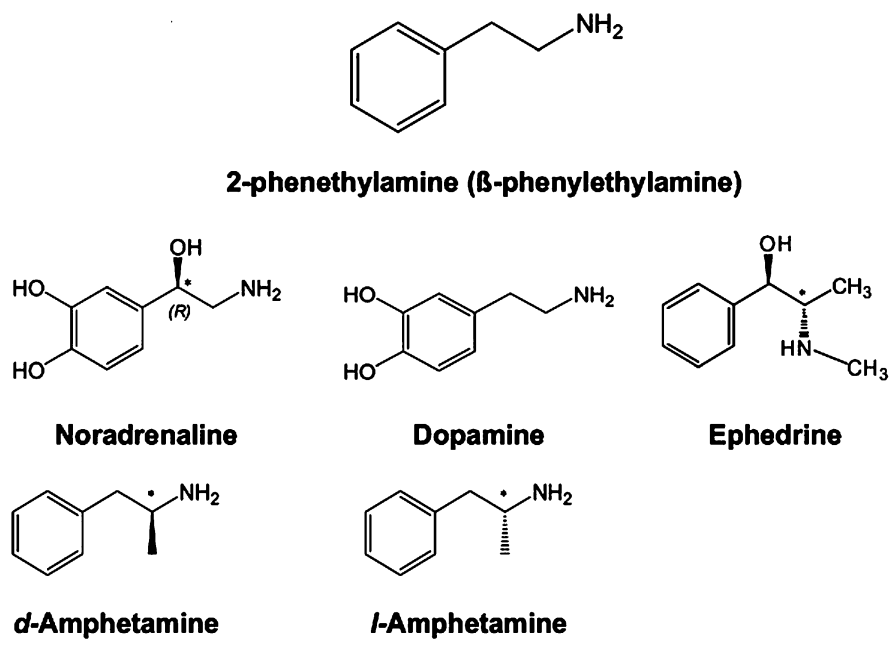

Fig. 3 Isomers of amphetamine

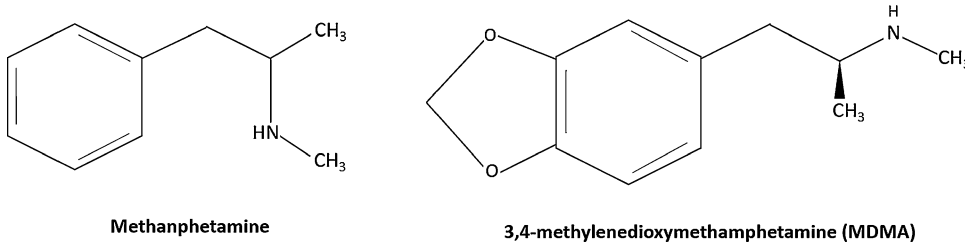

Fig. 4 Amphetamines' derivatives methamphetamine (METH) and 3,4-methylenedioxymethamphetamine (MDMA)

stimulation of postsynaptic DA receptors lead to rewarding effects and high degree of abuse liability.

Amphetamine and its derivative methamphetamine (METH), which are abused for decades, are typically sold under the street name "speed," while the 3,4-methylenedioxy derivative (MDMA) is associated with the name "ecstasy."

The pharmacological actions of MDMA are significantly distinct from those of other compounds. Stimulation of the CNS producing euphoria is commonly described as the subjective effect of amphetamine consumption [39], while MDMA is an entactogenic substance. Both amphetamine and MDMA act on monoamine reuptake transporters, blocking 5-HT, DA, and NE transporters, inhibiting the reuptake of the respective neurotransmitters, and increasing neurotransmitter concentrations in the synaptic cleft and transporter-mediated release of neurotransmitters [40]. Since these neurotransmitters are differentially involved in modulating behavior and subjective effects, a distinct pharmacological profile of these drugs of abuse is linked to specific psychotropic effects and intoxication.

Amphetamine blocks with preference DA transporter, while MDMA preferentially acts at human SERT and NET. Amphetamine and amphetamine-like substances induce psychostimulation, euphoria, and increased arousal. Other

clinical features of toxicity include hypertension, tachycardia and tachyarrhythmia, and increased body temperature [39]. Regular consumption bears a considerable risk for abuse and dependence. Drug-induced increase of DA levels activates the reward system and causes euphoria, but also psychotic states and aggressive behavior [41]. Life-threatening excited delirium syndrome has been associated with acute dopaminergic toxicity [42].

Trace amine-associated receptor 1 (TAAR1) is also a target of amphetamine and of many amphetamine derivatives; this receptor is involved in the regulation of DA activity, and activation of TAAR1, which reduces the abuse liability of psychostimulants. Amphetamine and MDMA induce more pronounced effects in animals not expressing TAAR1; however, species differences between the rodent and human TAAR1 are frequent [43]. MDMA is an entactogenic drug that retains some psychostimulant effects. It increases empathy, sociability, closeness to others, but also happiness and self-esteem. The effects on the cardiovascular system include increased blood pressure, heart rate, and hyperthermia.

In the literature [44], the classic histopathological alterations of fatal cardiotoxicity from MDMA manifest as contraction band and coagulative necrosis, myocyte hypereosinophilia, and inflammatory neutrophil infiltration. The increased muscle tension may cause bruxism which is frequently experienced. Moreover MDMA is a partial agonist of the 5-HT_{2A} receptors, and hallucinogen effects have been reported [45].

The binding affinity of MDMA for adrenergic receptors is low, but since MDMA increases NE levels via transporter-mediated NE release and NE uptake inhibition, the adrenergic system is deeply involved in the mechanism of toxicity induced by the substances. Beta-adrenoceptors are involved in MDMA-induced increase of heart rate and together with α_1-adrenoceptor stimulation implicated in hyperthermia and vasoconstriction [40]. MDMA-induced serotoninergic toxicity is due to an increase of serotonin level at synaptic cleft. This syndrome presents neuromuscular hyperactivity, clonus, autonomous hyperactivity, including hyperthermia, sweating, agitation, and confusion. Moreover, an inadequate diuretic hormone production can be present resulting in hyponatremia [46]. Hyperthermia, followed by life-threatening complications such as rhabdomyolysis, intravascular coagulation, and organ failure, is commonly involved in fatal intoxications with psychostimulants, especially with MDMA. Cardiovascular toxicity is typically associated with amphetamine but also occurs with MDMA use, via NE release and stimulation of α- and ß-adrenoceptors. $ß_3$-Adrenoceptor activation causes mitochondrial uncoupling, which can induce heat generation [47].

Aminoindan derivatives of MDMA, originally developed as potential therapeutic bronchodilators, have emerged as new psychostimulant compounds among recreational drug users, with a relatively low prevalence. Some aminoindans were developed as potential non-neurotoxic alternatives for MDMA because they don't cause 5-HT stimulation; however, recent animal studies indicate that these molecules can induce potentially life-threatening serotonin syndrome toxicity [48]; however few fatal intoxications have been described.

The pharmacology and toxicology of benzofuran derivatives are relatively poorly explored to date, but fatal, analytically confirmed intoxication with the benzofuran-5 has been reported. Benzofurans are described as substances inducing entactogenic and stimulant effects, with sympathomimetic toxicity, including hyperthermia.

Cannabinoids

Cannabinoids are a group of compounds that act on cannabinoid receptors. They include plant-derived phyto-cannabinoids, synthetic cannabinoids, and endogenously derived endocannabinoids. The primary source of cannabinoid toxicity is from plant-derived cannabinoids and synthetic cannabinoids. These agents act as cannabinoid receptor agonists. More than 60 - naturally occurring cannabinoids are found in *Cannabis sativa* and *indica,* and delta-9

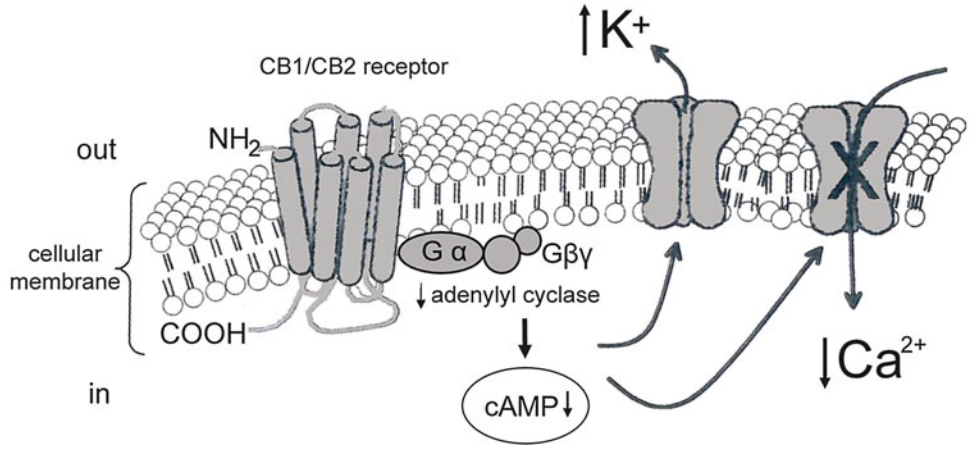

Fig. 5 Structure of cannabinoid receptors (CB_1/CB_2)

tetrahydrocannabinol (THC) is the main psychoactive compound. Other naturally occurring cannabinoids include cannabidiol (CBD) and cannabinol. Marijuana, hashish, and crushed, dried leaves, flowers, and resin of the *Cannabis* plant are the most common abused substances.

Internationally, *Cannabis* is the most commonly abused illicit substance with a high incidence of usage in adolescents. Over 140 million people use *Cannabis* worldwide. Synthetic cannabinoids are the most abused synthetic drug and the second most abused drug among adolescents. Reports of abuse and toxicity are steadily growing, as the number of synthetic cannabinoids produced increases [49]. Increasing varieties of synthetic cannabinoids have been synthesized over the last ten years for therapeutic and research purpose and to avoid classification as illegal agents by making chemical modifications to compounds. They became drug of abuse, sold under various street names such as *K2, Spice*, and *Black Mamba,* and are associated with much more morbidity and mortality than the phytocannabinoids [49].

The cannabinoid system is very complex, and research is still ongoing. Endogenous and exogenous cannabinoids act on specific cannabinoid binding receptors (CB_1 and CB_2). CB_1 receptors are primarily centrally located, but they are also present in the periphery, while the opposite is true for CB_2, which were identified primarily peripherally, but they are present also centrally (Fig. 5). Cannabinoid receptors are G protein-coupled receptors (G_i or G_o) with seven transmembrane segments with an extracellular amino-terminal domain (NH_2) and one intracellular carboxy-terminal (COOH) implicated in signal transduction.

CB_1 receptors are mainly involved in the central effects of cannabinoids, which include consequences on learning, memory cognition, emotion, movement, sensory perception, and nausea, as well as the psychoactive properties associated with cannabinoids. CB_2 receptors are located peripherally and are thought to affect inflammation and immune system regulation. Cannabinoid receptors are G protein-linked receptors that inhibit adenylyl cyclase and thereby cyclic AMP, which affects Ca^{2+} channels and K^+ channels, leading to a decrease in intracellular calcium and extracellular potassium concentrations. This, subsequently, leads to decreased neurotransmission. However, depending on the specific location of the CB and specific G-protein involved, stimulation of CB_1 results in the inhibition or stimulation of various neurotransmitters, including acetylcholine, L-glutamate, γ-aminobutyric acid, dopamine, norepinephrine, and 5-hydroxytryptamine. This neurotransmitter modulation may contribute to the central and peripheral effects of cannabinoids

The pharmacokinetics of cannabinoids and the effects observed depend on the formulation and route of administration. The administered dose of

therapeutic *Cannabis* should be tailored to individual patient requirements. Both THC and CBD are metabolized in liver. There is a risk of potential drug interactions via inhibition or induction of enzymes or transporters. Pharmacodynamic interactions may occur if Cannabis is administered with other central nervous system depressant drugs, and cardiac toxicity may occur via additive hypertension and tachycardia with sympathomimetic agents [50].

The cardiotoxic and neurotoxic effects of *Cannabis* can be more severe in special preparation called *"*dabs*"* obtained by the inhalation of heated extracted oil [51]. *Dabs* are cannabis extracts, being consumed via a new inhalation method called *"*dabbing." The act of consuming one dose is colloquially referred to as "*doing a dab." Dabs* can contain up to 75% of tetrahydrocannabinol (THC) and this molecule has been increasingly associated with agitation and cardiotoxicity [52]. Acute myocardial infarction (AMI) has been described in numerous case reports [53] and the trend of Emergency Department admission and severe morbidity due to AMI in cannabis users is also increasing [54]. THC may cause agitation and end-organ damage through sympathomimetic and serotonergic pathways, but the cardiac mechanism of toxicity is not yet fully understood [50]. THC binds to CB_1 receptors on glutamatergic and GABAergic neurons disrupting normal, endocannabinoid retrograde signaling from dopaminergic neurons. Acute THC use increases dopamine release and neuron activity, while chronic exposure to THC causes the blunting of the dopaminergic system. THC exposure during adolescence may be very detrimental for brain developmental processes as the endogenous cannabinoids play an important role in brain development. THC produces complex alterations in the dopamine system in a very important time for brain development. Adolescent cannabinoid exposure has consequences in adulthood [55]. Heavy *Cannabis* users are more likely to have impaired educational and occupational outcomes, and this may be linked to working memory impairments and amotivation. These functions are susceptible to mesocortical dopaminergic manipulation in prefrontal D_1 receptor blockade [56].

Cannabis is known to be associated with neuropsychiatric problems, but less is known about complications affecting the cardiovascular system like myocardial infarction and ischemic stroke

Conclusions

The effects of psychostimulants on the central nervous and cardiovascular systems are well described and yet, at the same time, lacking of basic understanding in many areas. Detailed knowledge related to amphetamines' toxicity, especially in relation to the newer novel psychoactive substances flooding recently in the illicit market, are lacking. Cannabinoids are widely investigated also for their therapeutic effects, but further studies on the aspects of cannabinoids toxicity should be ruled out, and the knowledge of the highly dangerous toxic effects of a drug that the common sense considers as safe should be disseminated.

References

1. United Nations. United Nations Office on Drug and Crimes (UNODC): world drug report 2018. New York: United Nations; 2018.
2. Castanedo MS, Gorelick DA, Desrosiers NA, Hartman RL, Pirard S, Huestis MA. Synthetic cannabinoids: epidemiology, pharmacodynamics, and clinical implications. Drug Alcohol Depend. 2014;144:12–41.
3. Hille B. Ion channels of excitable membranes. 3rd ed. Sunderland: Sinauer Associates, Inc. Publishers; 2001.
4. Karch SB, Stephens B, Ho CH. Relating cocaine blood concentrations to toxicity – an autopsy study of 99 cases. J Forensic Sci. 1998;43(1):41–5.
5. Flynn DD, Vaishnav AA, Mash DC. Interactions of cocaine with primary and secondary recognition sites on muscarinic receptors. Mol Pharmacol. 1992;41(4):736–42.
6. Crumb WJ, Clarkson CW. The pH dependence of cocaine interaction with cardiac sodium channels. J Pharmacol Exp Ther. 1995;274:1228–37.
7. Ferreira S, Crumb WJ, Carlton CG, Clarkson CW. Effects of cocaine and its major metabolites on the HERG-encoded potassium channel. J Pharmacol Exp Ther. 2001;299(1):220–6.
8. Heard K, Palmer R, Zahniser NR. Mechanisms of acute cocaine toxicity. Open Pharmacol J. 2008;2:70.

9. Howell LL, Kimmel HL. Monoamine transporters and psychostimulant addiction. Biochem Pharmacol. 2008;75(1):196–217.
10. Castlla-Ortega E, Ladron de Guevara-Miranda D, Serrano A, Pavon JF, Suarez J, Rodriguez de Fonseca F, Santin LJ. The impact of cocaine on adult hippocampal neurogenesis: potential neurological mechanisms and contributions to maladaptive cognition in cocaine addiction disorder. Biochem Pharmacol. 2017;141:100–17.
11. Castilla-Ortega E, Petraza C, Estivill-Torrus G, Santin LJ. When is adult hippocampal neurogenesis necessary for learning? Evidence from animal research. Rev Neurosci. 2011;22:267–83.
12. O'Dell LE, George FR, Ritz MC. Antidepressant drugs appear to enhance cocaine-induced toxicity. Exp Clin Psychopharmacol [Internet]. 2000 [cited 2018 Nov 18];8(1):133–41. Available from http://www.ncbi.nlm.nih.gov/pubmed/10743914
13. Vilke GM, DeBard ML, Chan TC, Ho JD, Dawes DM, Hall C, Curtis MD, Costello MW, Mash DC, Coffman SR, McMullen MJ, Metzger JC, Roberts JR, Sztajnkrcer MD, Henderson SO, Adler J, Czarnecki F, Heck J, Bozeman WP. Excited delirium syndrome (ExDS): defining based on a review of the literature. J Emerg Med. 2012;43:897–905.
14. Ben HS, Plute E, Cosquer B, Kelche C, Jones BC, Cassel J-C. Interactions between ethanol and cocaine, amphetamine, or MDMA in the rat: thermoregulatory and locomotor effects. Psychopharmacology. 2008; 197(1):67–82.
15. Matsumoto RR, Hewett KL, Pouw B, Bowen WD, Husbands SM, Cao JJ, et al. Rimcazole analogs attenuate the convulsive effects of cocaine: correlation with binding to sigma receptors rather than dopamine transporters. Neuropharmacology. 2001;41(7):878–86.
16. Heard K, Cleveland NR, Krier S. Benzodiazepines and antipsychotic medications for treatment of acute cocaine toxicity in animal models- a systematic review and meta-analysis. Hum Exp Toxicol. 2011; 30:1849–54.
17. Boutros NN, Lisanby SH, McClain-Furmanski D, Oliwa G, Gooding D, Kosten TR. Cortical excitability in cocaine-dependent patients: a replication and extension of TMS findings. J Psychiatr Res. 2005;39(3):295–302.
18. Hanlon CA, DeVreis W, Dowdie LT, West JA, Siekman B, Li X, George MS. A comprehensive study of sensorimotorcortex excitability in chronic cocaine users: integrating TMS and functional MRI data. Drug Alcohol Depend. 2015;157:28–35.
19. Hanlon CA, Dowdle LT, Scott Henderson J. Modulating neuronal circuits with transcranial magnetic stimulation: implication for addiction treatment development. Pharmacol Rev. 2018;70:661–83.
20. Garza-Villarreal EA, Chakravarty MM, Hansen B, Eskildsen SF, Devenyi GA, Castillo-Padilla D, et al. The effect of crack cocaine addiction and age on the microstructure and morphology of the human striatum and thalamus using shape analysis and fast diffusion kurtosis imaging. Transl Psychiatry. 2017;7(5):e1122.
21. Volkow ND, Koob GF, McLellan AT. Neurobiologic advances from the brain disease model of addiction. Longo DL, editor. N Engl J Med. 2016;374(4):363–71.
22. Stankowski RV, Kloner RA, Rezkalla SH. Cardiovascular consequence of cocaine use. Trends Cardiovasc Med. 2015;25:517–26.
23. Phillips K, Luk A, Soor GS, Abranam JR, Leong S, Butany J. Cocaine cardiotoxicity: a review of the pathophysiology, pathology, and treatment options. Am J Cardiovasc Drugs. 2009;9:177–96.
24. Mittleman RE, Wetli CV. Death caused by recreational cocaine use. An update. JAMA. 1984;252:1889–93.
25. O'Leary ME, Chahine M. Cocaine binds to a common site on open and inactivated human heart (Nav 1.5) sodium channels. J Physiol. 2002;541:701–16.
26. Lange RA, Cigarroa RG, Yancy CW, Willard JE, Popma JJ, Sills MN, et al. Cocaine-induced coronary-artery vasoconstriction. N Engl J Med. 1989; 321(23):1557–62.
27. Graziani M, Antonilli L, Togna AR, Grassi MC, Badiani A, Saso L. Cardiovascular and hepatic toxicity of cocaine: potential beneficial effects of modulators of oxidative stress. Oxidative Med Cell Longev. 2016;2016:8408479.
28. Goldstein RA, DesLauriers C, Burda A, Johnson-Arbor K. Cocaine: history, social implications, and toxicity: a review. Semin Diagn Pathol. 2009;26(1):10–7.
29. Gan X, Zhang L, Berger O, Stins MF, Way D, Taub DD, et al. Cocaine enhances brain endothelial adhesion molecules and leukocyte migration. Clin Immunol. 1999;91(1):68–76.
30. Moliterno DJ, Lange RA, Gerard RD, Willard JE, Lackner C, Hillis LD. Influence of intranasal cocaine on plasma constituents associated with endogenous thrombosis and thrombolysis. Am J Med. 1994; 96(6):492–6.
31. Laizure SC, Mandrell T, Gades NM, Parker RB. Cocaethylene metabolism and interaction with cocaine and ethanol: role of carboxylesterases. Drug Metab Dispos. 2003;31(1):16–20.
32. Spagnolo PA, Goldman D. Neuromodulation interventions for addictive disorders: challenges, promise, and roadmap for future research. Brain. 2017;140(5):1183–203.
33. Bett WR. Benzedrine sulphate in clinical medicine; a survey of the literature. Postgrad Med J. 1946; 22:205–18.
34. Di Chiara G, Bassareo V, Fenu S, De Luca MA, Spina L, Cadoni C, Acquas E, Carboni E, Valentini V, Lecca D. Dopamine and drug addiction: the nucleus accumbens shell connection. Neuropharmacology. 2004;47(Suppl 1):227–41.
35. Johnson RA, Eshleman AJ, Meyers T, Neve KA, Janowsky A. [3H]substrate- and cell-specific effects of uptake inhibitors on human dopamine and serotonin transporter-mediated efflux. Synapse. 1998;30(1):97–106.

36. JPifl C, Drobny H, Reither H, Hornykiewicz O, Singer EA. Mechanism of the dopamine-releasing actions of amphetamine and cocaine: plasmalemmal dopamine transporter versus vesicular monoamine transporter. Mol Pharmacol. 1995;47(2):368–73.
37. Fleckenstein AE, Volz TJ, Riddle EL, Gibb JW, Hanson GR. New insights into the mechanism of action of amphetamines. Annu Rev Pharmacol Toxicol. 2007;47:681–98.
38. Mantle TJ, Tipton KF, Garrett NJ. Inhibition of monoamine oxidase by amphetamine and related compounds. Biochem Pharmacol. 1976;25(18):2073–7.
39. Dolder PC, Strajhar P, Vizeli P, Hammann F, Odermatt A, Liechti ME. Pharmacokinetics and pharmacodynamics of lisdexamfetamine compared with D-amphetamine in healthy subjects. Front Pharmacol. 2017;8:617.
40. Hysek CM, Simmler LD, Nicola VG, Vischer N, Donzelli M, Krähenbühl S, et al. Duloxetine inhibits effects of MDMA ("ecstasy") in vitro and in humans in a randomized placebo-controlled laboratory study. Laks J, editor. PLoS One. 2012;7(5):e36476.
41. Harro J. Neuropsychiatric adverse effects of amphetamine and methamphetamine. Int Rev Neurobiol. 2015;120:179–204.
42. Mash DC, Duque L, Pablo J, Qin Y, Adi N, Hearn WL, et al. Brain biomarkers for identifying excited delirium as a cause of sudden death. Forensic Sci Int. 2009;190(1–3):e13–9.
43. Miner NB, Elmore JS, Baumann MH, Phillips TJ, Janowsky A. Trace amine-associated receptor 1 regulation of methamphetamine-induced neurotoxicity. Neurotoxicology. 2017;63:57–69.
44. Bonsignore A, Barranco R, Morando A, Fraternali Orciopni G, Ventura F. MDMA induced cardio-toxicity and pathological myocardial effects: a systematic review of experimental data and autopsy findings. Cardiovasc Toxicol. 2019;19:493.
45. Fitzgerald KT, Bronstein AC. Adderall® (amphetamine-dextroamphetamine) toxicity. Top Companion Anim Med. 2013;28(1):2–7.
46. Simmler LD, Hysek CM, Liechti ME. Sex differences in the effects of MDMA (ecstasy) on plasma copeptin in healthy subjects. J Clin Endocrinol Metab. 2011;96(9):2844–50.
47. Liechti ME. Effects of MDMA on body temperature in humans. Temperature. 2014;1(3):192–200.
48. Páleníček T, Lhotková E, Žídková M, Balíková M, Kuchař M, Himl M, et al. Emerging toxicity of 5,6-methylenedioxy-2-aminoindane (MDAI): pharmacokinetics, behaviour, thermoregulation and LD50 in rats. Prog Neuro-Psychopharmacol Biol Psychiatry. 2016;69:49–59.
49. European Drug Report 2016: trends and developments. www.emcdda.europa.eu
50. Lucas CJ, Galettis P, Schneider J. The pharmacokinetics and the pharmacodynamics of cannabinoids. Br J Clin Pharmacol. 2018;84(11):2477–82.
51. Rickner SS, Cao D, Kleinschmidt K, Fleming S. A little "dab" will do ya' in: a case report of neuro- and cardiotoxicity following use of cannabis concentrates. Clin Toxicol. 2017;55(9):1011–3.
52. Raber JC, Elzinga S, Kaplan C. Understanding dabs: contamination concerns of cannabis concentrates and cannabinoid transfer during the act of dabbing. J Toxicol Sci. 2015;40(6):797–803.
53. Cappelli F, Lazzeri C, Gensini GF, Valente S. Cannabis: a trigger for acute myocardial infarction? A case report. J Cardiovasc Med. 2008;9(7):725–8.
54. Patel RS, Katta SR, Patel R, Ravat V, Gudipalli R, Patel V, et al. Cannabis use disorder in young adults with acute myocardial infarction: trend inpatient study from 2010 to 2014 in the United States. Cureus. 2018;10(8):e3241.
55. Bloomfield MAP, Ashok AH, Volkow ND, Howes OD. The effects of Δ9-tetrahydrocannabinol on the dopamine system. Nature. 2016;539(7629):369–77.
56. Sawaguchi T, Goldman-Rakic PS. D1 dopamine receptors in prefrontal cortex: involvement in working memory. Science. 1991;251(4996):947–50.

New Drugs of Abuse and Cardiovascular Function

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Carlo Alessandro Locatelli, Davide Lonati, and Valeria Margherita Petrolini

Contents

Abstract

Over the past decade, several new chemical compounds (the so-called NPS, new or novel psychoactive substances) have been synthesized and placed on the abuse market. About a thousand agents are known and monitored by supranational and national agencies because they cause new intoxication, prolonged health adverse effects, and addiction. Synthetic cannabinoids, cathinones, ketamines, new phenethylamines, and other molecules are today readily available at low cost. The high potency of these compounds, the important effects on the cardiovascular and central nervous systems, the still little knowledge about the prolonged health consequences, together with the hope to identify contrastable mechanisms of toxicity, have conquered

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*,
https://doi.org/10.1007/978-3-030-28008-6_55

the scene of the scientific research on substances of abuse in the recent years. Clinically, the cardiotoxicity appears to be similar for the majority of NPS, with the prevalence of sympathomimetic and excitatory cardiovascular signs and symptoms. The mortality in the acute phase of intoxication, however, seems to be related not only to cardiac accidents, but in several cases, also to impairment of several organs/systems (multiorgan failure). The long-term consequences for the cardiovascular system, in addition, are not yet known. More in-depth mechanistic studies, still scarcely available today, will contribute in the future to a better therapeutic approach in the emergency setting.

Keywords

Cardiac toxicity · vascular toxicity · NPS · New psychoactive substances · Novel psychoactive substances · Synthetic cannabinoids · Synthetic cathinones · Ketamine · Phenethylamines · NBOMe · Tryptamines

Introduction

Recreational drug use is common worldwide, and the wide range of newer illicit drugs is today a challenge to physicians. Over the last decades, there has been a frenetic rush to the synthesis and marketing of new chemical agents that can be used as substitutes of the old/classic psychoactive drugs of abuse (e.g., cocaine, marijuana, heroin, amphetamines). These designer drugs are developed to provide rewarding effects similar to the old and illicit drugs of abuse, while circumventing existing legislative classification and penalty [1, 2]. These compounds are generally called "novel" or "new" or "newer" psychoactive substances (NPS) and sometimes referred to as "legal highs". The NPS are defined as "substances of abuse that are not controlled by the 1961 Single Convention on Narcotic Drugs or the 1971 Convention on Psychotropic Substances, but which may pose a public health threat" [3]. The term "new" does not necessarily refer to new inventions – several NPS were first synthesized decades ago for research or medicinal purposes in academia or in the pharmaceutical industry – but to substances that have recently become available on the web market, repurposed as drugs of abuse. The facts that the number of NPS has more than quintupled over the last 10 years is a critical challenge to governments, the scientific community, and civil society [4].

The NPS include both medicine substitutes that can be bought without a medical prescription, and recreational drugs that are sold freely, without any administrative or criminal consequences. The global trade in these compounds, often synthesized in hidden laboratories in a single country, is possible worldwide through Internet providers. Searching the Internet for these "designer drugs," "legal highs," "bath salts," "spice," "incense," and "research chemicals" today allows to easily buy hundreds of different agents at low cost, very powerful, with a good degree of purity and low contaminants [5, 6].

Together with the central nervous system (CNS) and other organs, all the potent NPS can affect the cardiovascular system [7, 8]. Both the short- and long-term effects of the NPS on the cardiovascular system can be expected to be the result of increased levels of neurotransmitters such as dopamine, serotonin, adrenaline, noradrenaline, histamine, and possibly other molecules, such as glutamate and endogenous opioids. Similarly to the psychotropic medications, the consequent and predominant clinical effects on the cardiovascular system are tachycardia, hypertension, myocardial ischemia, QT-interval prolongation, serious arrhythmias, and sudden death. Added effects of amphetamines-like NPS on the heart probably relate to disorders in cellular calcium signaling, with resultant dysregulation of myocyte function. Moreover, in vitro studies on human cardiomyocytes indicate that tachycardia in patients exposed to recreational drugs (comprehending MDMA, 4-fluoroamphetamine, α-PVP and MDPV) is likely due to indirect drug effects, while prolonged repolarization periods (prolonged QT-interval) could (partly) result from direct drug effects on cardiomyocyte function [9]. QT prolongation was also demonstrated in rats for the synthetic cannabinoid JWH-030 [10].

A general hazard for NPS users is the lack of awareness of consumption: in some cases, they consume a very different substance or a different "dose" from those they intended to take. As a result, the clinical effects can vary widely between patients, even if they report using the same NPS, and the risks of accidental overdoses and cardiotoxic effects are significantly increased. The polydrug abuse is also extremely common: alcohol, tobacco, and marijuana are frequently taken together with one or more NPS, with interactions that can be complex, unpredictable and that can increase the risk of cardiotoxicity.

This chapter attempts to summarize the cardiovascular complications associated with the major recreational drugs in use today, considering the relationships between the main families of NPS and the reported cardiotoxicity in medical literature. The reported cardiotoxic effects are based chiefly on the clinical evidences: some results from in vivo and in vitro studies related to the mechanistic aspects of neuro- and cardiotoxicity are however reported, even if experimental and preclinical studies are still scarce and not yet conclusive. An up-to-date guidance on aspects of current management is also reported.

Epidemiology

NPS have become a global phenomenon, with 119 countries and territories from all regions of the world having reported one or more NPS. Up to December 2018, 888 substances have been reported to the UNODC Early Warning Advisory (EWA) on NPS by Governments, laboratories, and partner organizations [3]. At the beginning of 2020, the number of NPS available on the online market and surveyed by UNODC, EMCDDA, and NIDA organizations accounts approximately 1.050 highly potent and toxic compounds belonging to different chemical families.

NPS can be classified based on their chemical structure (synthetic cannabinoids, synthetic cathinones, ketamines, new phenethylamines, piperazines, tryptamines, synthetic opioids, etc.), mechanism of action and effects (stimulants, hallucinogenic, anesthetic, dissociative, depressant, entactogen, etc.) (Table 1). Considering the number of the seized NPS, the EMCDDA attributes to the synthetic cannabinoid receptor agonists (SCs) approximately the 15–51% of the availability on the market, the 24–33% to the synthetic cathinones, and the 17% to the new phenethylamines [11]. Moreover, looking at the clinical effects that have been reported until December 2019 for NPS, the

Table 1 Summary of the toxic effects of the treated groups of New Psychoactive Substances (NPS)

Chemical class	Principal mechanism of toxicity	Major toxic effects
Synthetic cannabinoids	CB1 and CB2 receptors agonists displaying higher affinity, efficacy and potency compared to 19-THC	Euphoria, anxiolytic, and antidepressant-like effects, paranoia, tachycardia, panic, convulsions, psychosis, visual/auditory hallucinations, vomiting, and seizures
Synthetic cathinones	Sympathomimetic drugs that act on serotonin, dopamine, and noradreline pathways	Agitation, restlessness, vertigo, abdominal pain, paranoia, rhabdomyolysis, convulsions, and death
Arylcyclohexylamines	Dissociative anesthetics that act as 5HT2A agonist and NMDA receptor antagonist and show high affinity for opioid receptors	Distort perceptions of sight and sound, dissociation from the environment and self without hallucinations
Phenethylamines	Serotoninergic receptor agonists that cause psychedelic effects and inhibit monoamine reuptake	Hypertension, vomiting, hyperthermia, convulsions, dissociation, hallucinations, respiratory deficits, liver and kidney failure, and death in case of overdose
Piperazines	Stimulants that promote the release of dopamine and noradrenaline and inhibit the uptake of monoamines	Hyperthermia, convulsions, and kidney failure; hallucinations and death have been reported at high doses
Tryptamines	5HT2A receptor agonists and serotonin reuptake inhibitors	Visual hallucinations, alterations in sensory perception, depersonalization

majority are due to stimulants (36%), followed by synthetic cannabinoid receptor agonists (30%), hallucinogens (15%), opioids (7%), sedative/hypnotics (3%), dissociatives (3%) [11].

The case series relating to NPS intoxications provide data that are not always easily comparable. With respect to age, for example, the case series are generally little and homogeneous when referred to single substance users or to patients recruited in a single emergency department (ED). Larger case series, such as that of the NPS intoxications collected by the Pavia Poison Center in Italy in a 10-year period (2010–2019) (Fig. 1), show that young patients aged between 14 and 24 represent about half of the cases, whereas the other half concern patients between 25 and 60 years old; only a small percentage is represented by preteens and teenagers between 10 and 13 years old. Although most of these patients were discharged after few hours from the ED, approximately the 25% needed hospital admission, intensive care monitoring, and treatment; similar percentage is reported in USA [12].

The number of NPS-related severe poisoning reported has grown parallel to the increasing number of new synthetized agents. Several outbreaks verified in USA and EU [13, 14], with approximately 15% of cases admitted to intensive care units and some fatal cases.

The challenge to find out a pattern of intoxication and a compound-related risk, as well as specific treatment, it is a difficult task due to the different diffusion across EU/USA, and the highly dynamic market. Moreover, only few people are aware of the specific substance that they have taken, and even rarer is the awareness of the potential side effects. Moreover, NPS intoxications are also often associated with the intake of the "oldest" drugs of abuse (such as THC, alcohol, cocaine, methamphetamine, MDMA). NPS are often supplied in a mixture of several agents, and frequently it is impossible to say which one on the market is the most powerful and most cardiotoxic.

From a medical point of view, the challenge is to detect specific or usual pattern of clinical presentation that may be related to NPS use and treat the symptoms taking into account the increased risk of particular feature and of potentially dangerous medicines. Moreover, clinicians should take part to the early warning activities, reporting the event and performing laboratory test aiming to detect the NPS-related intoxications.

This chapter mainly focuses on the cardiotoxicity aspects of NPS groups representing

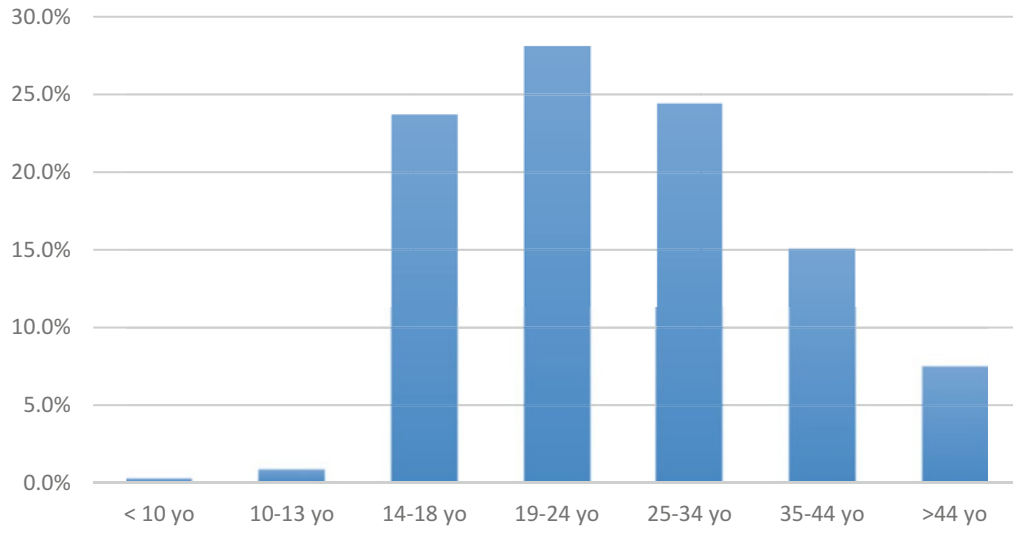

Fig. 1 Age distribution of 1.601 cases of NPS intoxications admitted to Italian Hospitals in a 10-year period (2010–2019) and reported to the Italian National Early Warning System for Drugs of Abuse

major clinical problems in the emergency setting, trying to highlight their clinical features, and, if elucidated, the toxicodynamic correlates. The groups of NPS treated in this chapter are the synthetic cannabinoids (Table 2), synthetic cathinones (Table 3), arylcyclohexylamines (Table 4), new psychostimulants (comprehending the subgroups of phenethylamines/amphetamines, piperazines, aminoindanes, benzofurans, piperidines/pyrrolidines) (Table 5), new predominant hallucinogens phenethylamines (Table 6), and synthetic tryptamines (Table 7). Other NPS (not included in this chapter as not "new" or not expressively cardiotoxic) are the new synthetic opioids (fentanils and others), plant-based substances (e.g., *Mitragyna speciosa*, S*alvia divinorum*, *Catha edulis*), and other substances (e.g., 1,3-dimethylamylamine, DMAA) [11]. Greater attention is given to cardiovascular damage due to synthetic cannabinoids, because for this group of compounds the cardiovascular damage is less easily known and understood compared to that of other groups of NPS. The most common management and therapeutic approaches are also reported.

Synthetic Cannabinoids/Synthetic Cannabinoids Receptor Agonists/CB1r "Super Agonists"

Synthetic cannabinoids (SCs) or synthetic cannabinoids receptor agonists (SCRA) began to appear as drugs of abuse in Europe around the mid-2000s, initially as products commonly called "spice." It was not until 2008 that researchers discovered that the smoked plant material was laced with SCs, such as JWH-018 and HU-210 [15]. Since that time, their market has grown continuously [16], and SCs represent today the largest group (45%) of NPS monitored by the European Monitoring Centre for Drugs and Drug Addiction (Table 2) [11].

SCs containing products are typically sold as smoking herbal mixtures in metal-foil sachets. Chemicals are mixed with or after dissolving in acetone, ethanol, or methanol sprayed onto pharmacologically inactive vegetable herbs such as Mellissa, Mentha, Thymus, and Damiana. The herbal material is then dried, packaged, and sold in smart shops or on the Internet in various forms, with fancy and catchy names. Less commonly, they are sold as bulk powders of high purity, or as liquid formulations for vaporization in electronic cigarettes [17]. The ingredients listed on the package are generally incomplete or false and, moreover, constituents of these products change rapidly in response to legislative controls, with little consistency between products [18]. Most products contain several SCs in a single preparation, thereby increasing a risk of overdose and acute intoxication. Further ingredients include β2-mimetic substances, which may be responsible for the sympathomimetic manifestations of "spice" intoxication (tachycardia, hypokalemia), and large amounts of tocopherol (vitamin E), possibly added in order to prevent detection [17]. The SCs that have become available in recent years (e.g., MDMB-CHMICA that appeared on the EU drug market in September 2014) are more powerful and more toxic than those initially placed on the market as synthetic cannabinoid. Outbreaks due to SCs are relatively frequent: 721 cases (11 deaths) were, for example, reported statewide [19].

Consumers of SCs often erroneously consider taking natural products similar to cannabis, as they certainly mimic in part the effects of Δ^9-tetrahydrocannabinol (delta-9-THC, Δ^9-THC, THC), a partial CB1 receptor (CB1r) agonist that is the main psychoactive constituent of cannabis [20]. However, these synthetic compounds are very powerful and toxic, with effects that are different, greater from those of cannabis, and more prolonged. SCs belong to at least 14 chemically diverse families that have structures unrelated to THC and different metabolic pathways with biotransformation to active metabolites able to interact with different type of receptors [16, 21–23]. In fact, in vitro studies have clearly demonstrated that SCs compounds are CB1r full agonists with higher potency as compared to THC [24]. Moreover, the affinity of JWH-018 for the CB1 receptor is five times as high as that of THC, while that of AM-694 is 500 times as high [17].

SCs exert a clinical THC-like effect, with alterations of mood, perception, sleep and

Table 2 Common and chemical name of representative compounds of NPS of the chemical group of SCs (nonexhaustive list)

Chemical group	*Common name*	*Chemical name*
Naphtoylindoles	JWH-018	Naphthalen-1-yl-(1-pentylindol-3-yl)methanone
	JWH-073	(1-butyl-1H-indol-3-yl)(naphthalen-1-yl)methanone
	JWH-022	1-naphthyl-(1-pent-4-enylindol-3-yl)methanone
	JWH-081	(4-methoxy-1-naphthyl)-(1-pentylindol-3-yl)methanone
	JWH-200	[1- [2- (4- morpholinyl) ethyl] – 1H- indol-3- yl] – 1- naphthalenyl-methanone
	JWH-122	(4-methyl-1-naphthyl)-(1-pentylindol-3-yl)methanone
	JWH-210	(4-ethyl-1-naphthyl)-(1-pentylindol-3-yl)methanone
	WIN-55212-2	[(3R) – 2, 3- dihydro- 5- methyl- 3- (4-morpholinylmethyl) pyrrolo[1, 2, 3- de] -1, 4- benzoxazin- 6- yl] – 1- naphthalenylmethanone
	AM-2201	[1-(5-fluoropentyl)-1H-indol-3-yl](naphthalen-1-yl)methanone
	MAM-2201	[1-(5-fluoropentyl)indol-3-yl]-(4-methyl-1-naphthyl)methanone
	UR-144	(1-pentylindol-3-yl)-(2,2,3,3-tetramethylcyclopropyl)methanone
Phenylacethylindoles	JWH-250	2-(2-methoxyphenyl)-1-(1-pentyl-1Hindol-3-yl)ethanone
	JWH-251	2-(o-tolyl)-1-(1-pentylindol-3-yl)ethanone
	JWH-203	2-(2-chlorophenyl)-1-(1-pentyl-1Hindol-3-yl)ethanone
Benzoylindoles	WIN-48,098	
	AM-694	[1-(5-fluoropentyl)-1H-indol-3-yl](2-iodophenyl)methanone
Cyclohexylphenols	CP 47497	5-(1,1-Dimethylheptyl)-2-[(1R,3S)-3-hydroxycyclohexyl]-phenol
	HU-210	(6aR,10aR)-3-(1,1-dimethylheptyl)-9-(hydroxymethyl)-6,6-dimethyl-6a,7,10,10atetrahydrobenzo[c]chromen-1-ol
Indole and indazole	AB-PINACA	*N*-(1-amino-3-methyl-1-oxobutan-2-yl)-1-pentyl-1H-indazole-3-carboxamide
	ADB-PINACA	*N*-(1-amino-3,3-dimethyl-1-oxobutan-2-yl)-1-pentyl-1H-indazole-3-carboxamide
	5F-AB-PINACA	*N*-(1-carbamoyl-2-methyl-propyl)-1-(5-fluoropentyl)indazole-3-carboxamide
	5F-ADB-PINACA	*N*-(1-amino-3,3-dimethyl-1-oxobutan-2-yl)-1-(5-fluoropentyl)-1H-indazole-3-carboxamide
	AB-FUBINACA	*N*-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(4-fluorobenzyl)-1H-indazole-3-carboxamide
	ADB-FUBINACA	*N*-(1-carbamoyl-2,2-dimethylpropyl)-1-[(4-fluorophenyl)methyl]indazole-3-carboxamide
	ADBICA	*N*-(1-amino-3,3-dimethyl-1-oxobutan-2-yl)-1-pentyl-1H-indole-3-carboxamide
	5F-ADBICA	*N*-(1-amino-3,3-dimethyl-1-oxobutan-2-yl)-1-(5-fluoropentyl)-1H-indole-3-carboxamide
	BB-22	8-Quinolinyl 1-(cyclohexylmethyl)-1Hindole-3-carboxylate
	5F-PB-22 (AM-2201 carboxylate analogue quinolinyl derivative)	1- (5- fluoropentyl) – 1H- indole- 3-carboxylic acid 8- quinolinyl ester
	AB-CHMINACA	*N*-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-1H-indazole-3-carboxamide
	AMB-CHMICA	Methyl 2-[[1-(cyclohexylmethyl)indole-3-carbonyl]amino]-3-methyl-butanoate

Table 3 Common and chemical name of representative compounds of psychostimulant NPS of the chemical group of synthetic cathinones (nonexhaustive list)

Chemical group	*Common name*	*Chemical name*
Synthetic cathinones/β-keto (βk) amphetamines	4-MMC	(RS)-1-(4-methylphenyl)-2-methylaminopropan-1-one
	4-EMC	1-(4-ethylphenyl)-2-(methylamino) propan-1-one
	3,4-DMMC	1-(3,4-dimethylphenyl)-2-(methylamino) propan-1-one
	Pentedrone	2-(methylamino)-1-phenylpentan-1-one
	Mephedrone	2-(methylamino)-1-phenylpentan-1-one
	Methylone (bk-MDMA)	1-(1,3-benzodioxol-5-yl)-2-(methylamino)propan-1-one
	MDPV 3,4-Methylenedioxypyrovalerone	1-(1,3-benzodioxol-5-yl)-2-pyrrolidin-1-ylpentan-1-one
	α-PVP	1-phenyl-2-pyrrolidin-1-ylpentan-1-one
	bk-PMMA	1-(4-methoxyphenyl)-2-(methylamino) propan-1-one
	α-PHiP	4-methyl-1-phenyl-2-pyrrolidin-1-yl-pentan-1-one
	3-MEC	2-(ethylamino)-1-(3-methylphenyl) propan-1-one
	Ephylone	1-(1,3-benzodioxol-5-yl)-2-(ethylamino) pentan-1-one
	N-Ethylheptedrone	2-(ethylamino)-1-phenylheptan-1-one
	4-Fluoropentedrone	1-(4-fluorophenyl)-2-(methylamino) pentan-1-one
	N-Butylpentylone	1-(1,3-benzodioxol-5-yl)-2-(butylamino) pentan-1-one
	2-MEC	2-(ethylamino)-1-(2-methylphenyl) propan-1-one
	2-Fluoromethcathinone (2-FMC)	1-(2-fluorophenyl)-2-(methylamino) propan-1-one
	bk-2C-B	2-amino-1-(4-bromo-2,5-dimethoxyphenyl)ethanone
	2,4-DMEC	1-(2,4-dimethylphenyl)-2-(ethylamino) propan-1-one
	Naphyrone	1-(2-Naphthalenyl)-2-(1-pyrrolidinyl)-1-pentanone
	Pentylone	1-(1,3-benzodioxol-5-yl)-2-(methylamino)pentan-1-one
	MDPHP	1-(1,3-benzodioxol-5-yl)-2-(pyrrolidin-1-yl)hexan-1-one
	3-Methylmethcathinone (3-MMC)	2-(methylamino)-1-(3-methylphenyl) propan-1-one
	4-MeO-alpha-PVP	1-(4-methoxyphenyl)-2-(pyrrolidin-1-yl) pentan-1-one
	Mexedrone	3-methoxy-2-(methylamino)-1-(4-methylphenyl)propan-1-one
	4-Fluorocathinone	2-amino-1-(4-fluorophenyl)propan-1-one
	4F-Buphedrone	1-(4-fluorophenyl)-2-(methylamino) butan-1-one

(continued)

Table 3 (continued)

Chemical group	*Common name*	*Chemical name*
	Flephedrone (4-FMC)	1-(4-fluorophenyl)-2-(methylamino) propan-1-one
	Butylone (bk-MBDB)	1-(1,3-benzodioxol-5-yl)-2-(methylamino)butan-1-one
	Buphedrone	2-(methylamino)-1-phenylbutan-1-one
	3F-α-PVP	1-(3-fluorophenyl)-2-(pyrrolidin-1-yl) pentan-1-one
	4F-α-PHiP	1-(4-fluorophenyl)-4-methyl-2-pyrrolidin-1-yl-pentan-1-one
	4-Fluoroethcathinone (4-FEC)	2-(ethylamino)-1-(4-fluorophenyl) propan-1-one
	4-Ethylethcathinone (4-EEC)	2-(ethylamino)-1-(4-ethylphenyl)propan-1-one

Table 4 Common and chemical name of representative compounds of dissociative NPS of the chemical group of arylcyclohexylamines (nonexhaustive list)

Chemical group	*Common name*	*Chemical name*
ketamine	keta	2-(2-chlorophenyl)-2-(methylamino)cyclohexanone
	MXE, Methoxetamine	2-(ethylamino)-2-(3-methoxyphenyl)cyclohexanone
	Deschloroketamine	2-(methylamino)-2-phenylcyclohexanone
	Methoxpropamine	2-(3-methoxyphenyl)-2-(propylamino)cyclohexan-1-one
	Deschloroketamine	2-(methylamino)-2-phenylcyclohexanone
	3-MeO-PCP	1-[1-(3-methoxyphenyl)cyclohexyl]piperidine
	4-MeO-PCP	1-[1-(4-methoxyphenyl)cyclohexyl]piperidine
	3-MeO-PCE	*N*-ethyl-1-(3-methoxyphenyl)cyclohexanamine
	2-fluorodeschloroketamine	2-(2-fluorophenyl)-2-methylamino-cyclohexanone

wakefulness, body temperature, and cardiovascular function. Their unwanted side effects, such as insomnia, memory impairment, headaches, dizziness, delusions, are more varied and more severe than those of THC.

The acute toxicity of SCs is not yet well defined, and clinical experiences confirm that acute toxic effects mimic sometimes those of cocaine more than those of cannabis, including neuro-excitatory manifestations up to convulsions and serious cardiotoxic effects [25, 26]. CNS and cardiovascular toxic signs and symptoms are present in approximately the 40–45% and 30–35% of cases, respectively. Clinical effects are frequently unpredictable due to the variety of SC, inconsistent dosing, and variable potency of individual compound.

The EDs presentation of SCs-intoxicated patients may include nausea, vomiting, hyperemesis, excessive sweating, anxiety, agitation, irritability, paranoia, hallucinations, delirium and toxic psychosis, aggressive and violent behavior, cognitive deficits, memory loss, catatonia, seizures, coma or central nervous system depression, central respiratory depression, hyperthermia, rhabdomyolysis liver toxicity, and/or acute kidney failure [27–30]. SCs are usually undetectable on conventional toxicology testing in the hospital's emergency settings.

Signs and symptoms of cardiovascular toxicity include arrhythmias (bradycardia or tachycardia), hypotension or hypertension, atrial fibrillation, prolonged QT-interval, Mobitz type II atrioventricular block, ventricular fibrillation, cardiogenic shock, myocardial infarction, and/or cardiac arrest, subarachnoid hemorrhage, ischemic stroke [31–33]. Tachycardia was reported in 76% of 33 SCs-intoxicated patients in Italy [34]. In a case

Table 5 Representative compounds of NPS with predominant psychostimulants effects belonging the chemical groups of the new phenethylamines/amphetamines, piperazines, aminoindanes, bonzofurans, and piperidine/pyrrolidines (nonexhaustive list)

Chemical group	*Common name*	*Chemical name*
New amphetamine derivatives	PMMA	1-(4-methoxyphenyl)-*N*-methylpropan-2-amine
	PMA	1-(4-methoxyphenyl)propan-2-amine
	4-FMA	1-(4-fluorophenyl)-*N*-methylpropan-2-amine
	4-CA	1-(4-chlorophenyl)propan-2-amine
	2-FA	1-(2-fluorophenyl)propan-2-amine
	2-FMA	1-(2-fluorophenyl)-*N*-methylpropan-2-amine
	2-PEA	2-phenylethanamine
	DMMA	2-(3,4-dimethoxyphenyl)-Nmethylpropan-2-amine
	DMA	*N*,*N*-dimethyl-1-phenylpropan-2-amine
	beta-Me-PEA2	2-phenylpropan-1-amine
	phenpromethamine	*N*-methyl-2-phenylpropan-1-amine
piperazines	BZP	1-benzylpiperazine
	DBZP	1,4-dibenzylpiperazine
	pCPP	1-(4-chlorophenyl)-piperazine
	mCPP	1-(3-chlorophenyl)-piperazine
	2C-B-BZP	1-[(4-bromo-2,5-dimethoxyphenyl)methyl] piperazine
	TFMPP	1-(3-trifluoromethylphenyl)-piperazine
	pMeOPP	1-(4-methoxyphenyl)piperazine
	pFPP	1-(4-fluorophenyl)piperazine
Aminoindanes	1-Aminoindan	2,3-dihydro-1H-inden-1-amine
	2-Aminoindan	2,3-dihydro-1H-inden-2-amine
	5-IAI	5-iodo-2,3-dihydro-1H-inden-2-amine
	MDAI	6,7-dihydro-5H-indeno[5,6-d][1,3]dioxol-6-amine
	MMDAI	5,6-Methylenedioxy-*N*-methyl-2-aminoindane
	MDAT	6,7- Methylenedioxy-2-aminotetralin
	N-methyl-2AI	*N*-methyl-2,3-dihydro-1H-inden-2-amine
Benzofurans and benzodifurans or arylalkylamines	5-APB	5-(2-aminopropyl)benzofuran
	5-APDB	1-(2,3-dihydro-1-benzofuran-5-yl)propan-2-amine
	5-MAPB	1-(benzofuran-5-yl)-*N*-methylpropan-2-amine
	6-APB	6-(2-aminopropyl)benzofuran
	6-APDB	1-(2,3-dihydro-1-benzofuran-6-yl)propan-2-amine
	Bromo-Dragonfly	1-(4-bromofuro[2,3-f]benzofuran-8-yl)propan-2-amine
	2C-B-Fly	2-(8-bromo-2,3,6,7-tetrahydrofuro[2,3-f][1] benzofuran-4-yl)ethanamine
Piperidines/pyrrolidines	2-DPMP	2-(Diphenylmethyl)piperidine
	Desoxy-D2PM	2-(Diphenylmethyl)pirrolidine
	Ethylphenidate	Ethyl phenyl(piperidin-2-yl)acetate
	Isopropylphenidate	Propan-2-yl phenyl(piperidin-2-yl)acetate
	4-F-Methylpenidate (4F-MPH)	Methyl (4-fluorophenyl)(piperidin-2-yl)acetate

Table 6 Representative compounds of predominant hallucinogen NPS belonging the agents-substituted phenethylamines subgroups (nonexhaustive list)

Chemical group	*Common name*	*Chemical name*
2C agents-substituted	2C-T-2	2-[4-(ethylsulfanyl)-2,5-dimethoxyphenyl]ethanamine
	2C-P	2,5-dimethoxy-4-propyl-benzeneethanamine
	2C-I	2-(4-iodo-2,5-dimethoxyphenyl)ethanamine
	4C-D	1-(2,5-dimethoxy-4-methylphenyl)butan-2-amine
	2C-D	2-(2,5-dimethoxy-4-methylphenyl)ethanamine
	2C-H	2,5-Dimethoxyphenethylamine
	2C-B	4-Bromo-2,5-dimethoxyphenethylamine
	2C-E	2,5-Dimethoxy-4-ethylphenethylamine
	2C-N	2,5-Dimethoxy-4-nitrophenethylamine
	2C-G	2-(2,5-Dimethoxy-3,4-dimethylphenyl)ethanamine
2D agents-substituted	DOI	1-(4-iodo-2,5-dimethoxyphenyl)-propan-2-amine
	DOC	1-(4-chloro-2,5-dimethoxyphenyl)-propan-2-amine
	DOB	1-(4-bromo-2,5-dimethoxyphenyl)propan-2-amine
	DOM	2,5-Dimethoxy-4-methylamphetamine
	DOF	4-fluoro-2,5-dimethoxy-α-methyl-benzeneethanamine
NBOMe agents-substituted	25H-NBOMe	1-(2,5-dimethoxyphenyl)-*N*-[(2- methoxyphenyl)methyl]ethanamine
	25I-NBOMe	4-Iodo-2,5-dimethoxy-*N*-(2- methoxybenzyl)phenethylamine
	25B-NBOMe	2-(4-bromo-2,5-dimethoxyphenyl)-*N*-[(2- methoxyphenyl)methyl] ethanamine
	25E-NBOMe	2-(2,5-dimethoxy-4-ethylphenyl)-*N*-(2- methoxybenzyl)ethanamine
	25N-NBOMe	2-(2,5-Dimethoxy-4-nitrophenyl)-*N*-(2- methoxybenzyl)ethanamine
	25G-NBOMe	2-(2,5-Dimethoxy-3,4-dimethylphenyl)-*N*-(2-methoxybenzyl) ethanamine
	25D-NBOMe	2-(2,5-dimethoxy-4-methylphenyl)-*N*-(2-methoxybenzyl)ethanamine
	25C-NBOMe	2-(4-chloro-2,5-dimethoxyphenyl)-*N*-(2-methoxybenzyl)ethanamine
	25I-NB4OMe	2-(4-iodo-2,5-dimethoxyphenyl)-*N*-(4-methoxybenzyl)ethanamine
	30C-NBOMe	4-Chloro-2,5-dimethoxy-*N*-[(3,4,5-trimethoxyphenyl)methyl]-benzeneethanamine

series of "Bonzai" intoxication in adolescents, hypotension and bradycardia were reported in 50% and 31.3% of the patients, respectively: 25% of patients needed intensive care admission [35]. In a case series of 322 SCs-intoxicated patients, severe vital sign abnormalities were present in 28.1%: 12.5% had tachycardia (heart rates above 140 beats per minute), 5.7% bradycardia (heart rates of less than 50 beats per minute), 4.2% patients had hypotension, 1.4% had both severe tachycardia and severe hypotension, 1.1% had severe tachycardia and severe hyperthermia, and 0.9% progressed from severe hypertension to severe hypotension [12, 36]. In another case series of 119, 2% died and 10% was admitted to ICU: hypertension (33%) and tachycardia (42%) were common [19].

SCs severe and fatal poisonings in young people are also frequent [29]: the number of deaths reported in the medical literature appears to be increasing and mostly related to the use of the most recent and powerful SCs, such as 5F-ADB/FUB-AMB, 5F-PB-22, and AB-CHMINACA [19, 37, 38].

Table 7 Representative compounds of hallucinogen NPS belonging the chemical groups of synthetic tryptamines (nonexhaustive list)

Chemical group	*Common name*	*Chemical name*
Synthetic tryptamines	AMT	1-(1H-indol-3-yl)propan-2-amine
	5-IT, 5-API	1-(1H-indol-5-yl)propan-2-amine
	5-APDI	1-(2,3-Dihydro-1H-inden-5-yl)-2-propanamine
	4-AcO-DPT	4-Acetoxy-*N*,*N*-dipropyltryptamine
	5-MeO-DPT	5-Methoxy-*N*,*N*-dipropyltryptamine
	4-AcO-DMT	4-Acetoxy-*N*,*N*-dimethyltryptamine
	4-AcO-DALT	4-Acetoxy-*N*,*N*-diallyltryptamine
	5-MeO-AMT	5-Methoxy-a-methyltryptamine
	5-MeO-DMT	5-Metossi-*N*,*N*-dimethyltryptamine
	4-AcO-DET	3-[2-(diethylamino)ethyl]-1H-indol-4-yl] acetate
	4-HO-MET	3-[2-[ethyl(methyl)amino]ethyl]-1H-indol-4-ol
	4-AcO-MET	3-{2-[ethyl(methyl)amino]ethyl}-1H-indol-4-yl acetate
	4-AcO-MPT	3-(2-[methyl(propyl)amino]ethyl)-1H-indol-4-yl acetate
	MIPT	*N*-[2-(1H-indol-3-yl)ethyl]-*N*-methylpropan-2-amine
	DMT	2-(1H-indol-3-yl)-*N*,*N*-dimethylethanamine
	5-MeO-tryptamine	2-(5-methoxy-1H-indol-3-yl)ethanamine
	DALT	*N*-[2-(1H-indol-3-yl)ethyl]-*N*-(prop-2-en-1-yl)prop-2-en-1-amine
	4-AcO-DALT	3-{2-[di(prop-2-en-1-yl)amino]ethyl}-1H-indol-4-yl acetate
	5-Meo-DALT	*N*-[2-(5-methoxy-1H-indol-3-yl)ethyl]-*N*-(prop-2-en-1-yl)prop-2-en-1-amine
	DPT	*N*-[2-(1H-indol-3-yl)ethyl]-*N*-propylpropan-1-amine

Cardiotoxic effects are reported also in experimental studies. Administration of high doses of the SCs AKB48 ([APINACA, *N*-(1-adamantyl)-1-pentyl-1H-indazole-3-carboxamide]) in rats, for example, induces bradycardia, mild bradypnea and SpO_2 reduction [39]. Hypothermia and bradycardia induced in rats by the third generation SCs AB-FUBINACA and AB-PINACA can be reversed by pretreatment with a CB1 antagonist [40].

SCs compounds originate from different molecular families with different receptor affinity and toxicological potency. It is therefore possible, for example, that SCs with adamantane moieties have higher potency at target receptors causing myocardial infarction and cardiac arrest more frequently than other SCs group [41].

Myocardial ischemia/infarction (MI) has been reported both in adult [42] and in young healthy patients associated with SCs that have higher binding affinity for CB1r (e.g., JWH-018, JWH-073, PB-22, AMBFUBINACA) [43]. Three teenagers presented separately to an ED complaining chest pain within days after the smoking a SC named K2, together with ST-elevation electrocardiogram changes, elevated troponin levels, and normal coronary angiography [44]. Similar acute effects were reported in a 17-year-old adolescent boy after smoking the SC named K9, with analytical confirmation of the two causing synthetic cannabinoids (JWH-018 and JWH-073) [45]. Even if MI is exceedingly rare in the pediatric population; however, drugs of abuse such as marijuana have led to MI, ventricular tachycardia and fibrillation, and sudden death in adolescents and adult who had normal coronary arteries [46–50]. The risk of MI is postulated to increase 4.8 times in the first hour after marijuana use. On the other hand, it is well known that marijuana (as THC) at low or moderate doses has pathophysiological effects on the cardiovascular system mediated both by stimulation of the sympathetic nervous system through release of norepinephrine and by parasympathetic blockade [51]. This result is an increase of cardiac output by as much as 30% [52] and a rapid dose-dependent

increase of the heart rate (and related oxygen demands) from 20% to 100% lasting up to 3 h [46, 49, 50, 53, 54]. At higher doses, THC can result in increased parasympathetic activity, leading to hypotension and bradycardia that can lead to decreased coronary perfusion pressure, possibly further contributing to myocardial ischemia [55]. Cardiac tamponade was also reported [56].

Likewise to the cardiotoxic effects, the CB1r stimulating substances (marijuana and SCs) are responsible of other vascular effect due to vasoconstriction such as in cases of transient ischemic events and strokes [57–60], even in young population (range 15–63). A recent review [61] reports 98 patients described in the literature as having a cannabinoids-related stroke (85 after cannabis use and 13 after SCs). The type of stroke was ischemic stroke and/or a transient ischemic attack, hemorrhagic stroke, or undetermined type of stroke in 85, 9, and 4 patients, respectively. Even if the prognosis was globally favorable (no or few sequelae) in 46% of cases, 5 patients died after the neurovascular event. The reversible cerebral vasoconstriction triggered by cannabinoids use may be a convincing mechanism of stroke in 27% of cases, even if a cellular effect of cannabis on brain mitochondria, the generation of reactive oxygen species leading to an oxidative stress, and a genetic predisposition to their neurovascular toxicity can be involved too. The author suggests obtaining a noninvasive intracranial arterial investigation (i.e., CT-angiography or cerebral MRA) in order to search for cerebral vasoconstriction.

An additional important effect associated to the SCs use, and possibly related also to acute coronary syndrome and stroke, is represented by the thromboembolic events involving both venous and arterial vessels, suggesting activation of coagulation or inflammatory pathways [62].

Prospective studies of cannabis users demonstrated increased risks of psychosis or psychotic symptoms [63] with odds ratios ranging from 1.77 to 10.9. SCs have a great potential for inducing psychosis, and users (both frequent or even short or occasional user) can manifest delirium and persistent psychotic effects up to more than 40% of cases [12, 60]. These effects may be related to (i) the lack of cannabidiol normally present in cannabis (for which evidence suggests provides antipsychotic properties) [64, 65], and (ii) the potent agonist actions of SCs at CB1r that can de-regulate the function of DA, 5-HT, and Glu systems implicated in schizophrenia and psychosis. Furthermore, some SCBs might exhibit pharmacologically relevant affinity for psychosis-associated receptors, including D2, 5-HT_{2A}, or NMDA [66]. The recent emerging class of "ultrapotent" SCs, such as AMB-FUBINACA (also known as MMB-FUBINACA or FUB-AMB), caused strong depressant effects that account for the "zombielike" behavior reported in mass intoxication [67]. In another case series of 39 patients, the third generation SCs AB-CHMINACA and MDMB-CHMICA resulted are associated with severe neuropsychiatric symptoms such as CNS-depression (61%), disorientation (45%), generalized seizures (27%), combativeness (18%), and extreme agitation (16%) [68].

Symptomatic (i.e., benzodiazepines, antipsychotics, anticonvulsant) and/or intensive (i.e., neuromuscular blockers, mechanical ventilation, vasopressors) and mechanical ventilation treatments for the wide range of SCs toxic effects are needed in approximately 60% of patients presenting in EDs [42]. A 24–48 h ECG and cardiac enzymes monitoring is mandatory if patients present to EDs after use of SCs with cardiac signs/symptoms.

Synthetic Cathinones (β-keto Amphetamines)

Synthetic cathinones (SCath) are, by number of compounds under EMCDDA control, the second largest group of NPS abused in the EU (25–33%). They became widespread in early 2009, leading to legislative classification throughout Europe in 2010 and the United States in 2011. The SCath differs from other amphetamines in that they have a ketone functional group [5]. All the synthetic cathinones are derivatives of cathinone, a naturally occurring stimulant found in the leaves of khat plant (*Catha edulis*), the leaves of which are chewed in certain communities for their stimulant effects.

Available in tablets, capsules, powder/crystal that are insufflated (snorted), ingested, or injected

by users seeking psychostimulant effects similar to cocaine, ecstasy (MDMA), or other amphetamines [69]. They are generally falsely sold on the web market as "bath salts" or "plant fertilizers" [1], even if they can be co-component of ecstasy or other psychostimulant NPS [70]. More than 150 synthetic cathinones are available on the web market: the most representatives (such as MDPV, mephedrone, methylone, butylone, and a-PVP) are reported in Table 3.

In vivo and *in vitro* studies have demonstrated that the pharmacodynamic profile of cathinones is similar to that of other psychomotor stimulants [71]. All the SChat show high blood-brain barrier permeability in in vitro models, with mephedrone and MDPV that have particularly high permeability. The synthetic cathinones exert their action by increasing extracellular levels of norepinephrine (NE), dopamine (DA), and serotonin (5-HT) [72, 73]. All the synthetic cathinones are potent NE reuptake inhibitors, but they can differ in their DA and 5-HT transporter inhibition profiles and monoamine release effects. Some of them (e.g., mephedrone, methylone, ethylone, butylone, and naphyrone) act as nonselective monoamine reuptake inhibitors, like cocaine, and induce the release of 5-HT like ecstasy (MDMA) and other entactogens. Some other (e.g., methcathinone and flephedrone) are preferential DA and NE uptake inhibitors and induce the release of DA like amphetamine and methamphetamine. Moreover, pyrovalerone and MDPV are highly potent and selective DA and NE transporter inhibitors but, unlike amphetamines, did not cause release of monoamines. In cases of acute intoxication, however, it is difficult to distinguish these differences. Moreover, the relevant action of all cathinones on the DA transporter can be probably associated with a considerable risk of addiction.

The users report euphoria, increased energy, loquacity, a subjective need to move and act, lightening of mood, empathy, openness, sexual stimulation, and increased libido.

The toxic effects of synthetic cathinones are cardiovascular, neurological, and psychiatric and are frequently indistinguishable from the acute effects of MDMA or cocaine [74–76]. The psychotic manifestations of SCath use often consist of paranoia with auditory and visual hallucinations, which can persist for up to 4 weeks and take a more severe course than with other amphetamines. Several cases of SCath intoxication with psychotic symptoms are related to MDPV [77].

Intoxication is clinically characterized by sympathomimetic effects, delirium, and serotonin syndrome. Clinical features included anxiety, impaired concentration and memory, confusion, agitation, restlessness, paranoia, associated to nausea, vertigo, abdominal pain, irritation of the nasal mucosa, headache, convulsions, hyperthermia (up to 41.5 °C), metabolic acidosis, elevated creatine kinase (CK) level and muscle damage, rhabdomyolysis, palpitations, tachycardia, hypertension, chest pain, ST-segment changes, breathlessness, peripheral vasoconstriction, mydriasis, reduced level of consciousness, syncope, myocarditis, cardiac arrest [17]. Symptoms may persist for 24–48 h in 45% of cases, and neurological and cardiovascular symptoms can be long-lasting. There have been several reports of serious toxicity associated with synthetic cathinones, including many fatalities in EU, USA, and Japan: cardiac ischemia and heart failure can be the most plausible cause of death [5, 78–80]. Cardiac toxicity and death have been reported also to be related to the triggering effect of synthetic cathinones on torsade de pointes due to QT prolongation [81]. Severe reversible cardiomyopathy has been reported following use of a "bath salt" compound containing mephedrone and MDPV [82–84].

Synthetic cathinones can be detected in serum for 15–48 h after use [85]: no specific antidotes are available for the treatment of these intoxications.

Ketamine and Ketamine Derivatives (Arycyclohexylamines)

The dissociative narcotic and anesthetic drug ketamine (KET), frequently used as NPS, is structurally and toxicologically similar to the new NPS compound methoxetamine (MXE) and to phencyclidine (PCP). Several other arycyclohexylamines are available for abuse on the web market (Table 4).

The users develop multimodal hallucinations, floating sensations, paranoia, dissociation, nightmares, reduction or loss of motor activity, changes in sexual and musical perceptions. Tolerance, dependence, flashbacks, and withdrawal symptoms are commonly reported.

The pharmacology of KET and derivatives is not completely understood. CNS effects are the result of complex dose- and time-dependent interactions on many types of receptors on which these substances exert agonist (glutamate, acetylcholine) or antagonist (NMDA) effects, direct or indirect (e.g., dis-inhibition of glutamatergic activity, activation of dopamine transmission, 5-HT release), which can also be different in different brain areas. Several toxic effects are reported also on bladder, kidney, adrenal gland, pancreas, and intestinal tract. On the other hand, ketamine is relatively safe on the hearth of children and in elderly, both of whom are more vulnerable to cardiovascular effects. Ketamine is used for short-term surgery in humans and animals; cardiac alterations and increase in hearth rate and blood pressure have been documented following administration of KET during anesthesia procedures [86, 87]. In acute ketamine recreational use, the heart risk is considered minimal if ketamine is not taken together with sympathomimetic agents. Animal studies, however, would show that 10% of mice chronically treated with ketamine undergo dilatation of the heart with cell hypertrophy and lytic and coagulative necrosis, as well as ischemic damage with depression of the ST tract to the ECG and increase in troponin I blood levels [88]. Similarly, a significant increase in basal systolic and diastolic blood pressure by ketamine and methoxetamine was recently reported in mice, with the longer-lasting effects for MXE [89].

MXE acts through blockade of the NMDA receptor and dopamine reuptake: other mechanisms not fully elucidated are the agonist effect on D_2 dopaminergic receptors and the interaction with serotonergic 5-HT_2 receptors, opioids (μ, κ) receptors, σ receptors, and muscarinic cholinergic receptors [90].

KET and MXE recreational use causes euphoria, increased empathy, intensified sensory experiences, distortion of the sense of reality and of time, vivid and persistent visual hallucinations, paranoia, and anxiety. These are associated with effects (sometimes called "not sought") such as sensory deprivation, derealization, and dissociation (generally described as "near-death experience") [91].

KET and MXE are the most frequent NPS involved in severe intoxication in several countries [92]. They have relevant psychotropic effects and their use cause severe psychiatric diseases. Intoxication is characterized by hallucinations, agitation, violent behavior, severe psychomotor agitation, paranoia, catatonia, respiratory depression and tachycardia, hypertension, palpitations, and chest pain [92–99]. Other signs and symptoms are mydriasis, nausea, vomiting, diarrhea, serious mental confusion, dizziness, aphasia, synesthesia [100].

Cardiac alterations have been long documented also after use of MXE, PCP, and other NMDA receptor antagonists, such as the methoxylated-PCP analogs 3-MeO-PCP and 4-MeO-PCP [101]. The MXE-related more powerful and long-lasting alterations in cardiorespiratory functions have important clinical implications while managing intoxication cases presenting at emergency departments.

Isolated reports describe also withdrawal-like symptoms such as insomnia, deflection of mood, and postintake depressive states. The treatment in EDs is based on rapid benzodiazepine administration and all the specified symptomatic treatments.

NPS Psychostimulants

All the NPS psychostimulant inhibit, even if in different degree related to the specific compound, the monoamine reuptake increasing the quantity of noradrenaline, dopamine, and serotonin in the synaptic cleft leading to sympathomimetic effects that are responsible for most of the cardiotoxic effects. The NPS with dominant psychostimulant effects, also called "entactogens," are generally sold on the market as "party pills" that enhance feelings of empathy, and emotional closeness to others. Most of them are the novel substitutes of the old drug of abuse ecstasy (MDMA).

Adverse reaction may vary between each class ad each compound: agitation and euphoria are common feature after use of all these substances. The cardiovascular effects include tachycardia, hypertension, vasoconstriction of coronary arteries, chest pain caused by an increase in oxygen demand, and thrombosis due to platelet activation. This could lead to increased risk of myocardial infarction, stroke, and upon prolonged abuse, dilated cardiomyopathy. The effect on serotonin neurotransmission can also be substantial and hyperthermia and dehydration are observed. Acute coronary syndrome from abuse has been described in case reports, and fatal outcomes have been described [102].

Phenethylamines-derived compounds comprehend a vast number of NPS (new amphetamine derivatives, piperazines, tryptamines, pipradrols/piperidines, aminoindanes, benzofurans, and others) that have dominant psychostimulant and/or hallucinogenic effects, in part predictable based on their chemical structure (Table 5). However, if from the chemical point of view it is quite simple to classify these molecules, from the clinical point of view it is very difficult to identify the involved compound based only on the signs and symptoms, both for the different individual response to each agent, and for the modification of the effects with the increase of the taken dose. Moreover, most compounds have a combination of such effects.

The treatment also is similar to that of amphetamines or cocaine overdose. In cases of acute myocardial infarction, the initial treatment should be with benzodiazepines eventually associated with nitrates. On the other hand, β-blockers should be avoided, because β-blockade will potentially leave α1-receptors unopposed resulting in more severe coronary spasm, or arterial blood pressure increase. Concerning the sodium channel blockage, in case of QRS widening and consequent risk of dysrhythmias, sodium bicarbonate, or hypertonic saline should be used as the first-line treatment [103].

Serotonin toxicity (CNS activation, autonomic dysregulation, and neuromuscular impairment) could also be present as a lot of compounds share serotoninergic properties. A syndrome of inappropriate antidiuretic hormone secretion (SIADH) resulting in hyponatremia has been also described [104, 105]. Extensive cooling is needed in case of hyperthermia, whereas first line treatment of serotoninergic symptoms is benzodiazepines, followed by cyproheptadine, a first-generation antihistamine with antiserotoninergic properties.

Synthetic Amphetamine Derivatives

This first group of phenethylamines (such as PMMA, PMA, 4-FMA, 4-CA, 4-FA, 2-FA, 2-FMA, DMA, DMMA, 2-PEA) show clinical effects almost completely superimposable to those of the classic amphetamines [106]. The intoxicated patients presenting to the ED with toxicity from this group of compound present agitation, severe tachycardia and hypertension, elevated heart and respiratory rate, mydriasis, hallucinations, severe limb ischemia, seizures, liver and renal failure have been reported, with toxicity seemingly dose related. PMA, PMMA, and 4-MTA (paramethoxyamphetamine, paramethoxymethamphetamine, and 4-methyltrioamphetamine, respectively) intoxicated patients present frequently convulsions, sudden collapse, severe hyperthermia, and death due to cardiac arrest and/or multiple organ failure [106–109]. In a series of 22 PMA intoxicated patients, tachycardia was reported in 64%, hyperthermia in 36%, and seizures in 34% of the patients: QT prolongations were also reported [110]. A high number of fatalities are reported in PMA and PMMA users.

Potential mechanisms of acute cardiac syndrome following amphetamine analogues and derivative use are multifactorial, and include epicardial and microvascular coronary artery vasospasm, catecholamine-mediated platelet aggregation and thrombus formation, accelerated atherosclerotic plaque formation and rupture, increased myocardial oxygen demand, and direct myocardial toxicity. Coronary artery disease and coronary thrombosis can be present in some patients with acute coronary syndrome following use of amphetamine derivatives. Dilated cardiomyopathy, reverse (or inverted) Takotsubo cardiomyopathy, direct myocardial damage, myonecrosis,

mitochondrial derangement, enlargement of sarcoplasmic reticulum, apoptosis, oxidative stress from accumulation of reactive oxygen and nitrogen species, cardiac remodeling with subsequent hypertrophy and fibrosis have been well-documented in prolonged amphetamine, methamphetamine, and analogues derivatives abuse [111].

A case series of 33 intoxicated patients with 4-FA (4-fluoroamphetamine) showed that eight had important complications, including two deaths, four cerebral hemorrhages, two instances of Takotsubo's cardiomyopathy, one myocardial infarction, and one acute heart failure [112].

Piperazines

Piperazines (1-benzylpiperazines and 1-phenylpiperazines) are synthetic compound developed as antihelminthic agents and later evaluated as antidepressant. Due to amphetamine-like effects, they have not been further developed: there are, however, nonstimulant piperazine compounds with legitimate medicinal uses, for example, cyclizine (1-diphenyl-methyl-4-methylpiperazine) and precursors of trazodone.

The lead compound *N*-benzylpiperazine (BZP) enhances the release of dopamine and norepinephrine and inhibits the uptake of dopamine, norepinephrine, and serotonin, increasing activation of both central and peripheral α- and β-adrenergic postsynaptic receptors. Although structurally similar to amphetamine, it is reported to have only one-tenth the potency [113]: a mix of different piperazine is often sold as "ecstasy" [114]. BZP has primarily dopaminergic and noradrenergic action, while TFMPP (trifluoromethylphenylpiperazine) has a more direct serotonin agonist activity.

High doses of BZP are usually associated with a sympathomimetic toxidrome and paranoid psychosis: palpitations, tachycardia, agitation, anxiety, confusion, dizziness, headache, tremor, mydriasis, insomnia, urine retention, and vomiting. Seizures are induced in some patients even at low doses. Severe multiorgan failure, QT prolongation, hallucinations, and metabolic acidosis have been reported, though fatalities from the confirmed sole use of 1-BZP have not been reported, although the combination of MDMA and BZP has been linked to fatalities in Sweden and Switzerland [5, 115]. A case series of 178 patients admitted to EDs had long-lasting (more than 24 h) effects, comprehending extreme hyperthermia (> 40 °C) and multiorgan failure, palpitations, tachycardia, seizures, metabolic acidosis, and hyponatremia [116].

Benzofurans and Benzodifurans (Fly Drugs)

Benzofurans (APB, APDB) are structurally considered analogues of phenethylamines, and they can be defined as deoxygenated derivatives of MDA (methylenedioxyamphetamine) (Table 5). 6-APB (street name "benzofury") appeared on the web market from 2010, sold as synthesized research chemical in form of pressed plant material ("pellets"), gel, or powder. "Benzofury" product taken more frequently by ingestion or sniffing resulted contains also 2-DPMP, 5-APB, and caffeine.

Some APB derivatives (e.g., 6-APB and 4-APB) were described in a 2006 patent relating to a series of compounds with agonist action on 5-HT_{2C} receptors, potentially usable in treatment of disorders related to the decrease in the serotonin neurotransmission [117]. However, the pharmacodynamic properties are not well studied, especially for the benzodifurans bromo-dragonfly and 2C-B-Fly: they are likely to act as catecholamine releasing or re-uptake inhibiting agents. In animal studies, bromo-dragonfly and 2C-B-Fly are potent $5HT_{2A}$ agonists, but they are also both $5HT_{2B}$ and $5HT_{2C}$ agonists. Bromo-dragonfly have more potent hallucinogenic properties [118].

According to users, the effects of using 6-APB are similar to, but much more intense, than those resulting from taking MDMA and arise quickly after oral intake (within 30 min) reaching the maximum of intensity in about 2–3 h. In some case hallucinogenic effects last 2–3 days, and the come down phase lasts from 4 h up to 72 h.

Acute intoxication manifest with severe psychomotor agitation, violent attitude, prolonged sympathomimetic effect on the heart (severe tachycardia, hypertension), hyperthermia,

rhabdomyolysis, pronounced mydriasis, gastrointestinal symptoms (nausea and vomiting), auditory/visual hallucinations, and sensory disturbances and convulsions [119]. Several death and severe peripheral vasoconstriction are described in patients with bromo-dragonfly intoxication in US and EU [120–122]. Deaths apparently result from severe and prolonged arteriolar vasoconstriction mediated by very potent agonism at 5-HT_2 and α-adreno-receptors, which may persist for days. It has been suggested that cases of sudden death may be due to coronary arterial vasoconstriction.

Large doses of benzodiazepines, nitrates, nitroprusside, calcium-channel blocker have been used to counteract neuropsychiatric and cardiovascular sign and symptoms: vasodilators are needed to control the severe vasospasm.

New Hallucinogen Phenethylamine-Derived Drugs (Agents-Substituted Phenethylamines Subgroups)

The phenethylamines are a large family of monoamine alkaloids that includes also the old drugs of abuse amphetamine, methamphetamine and MDMA. Most phenethylamines have stimulant properties, although "designer" substitutions have created substances with additional or alternative psychoactive properties such as double potency and prolonged effects (e.g., D-series ring substituted) due to the resistance to the breakdown enzymes. Depending on the modification, such as extension of either the side chain or amino group substitutions or aromatic ring substitution, stimulant or hallucinogenic properties are conferred to the new compounds. The principal substituted phenethylamines subgroups are the 2C agents, the 2D agents, and the NBOMe agents (Table 6). In Europe, the EMCDDA has reported an increase in the consumption of phenethylamines associated with serious health risks, including cases of death and severe acute poisoning.

2C Agents

Phenethylamines of the 2C-series are a large group of chemicals characterized by methoxy groups at positions 2 and 5 of the benzene ring. The 2C-serie agents have affinity for 5-HT_2 receptors and alpha-adrenergic receptors [123]. They have a prevalent effect of inhibition of monoamine reuptake (mainly serotonin and noradrenaline) and can exert also important postsynaptic direct effects [124]. These compounds can carry out agonist or antagonist activity in relation to the specific receptor subtypes involved [123, 125, 126].

Compounds with different substituents in position 4 of the benzene ring are part of the 2C series: ethyl group for 2C-E, bromine for 2C-B (2,5-dimethoxy-4-bromophenethylamine), iodine for 2C-I.

Clinically the 2C series are primarily stimulant at lower doses (e.g., 10 mg for 2C-B), but doses of more than 10 mg tend to be psychoactive with hallucinogenic and entactogenic effects, while doses of 30 mg or more may cause intense hallucinations or psychosis. Deaths have been associated with the 2C-series agents.

The psychedelic phenylethylamine derivative 2C-B was used in the 1990s also in psychotherapeutic field; it is currently being sold as a substitute for substances similar to MDMA. 2C-B is a partial agonist on the serotonin receptor subtypes 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C}. It has been reported that 2C-B induces mild psychedelic effects, although its acute pharmacological effects and pharmacokinetics have not yet been fully studied in humans. Acute administration of 2C-B in 16 healthy, experienced drug users (oral dose of 10, 15, or 20 mg) increased blood pressure and heart rate and induced a constellation of psychedelic/psychostimulant-like effects like those associated with serotonin-acting drugs [127]. Acute intoxications are characterized by vomiting, seizures, coma, mydriasis, tachypnea, hypertension, tachycardia, metabolic acidosis.

2C-E agents are sold as "mescaline" for their predominant hallucinatory effects. The 2C-E agents are synthetic phenethylamines, which exhibits characteristics similar to other 2C-series phenethylamines, such as 2C-B. Intoxicated patients present with delirium, hallucinations, psychomotor agitation, euphoria, paranoid delusions, persistent acute psychosis, violent attitude, hyperactivity (sometimes defined as "excited

delirium syndrome") [128–130], hyperthermia, potentiation and distortion of sensations (tactile, auditory and olfactory), nausea, vomiting, tachycardia, hypertension, hypoxia, tachypnea, and convulsions. A lethal toxic leukoencephalopathy related to assumption of 2C-E compounds has also been described in a psychiatric patient [131]. 2-CE fatalities have been reported [132].

Similarly, 2C-I acute intoxication is characterized by tachycardia, severe systolic hypertension (greater than 220–235 mmHg), hyperthermia, severe psychomotor agitation, seizures, spontaneous clone, hypertonia, muscle stiffness, delirium, coma, and reduction of oxygen saturation [133]. Some symptoms are compatible with severe serotonin syndrome, and in these cases benzodiazepines, fentanyl, phenobarbital, cyproheptadine, propofol Intubation, and assisted ventilation can be needed [134]. Some cases of intoxication have had lethal outcome.

2D Agents

The 2D-series or D-series (e.g., DOI, DOC, DOB, DOM, DOF) are dimethoxy amphetamine characterized by methoxy ring substitution at the 2 and 5 position of the aromatic ring with varying additional substitution of hydrophobic moieties at the 4 position.

The 2D-serie agents are potent 5-HT_2 receptors agonists, and full agonist at 5-HT_{2A} and 5-HT_{2C} subtypes, producing potent hallucinogenic effects, prolonged vasoconstriction and dopaminergic agonism [135, 136].

Potent hallucinogenic effects, extreme dysphoria, sensation of limb and generalized body pain, agitation, vomiting are the user's reported effects. In cases of intoxication, the potent hallucinogenic effect can last more than 24 h, accompanied by vasospasm in upper and lower extremities, hypertension, convulsion, tachycardia, mydriasis, and coma [137, 138]. The treatment requires phentolamine and/or nitroprusside administration: fatalities are reported.

NBOMe Agents

25-NBOMe series (firstly synthesized in 2003 as activators of the 5-HT_{2A} serotonin receptors) have been available since at least 2012 in the abuse market, where they are sold as "blotter," "trip," "smiles," "N-bomb," "LSD," "new LSD," "synthetic LSD," "synthetic speed," "25 L," "25B," "25C" or with other slang terms.

Tens of NBOMe are reported today in the EMCDDA database. They are very powerful compounds, at least as much as LSD: the effects (reported by users) last from 3 to 13 h, and about 100–250 μg (with reference to 2C-NBOMe: different data are possible for the other NBOMe) are sufficient to cause significative effects.

Acute NBOMe intoxications are characterized by important and prolonged hallucinations, violent agitation, mental confusion, a state of great concern with anxiety, and self-injurious gestures: accompanying symptoms are mydriasis, tachycardia, hypertension, hyperthermia, sweating, hyperreflexia, muscle hypertonicity, convulsions, rhabdomyolysis, and kidney damage (partly attributable to powerful serotonergic stimulation).

The initial therapeutic approach of these cases of intoxication is in fact precisely aimed at the important and rapid sedation of the patient to prevent other damage from being caused; in fact, often these patients come to the observation of emergency medical services following (unconscious) gestures of self-harm.

Several dozens of cases of severe and lethal intoxication are reported to date in the medical literature: the lethality turns out to be 15% of the reported cases, and the need of ICU admission 40% of the cases [139]. The presence of hallucinations, self-injurious gestures, state of severe agitation is the most evident clinical feature of NBOMe intoxications. On the other hand, most cases of serious injury and death in NBOMe-series intoxicated patients are due to self-injurious acts and/or reckless gestures (e.g., throwing themselves thinking of flying) in people who lose control of themselves: the cardiovascular lethal accidents are not sufficiently demonstrated.

Synthetic Tryptamines

Serotonin (5-hydroxytryptamine,5-HT) and melatonin are naturally occurring tryptamines in humans. The natural occurring tryptamines and ergolines have been used for centuries as psychoactive substance from ayahuasca (DMT, dimethyltryptamine), mushrooms (psylocibin, psilocin), plants (e.g., ergine, mytragynine), whereas LSD

(lysergic acid diethylamide) is perhaps the best know synthetic tryptamine and one of the most potent hallucinogens. The new synthetic tryptamines (e.g., 5-MeO-AMT, 5-MeO-DMT) (Table 7) are a group of monoamine alkaloids that have emerged as recreational psychoactive substances in the last decades on the online drug market. They act both as 5-HT_{2A} and 5-HT_{1A} receptor agonists and serotonin reuptake inhibitors [140–143] provoking visual hallucinations, alterations in sensory perception, and depersonalization [144, 145]. Tryptamines exhibit less selectivity and affinity for 5-HT_{2A} receptor subtype compared to hallucinogenic phenyethylamines, but the effects vary from compound to compound in relation to molecular changes and substitutions: some tryptamines (e.g., AMT) are also serotonin reuptake inhibitors and releaser of serotonin, noradrenaline, and dopamine [5].

The experimental in vivo and in vitro evaluation of 4-AcO-DET and 4-HO-MET showed that the two synthetic tryptamines exert toxic effect increasing the QT intervals (as determined using ECG) in rats and inhibit potassium channels using the human ether-a-go-go-related gene (hERG) assay in Chinese hamster ovary cells [146].

The predominant clinical effect of synthetic tryptamines is hallucinations related to the agonism at 5-HT_{1A} and 5-HT_{2A} receptors. However, even cardiovascular toxic effects are possible. DMT administration in man (controlled studies) causes a modest increase in systolic and diastolic blood pressure and heart rate [147]. Intoxicated patients present to Eds with hallucination, paranoia, agitation, mydriasis, severe tachycardia, arrhythmias, hypertension, hyperthermia, and diaphoresis: metabolic acidosis, rhabdomyolysis, and renal impairment can be present. Deaths are reported, but they do not typically appear related to cardiovascular toxic effects.

Treatment of the Cardiotoxic Effect of NPS

No specific antidotal treatments are available for the management of both the intoxications and the cardiotoxic effects due to NPS (apart for that for the opioid's family and few other compounds). In several cases, moreover, the treating physicians cannot understand which NPS may be the cause of the clinical presentation and of the cardiac effects. So, treatment options are usually symptomatic and supportive, at least in the first phase of the care.

The initial treatment of severe hypertension should include nitrates and benzodiazepines (BDZ) if a heightened central and peripheral sympathetic tone is present: a second choice can also be represented by α-adrenergic antagonists such as prazosin and phentolamine. β-blockers administration should be approached with caution, because they can potentially cause paradoxical hypertension (as reported for cocaine), even if recent recommendations stated that β-blockers may be beneficial if the patient has been pretreated with vasodilators.

The treatment of acute coronary syndromes related to NPS is based on whether the cause of chest pain is vasospasm (without myocardial ischemia), or coronary artery occlusion with myocardial infarction. Initial treatment for vasospasm should include nitrates or Ca^{++}-channel blockers, together with a prudent antiplatelet treatment (e.g., acetylsalicylates) and serial troponin measurement and ECG monitoring. There is no evidence to support routine coronary angiography in patients without ST-segment or T-wave changes. The application of defibrillators and pacing devices follows the normal good clinical practice and procedures.

Rapid and consensual treatment of agitation is a priority. This can be, at least in part, also useful for the treatment of cardiovascular toxic effects even if some patients may continue to have tachycardia, hypertension, and hyperthermia for several hours after the agitation is controlled. Benzodiazepines (e.g., lorazepam, diazepam, midazolam) are the first line treatment for generalized agitation in NPS-related in the ED, as they enhance the inhibitory effects of γ-aminobutyric acid (GABA), neurotransmitter that is not involved in the toxic mechanisms of NPS reported in this chapter. The second option, often effective when BDZ have failed to control symptoms on their own, is barbiturates: they can act on the same GABA-receptor through a different receptor and are frequently effective in cases resistant to BDZ.

Propofol is an efficient sedative acting selectively as GABA-receptor agonist at $GABA_A$ receptors that contain α2 and α3 subunits. Used via continuous infusion, it decreases the systolic and diastolic blood pressure by approximately 20–30% with minimal change in heart rate. The cardiovascular and respiratory effects of propofol, however, should not cause major concern in otherwise healthy patients.

Antipsychotics (the CNS dopaminergic receptor antagonists such as haloperidol, ziprasidone, olanzapine) are useful to block the increased CNS dopamine levels resulting from several NPS toxicity, but they have to be used only if the BDZ and barbiturate treatment is unsuccessful, or in a second phase, jointly to a continuous monitoring to avoid the risk of increase in QT interval prolongation.

The NMDA-receptor antagonist ketamine, frequently used in EDs for control of generalized agitation, is a contraindicated drug because it produces dissociation, a trance-like cataleptic state, and catecholamine surge (decreased catecholamine uptake and stimulation of CNS sympathetic outflow) leading to a potentially detrimental acute rise in blood pressure, heart rate, and cerebral blood flow. In fact, NPS patients often have hypertension and tachycardia.

Dexmedetomidine, a highly selective α2-adrenoceptor agonist leading to inhibitory effects on CNS sympathetic outflow (that counteract the cardiovascular and CNS overstimulation from NPS), produces sedation, analgesia, and no respiratory depression. Its use can be advantageous in case of high sympathetic stimulation due to several NSP.

The hyperthermia caused by NPS may be due to excessive sympathetic stimulation with skeletal muscle thermogenesis, to the serotonin syndrome, or to other mechanism [148]. The rapid reduction of body temperature can be accomplished in EDs by several means (e.g., cool mist application, fan, ice packs and/or cooling blanket, gel packs, administration of cold IV crystalloid). When related to MDMA-like NPS and synthetic cathinones (such as MDPV), the hyperthermia can be due to a form of serotonin syndrome. In this case, cyproheptadine, a first-generation antihistamine with antiserotoninergic and anticholinergic properties, can be the solution to choose. The skeletal muscle relaxant dantrolene, a depressor of the excitation-contraction coupling, has been used successfully for severe MDMA-induced hyperpyrexia with improved survival and reduced complications [149]. Carvedilol, a mixed β/α1-adrenoceptor antagonist, is able to modulate peripheral vasoconstriction and heat dissipation attenuating MDMA-induced hyperthermia in humans and in animal models [150, 151].

The treatment of persistent tachycardia and hypertension due to NPS may be necessary to prevent secondary cardiovascular, renal, and cerebral injury. Some β-blockers (e.g., labetalol, carvedilol, atenolol), α1-adrenoceptor antagonists, nitric oxide-mediated vasodilators, and Ca-channel blockers (diltiazem) have been used to antagonize the hyperadrenergic state that may persist even after adequate sedation has been achieved. Labetalol probably represents the better choice among β-blockers [103, 111, 152], even if the theoretical risk of "unopposed α-stimulation" after β-blocker use in hyperadrenergic states has not yet been fully elucidated. Ca^{++}-channel blockers, phentolamine, nitroprusside, and nitroglycerin mitigate hypertension, but not uniformly tachycardia: results of these studies have been inconsistent [111].

Conclusions

Cardiac morbidity and mortality associated with NPS use is mostly associated with overdose. All the NPS demonstrate multiple interactions and a large range of effects on the CNS and other organs, comprehending the cardiovascular system, on which the majority of NPS exerts a variety of sympathomimetic effects that mimic those of the amphetamines. The life-threatening effects by NPS largely involve the heart, either directly or indirectly, and can present clinically acutely as hypertension, chest pain, acute coronary syndromes, myocardial infarction, major vessel dissection, strokes [153]. It is also possible that, like for cocaine and amphetamines, patient will

develop, after a prolonged NPS use, chronic cardiac disease such as, for example, hypertensive or ischemic heart disease, cardiomyopathy, infective endocarditis, cardiac tamponade [56].

The large number of NPS that are cause of acute intoxication with serious cardiovascular effects, the frequent simultaneous mixing of several NPS, the different analytical techniques used to highlight the individual NPS, and the different sampling times in every patient does not allow today to define which can be the toxic and/or lethal blood concentration for each agent. It is therefore not possible today to identify with certainty what serum concentration of each NPS can be related to cardiotoxic manifestations. Although some of these data are beginning to be available, we are still far from having a scientifically proven dose-effect correlation for each NPS.

In assessing the cardiotoxicity of NPS, it should be considered that, for most of these compounds, (i) the kinetics in humans and animals are not yet known, (ii) all the effects on the various targets have not yet been elucidated, and (iii) the available information derives from a few instances, often not comparable in terms of doses and method applied. On the other hand, it is also evident that the toxicity of these new compounds, which appear on the abuse market in the number of 50–100 every year, could not have been studied in advance. Many research groups around the world are now chasing NPS and trying to elucidate their toxicokinetic and toxicodynamic, but this research will take a long time as for any new compound with which the man comes into contact.

Acknowledgments Italian clinical data reported in this chapter come from the activity of the Pavia Poison Centre as clinical and toxicological coordinating center for the Italian National Early Warning System for Drugs of Abuse (Department of Antidrug Policies – Presidency of the Council of Ministers) and are in part supported by the Ricerca Corrente funding of the Italian Ministry of Health.

References

1. German CL, Fleckenstein AE, Hanson GR. Bath salts and synthetic cathinones: An emerging designer drug phenomenon. Life Sci. 2014;97(1):2–8.
2. Locatelli CA, Petrolini VM, Giampreti A, Vecchio S, Buscaglia E, Coccini T, Aloise M, Chiara F, Cortini E, Papa P, Serpelloni G. Clinica delle intossicazioni acute da "nuove sostanze psicoattive e tossiche" identificate nel triennio 2010–2013. Ital J Addict. 2014;4(1):28–41.
3. UNODC Early Warning Advisory (EWA) on New Psychoactive Substances (NPS). United Nation Office on Drugs and Crime. https://www.unodc.org/LSS/Home/NPS. Consulted in 2019.
4. Buscaglia E, Schicchi A, Lonati D, Calabrò G, Papa P, Valli A, Di Tuccio M, Locatelli CA. An example of a new toxicological disease and a new social problem related to the abuse of and addiction to new psychoactive substances. Clin Toxicol (Phila). 2017;55(5):441.
5. Hill SL, Thomas SHL. Clinical toxicology of newer recreational drugs. Clin Toxicol. 2011;49(8):705–19.
6. Carhart-Harris RL, King LA, Nutt DJ. A web-based survey on mephedrone. Drug Alcohol Depend. 2011;118(1):19–22.
7. Duflou J. Psychostimulant use disorder and the heart. Addiction. 2020;115(1):175–83.
8. Qureshi Al, Suri MF, Guterman LR, Hopkins LN. Clinical investigation and reports cocaine use and the likelihood of nonfatal myocardial infarction and stroke data from the Third National Health and Nutrition Examination survey. Circulation. 2001;103(4):502–6.
9. Zwartsen A, de Korte T, Nacken P, de Lange DW, Westerink RHS, Hondebrink L. Cardiotoxicity screening of illicit drugs and new psychoactive substances (NPS) in human iPSC-derived cardiomyocytes using microelectrode array (MEA) recordings. J Mol Cell Cardiol. 2019;136:102–12.
10. Yun J, Yoon KS, Lee TH, Lee H, Gu SM, Song YJ, Cha HJ, Han KM, Seo H, Shin J, Park HK, Kim HS, Kim YH. Synthetic cannabinoid, JWH-030, induces QT prolongation through hERG channel inhibition. Toxicol Res. 2016;5(6):1663–71.
11. EMCDDA-Europol European Monitoring Centre for Drugs and Drug Addiction and Europol. EU Drug Markets Report 2019. Publications Office of the European Union, 2019, Luxembourg.
12. Monte AA, Calello DP DP, Gerona RR, Hamad E, Campleman SL, Brent J, Wax P, Carlson RG, On behalf of the ACMT Toxicology Investigators Consortium (ToxIC). Characteristics and treatment of patients with clinical illness due to synthetic cannabinoid inhalation reported by Medical Toxicologists: a ToxIC Database Study. J Med Toxicol. 2017;13(2):146–52.
13. Monte AA, Bronstein AC, Cao DJ, Heard KJ, Hoppe JA, Hoyte CO, Iwanicki JL, Lavonas EJ. An outbreak of exposure to a novel synthetic cannabinoid. N Engl J Med. 2014;370(4):389–90.
14. Adamowicz P. Fatal intoxication with synthetic cannabinoid MDMB-CHMICA. Forensic Sci Int. 2016;261:e5–10.
15. Auwärter V, Dresen S, Weinmann W, Müller M, Pütz M, Ferreirós N. 'Spice' and other herbal blends:

harmless incense or cannabinoid designer drugs? J Mass Spectrom. 2009;44(5):832–7.
16. Castaneto MS, Gorelick DA, Desrosiers NA, Hartman RL, Pirard S, Huestis MA. Synthetic cannabinoids: epidemiology, pharmacodynamics, and clinical implications. Drug Alcohol Depend. 2014;144:12–41.
17. Hohmann N, Mikus G, Czock D. Effects and risks associated with novel psychoactive substances: mislabeling and sale as bath salts, spice, and research chemicals. Dtsch Arztebl Int. 2014;111(9):139–47.
18. Dresen S, Ferreirós N, Pütz M, Westphal F, Zimmermann R, Auwärter V. Monitoring of herbal mixtures potentially containing synthetic cannabinoids as psychoactive compounds. J Mass Spectrom. 2010;45 (10):1186–94.
19. Kasper AM, Ridpath AD, Gerona RR, Cox R, Galli R, Kyle PB, Parker C, Arnold JK, Chatham-Stephens K, Morrison MA, Olayinka O, Preacely N, Kieszak SM, Martin C, Schier JG, Wolkin A, Byers P, Dobbs T. Severe illness associated with reported use of synthetic cannabinoids: a public health investigation (Mississippi, 2015). Clin Toxicol. 2019;57(1):10–8.
20. Huestis MA, Gorelick DA, Heishman SJ, Preston KL, Nelson RA, Moolchan ET, Frank RA. Blockade of effects of smoked marijuana by the CB1-selective cannabinoid receptor antagonist SR141716. Arch Gen Psychiatry. 2001;58(4):322–8.
21. Brents LK, Reichard EE, Zimmerman SM, Moran JH, Fantegrossi WE, Prather PL. Phase I hydroxylated metabolites of the K2 synthetic cannabinoid JWH-018 retain in vitro and in vivo cannabinoid 1 receptor affinity and activity. PLoS One. 2011;6(7):e21917.
22. Elsohly MA, Gul W, Wanas AS, Radwan MM. Synthetic cannabinoids: analysis and metabolites. Life Sci. 2014;97(1):78–90.
23. Fantegrossi WE, Moran JH, Radominska-Pandya A, Prather PL. Distinct pharmacology and metabolism of K2 synthetic cannabinoids compared to Δ(9)-THC: mechanism underlying greater toxicity? Life Sci. 2014;97(1):45–54.
24. Marshell R, Kearney-Ramos T, Brents LK, Hyatt WS, Tai S, Prather PL, Fantegrossi WE. In vivo effects of synthetic cannabinoids JWH-018 and JWH-073 and phytocannabinoid Δ9-THC in mice: inhalation versus intraperitoneal injection. Pharmacol Biochem Behav. 2014;124:40–7.
25. Locatelli CA, Vecchio S, Giampreti A, Buscaglia E, Schicchi A, Grignani P, Serpelloni G. Acute intoxications by synthetic cannabinoids in the emergency system: an Italian cases series. Clin Toxicol. 2015;53:360.
26. Lonati D, Buscaglia E, Papa P, Valli A, Coccini T, Giampreti A, Petrolini VM, Vecchio S, Serpelloni G, Locatelli CA. MAM-2201 (Analytically confirmed) intoxication after “Synthacaine” consumption. Ann Emerg Med. 2014;64(6):629–32.
27. Trecki J, Gerona RR, Schwartz MD. Synthetic cannabinoid–related illnesses and deaths. NEJM. 2015;373(2):103–7.
28. Winstock AR, Barratt MJ. The 12-month prevalence and nature of adverse experiences resulting in emergency medical presentations associated with the use of synthetic cannabinoid products. Hum Psychopharmacol. 2013b;28(4):390–3.
29. Zaurova M, Hoffman RS, Vlahov D, Manini AF. Clinical effects of synthetic cannabinoid receptor agonists compared with marijuana in emergency department patients with acute drug overdose. J Med Toxicol. 2016;12(4):335–40.
30. Harris CR, Brown A. Synthetic cannabinoid intoxication: a case series and review. J Emerg Med. 2013;44(2):360–6.
31. Tait RJ, Caldicott D, Mountain D, Hill SL, Lenton S. A systematic review of adverse events arising from the use of synthetic cannabinoids and their associated treatment. Clin Toxicol (Phila). 2016;54(1):1–13.
32. Moeller S, Lücke C, Struffert T, Schwarze B, Gerner ST, Schwab S, Köhrmann M, Machold K, Philipsen A, Müller HH. Ischemic stroke associated with the use of a synthetic cannabinoid (spice). Asian J Psychiatr. 2017;25:127–30.
33. Yamanoglu A, Celebi Yamanoglu NG, Evran T, Sogut O. How much can synthetic cannabinoid damage the heart? A case of cardiogenic shock following resistant ventricular fibrillation after synthetic cannabinoid use. J Clin Ultrasound. 2018;46(9):605–9.
34. Lonati D, Buscaglia E, Papa P, Petrolini V, Vecchio S, Giampreti A, Rocchi L, Chiara F, Aloise M, Rognoni C, Manzo L, Serpelloni G, Rimondo C, Macchia T, Locatelli CA. Prevalence of intoxication by new recreational drugs: preliminary data by the Italian network of emergency departments involved in the national early identification system. Clin Toxicol. 2012;50:344.
35. Besli GE, Ikiz MA, Yildirim S, Saltik S. Synthetic cannabinoid abuse in adolescents: a case series. J Emerg Med. 2015;49(5):644–50.
36. Hermanns-Clausen M, Kneisel S, Szabo B, Auwärter V. Acute toxicity due to the confirmed consumption of synthetic cannabinoids: clinical and laboratory findings. Addiction. 2013;108(3):534–44.
37. Angerer V, Jacobi S, Franz F, Auwärter V, Pietsch J. Three fatalities associated with the synthetic cannabinoids 5F-ADB, 5F-PB-22, and AB-CHMINACA. Forensic Sci Int. 2017;281:e9–e15.
38. Ivanov ID, Stoykova S, Ivanova E, Vlahova A, Burdzhiev N, Pantcheva I, Atanasov VN. A case of 5F-ADB/FUB-AMB abuse: drug-induced or drug-related death? Forensic Sci Int. 2019;297:372–7.
39. Bilel S, Tirri M, Arfè R, Stopponi S, Soverchia L, Ciccocioppo R, Frisoni P, Strano-Rossi S, Miliano C, De-Giorgio F, Serpelloni G, Fantinati A, De Luca MA, Neri M, Marti M. Pharmacological and behavioral effects of the synthetic cannabinoid AKB48 in rats. Front Neurosci. 2019;13:1163.
40. Banister SD, Moir M, Stuart J, Kevin RC, Wood KE, Longworth M, Wilkinson SM, Beinat C, Buchanan AS, Glass M, Connor M, McGregor IS, Kassiou M.

Pharmacology of indole and indazole synthetic cannabinoid designer drugs AB-FUBINACA, ADB-FUBINACA, AB-PINACA, ADB-PINACA, 5F-AB-PINACA, 5F-ADB-PINACA, ADBICA, and 5F-ADBICA. ACS Chem Neurosci. 2015;6(9):1546–59.
41. McIlroy G, Ford L, Khan JM. Acute myocardial infarction, associated with the use of a synthetic adamantyl-cannabinoid: a case report. BMC Pharmacol Toxicol. 2016;17:2.
42. Hamilton RJ, Keyfes V, Banka SS. Synthetic cannabinoid abuse resulting in ST-segment elevation myocardial infarction requiring percutaneous coronary intervention. J Emerg Med. 2017;52(4):496–8.
43. Clark BC, Georgekutty J, Berul CI. Myocardial ischemia secondary to synthetic cannabinoid (K2) use in pediatric patients. J Pediatr. 2015;167(3):757–61.e1.
44. Mir A, Obafemi A, Young A, Kane C. Myocardial infarction associated with use of the synthetic cannabinoid K2. Pediatrics. 2011;128(6):e1622–7.
45. Young AC, Schwarz E, Medina G, Obafemi A, Feng SY, Kane C, Kleinschmidt K. Cardiotoxicity associated with the synthetic cannabinoid, K9, with laboratory confirmation. Am J Emerg Med. 2012;30(7):1320.e5–7.
46. Bachs L, Mørland H. Acute cardiovascular fatalities following cannabis use. Forensic Sci Int. 2001;124(2–3):200–3.
47. Kocabay G, Yildiz M, Duran N, Ozkan M. Acute inferior myocardial infarction due to cannabis smoking in a young man. J Cardiovasc Med. 2009;10(9):669–70.
48. Woodward G, Selbst S. Chest pain secondary to cocaine use. Pediatr Emerg Care. 1987;3(3):153–4.
49. Mittleman MA, Lewis RA, Maclure M, Sherwood JB, Muller JE. Triggering myocardial infarction by marijuana. Circulation. 2001;103(23):2805–9.
50. Charles R, Holt S, Kirkham N. Myocardial infarction and marijuana. Clin Toxicol. 1979;14(4):433–8.
51. Gash A, Karliner JS, Janowsky D, Lake CR. Effects of smoking marijuana on left ventricular performance and plasma norepinephrine: studies in normal men. Ann Intern Med. 1978;89(4):448–52.
52. Weiss JL, Watanabe AM, Lemberger L, Tamarkin NR, Cardon PV. Cardiovascular effects of delta-9-tetrahydrocannabinol in man. Clin Pharmacol Ther. 1972;13(5):671–84.
53. Aryana A, Williams MA. Marijuana as a trigger of cardiovascular events: speculation or scientific certainty? Int J Cardiol. 2007;118(2):141–4.
54. Mukamal KJ, Maclure M, Muller JE, Mittleman MA. An exploratory prospective study of marijuana use and mortality after acute myocardial infarction. Am Heart J. 2008;155(3):465–70.
55. Ghuran A, Nolan J. Recreational drug misuse: issues for the cardiologist. Heart. 2000;83:627–33.
56. Anzillotti L, Marezza F, Calò L, Banchini A, Cecchi R. A case report positive for synthetic cannabinoids: are cardiovascular effects related to their protracted use? Legal Med. 2019;41:101637.
57. Barnes D, Palace J, O'Brien MD. Stroke following marijuana smoking. Stroke. 1992;23(9):1381.
58. Freeman MJ, Rose DZ, Myers MA, Gooch CL, Bozeman AC, Burgin WS. Ischemic stroke after use of the synthetic marijuana "spice". Neurology. 2013;81(24):2090–3.
59. Lawson TM, Rees A. Stroke and transient ischaemic attacks in association with substance abuse in a young man. Postgrad Med J. 1996;72(853):692–3.
60. Bernson-Leung ME, Leung LY, Kumar S. Synthetic cannabis and acute ischemic stroke. J Stroke Cerebrovasc Dis. 2014;23(5):1239–41.
61. Wolff V, Jouanjus E. Strokes are possible complications of cannabinoids use. Epilepsy Behav. 2017;70(Pt B):355–63.
62. Raheemullah A, Laurence TN. Repeated thrombosis after synthetic cannabinoid use. J Emerg Med. 2016;51(5):540–3.
63. Weinstein AM, Rosca P, Fattore L, London ED. Synthetic cathinone and cannabinoid designer drugs pose a major risk for public health. Front Psych. 2017;8:156.
64. Müller H, Sperling W, Köhrmann M, Huttner HB, Kornhuber J, Maler JM. The synthetic cannabinoid spice as a trigger for an acute exacerbation of cannabis induced recurrent psychotic episodes. Schizophr Res. 2010;118(1–3):309–10.
65. Zullino DF, Rathelot T, Khazaal Y. Cannabis and psychosis. Lancet. 2007;370(9598):1540.
66. Fantegrossi WE, Wilson CD, Berquist MD III. Pro-psychotic effects of synthetic cannabinoids: interactions with central dopamine, serotonin and glutamate systems. Drug Metab Rev. 2018;50(1):65–73.
67. Adams AJ, Banister SD, Irizarry L, Trecki J, Schwartz M, Gerona R. "Zombie" outbreak caused by the synthetic cannabinoid AMB-FUBINACA in New York. N Engl J Med. 2017;376(3):235–42.
68. Hermanns-Clausen M, Müller D, Kithinji J, Angerer V, Franz F, Eyer F, Neurath H, Liebetrau G, Auwärter V. Acute side effects after consumption of the new synthetic cannabinoids AB-CHMINACA and MDMB-CHMICA. Clin Toxicol (Phila). 2018;56(6):404–11.
69. Schifano F, Albanese A, Fergus S, Stair JL, Deluca P, Corazza O, Davey Z, Corkery J, Siemann H, Scherbaum N, Farre M, Torrens M, Demetrovics Z, Ghodse AH, Psychonaut Web Mapping, ReDNet Research Groups. Mephedrone (4-methylmethcathinone; 'meow meow'): chemical, pharmacological and clinical issues. Psychopharmacology. 2011;214(3):593–602.
70. Gregg RA, Rawls SM. Behavioral pharmacology of designer cathinones: a review of the preclinical literature. Life Sci. 2014;97(1):27–30.
71. Tyrkkö E, Andersson M, Kronstrand R. The toxicology of new psychoactive substances: synthetic Cathinones and Phenylethylamines. Ther Drug Monit. 2016;38(2):190–216.

72. Simmler LD, Buser TA, Donzelli M, Schramm Y, Dieu LH, Huwyler J, Chaboz S, Hoener MC, Liechti ME. Pharmacological characterization of designer cathinones in vitro. Br J Pharmacol. 2013;168 (2):458–70.
73. Simmler LD, Rickli A, Hoener MC, Liechti ME. Monoamine transporter and receptor interaction profiles of a new series of designer cathinones. Neuropharmacology. 2014;79:152–60.
74. Prosser JM, Nelson LS. The toxicology of bath salts: a review of synthetic cathinones. J Med Toxicol. 2012;8(1):33–42.
75. Baumann MH, Partilla JS, Lehner KR. Psychoactive "bath salts": not so soothing. Eur J Pharmacol. 2013;698(1–3):1–5.
76. Valente MJ, Guedes de Pinho P, de Lourdes Bastos M, Carvalho F, Carvalho M. Khat and synthetic cathinones: a review. Arch Toxicol. 2014;88(1):15–45.
77. Locatelli CA, Buscaglia E, Scaravaggi G, Schicchi A, Papa P, Lonati D. Trends in synthetic cathinone use in poisoned patients in Italy from the National Alert System observatory. Clin Toxicol. 2019;57(6):431.
78. Fujita Y, Koeda A, Fujino Y, Onodera M, Kikuchi S, Niitsu H, Iwasaki Y, Usui K, Inoue Y. Clinical and toxicological findings of acute intoxication with synthetic cannabinoids and cathinones. Acute Med Surg. 2015;3(3):230–6.
79. Ezaki J, Ro A, Hasegawa M, Kibayashi K. Fatal overdose from synthetic cannabinoids and cathinones in Japan: demographics and autopsy findings. Am J Drug Alcohol Abuse. 2016;42(5):520–9.
80. Kovács K, Kereszty É, Berkecz R, Tiszlavicz L, Sija É, Körmöczi T, Jenei N, Révész-Schmehl H, Institóris L. Fatal intoxication of a regular drug user following N-ethyl-hexedrone and ADB-FUBINACA consumption. J Forensic Legal Med. 2019;65:92–100.
81. Nagasawa S, Saitoh H, Kasahara S, Chiba F, Torimitsu S, Abe H, Yajima D, Iwase H. Relationship between KCNQ1 (LQT1) and KCNH2 (LQT2) gene mutations and sudden death during illegal drug use. Sci Rep. 2018;8(1):8443.
82. Movahed MR, Mostafizi K. Reverse or inverted left ventricular apical ballooning syndrome (reverse takotsubo cardiomyopathy) in a young woman in the setting of amphetamine use. Echocardiography. 2008;25:429–32.
83. Alsidawi S, Muth J, Wilkin J. Adderall induced inverted-takotsubo cardiomyopathy. Catheter Cardiovasc Interv. 2011;78:910–3.
84. Sivagnanam K, Chaudari D, Lopez P, Sutherland ME, Ramu VK. "Bath salts" induced induced severe reversible cardiomyopathy. Am J Case Rep. 2013;14:288–91.
85. Roda E, Lonati D, Buscaglia E, Papa P, Rocchi L, Locatelli CA, Coccini T. Evaluation of two different screening ELISA assays for synthetic cathinones (Mephedrone/Methcathinone and MDPV) with LC-MS method in intoxicated patients. Clin Toxicol. 2016;6:3.
86. Lippmann M, Appel PL, Mok MS, Shoemaker WC. Sequential cardiorespiratory patterns of anesthetic induction with ketamine in critically ill patients. Crit Care Med. 1983;11:730–4.
87. Spotoft H, Korshin JD, Sørensen MB, Skovsted P. The cardiovascular effects of ketamine used for induction of anaesthesia in patients with valvular heart disease. Can Anaesth Soc J. 1979;26(6):463–7.
88. Chan WM, Xu J, Fan M, Jiang Y, Tsui TY, Wai MS, Lam WP, Yew DT. Downregulation in the human and mice cerebella after ketamine versus ketamine plus ethanol treatment. Microsc Res Tech. 2012;75(3): 258–64.
89. Ossato A, Bilel S, Gregori A, Talarico A, Trapella C, Gaudio RM, De-Giorgio F, Tagliaro F, Neri M, Fattore L, Marti M. Neurological, sensorimotor and cardiorespiratory alterations induced by methoxetamine, ketamine and phencyclidine in mice. Neuropharmacology. 2018;141:167–80.
90. Zarantonello P, Bettini E, Paio A, Simoncelli C, Terreni S, Cardullo F. Novel analogues of ketamine and phencyclidine as NMDA receptor antagonists. Bioorg Med Chem Lett. 2011;21:2059–63.
91. Hondebrink L, Kasteel EEJ, Tukker AM, Wijnolts FMJ, Verboven AHA, Westerink RHS. Neuropharmacological characterization of the new psychoactive substance methoxetamine. Neuropharmacology. 2017;123:1–9.
92. Kalsi SS, Wood DM, Dargan PI. The epidemiology and patterns of acute and chronic toxicity associated with recreational ketamine use. Emerg Health Threats J. 2011;4:7107.
93. Wiergowski M, Anand JS, Krzyżanowski M, Jankowski Z. Acute methoxetamine and amphetamine poisoning with fatal outcome: a case report. Int J Occup Med Environ Health. 2014;27:683–90.
94. Imbert L, Boucher A, Delhome G, Cueto T, Boudinaud M, Maublanc J, Dulaurent S, Descotes J, Lachâtre G, Gaulier JM. Analytical findings of an acute intoxication after inhalation of methoxetamine. J Anal Toxicol. 2014;38:410–5.
95. Zawilska JB. Methoxetamine–a novel recreational drug with potent hallucinogenic properties. Toxicol Lett. 2014;230:402–7.
96. Adamowicz P, Zuba D. Fatal intoxication with methoxetamine. J Forensic Sci. 2015;60:264–8.
97. Łukasik-Głebocka M, Sommerfeld K, Tezyk A, Zielińska-Psuja B, Druzdz A. Acute methoxetamine intoxication–a case report with serum and urine concentrations. Przegl Lek. 2013;70:671–3.
98. Thornton S, Lisbon D, Lin T, Gerona R. Beyond ketamine and phencyclidine: analytically confirmed use of multiple novel arylcyclohexylamines. J Psychoactive Drugs. 2017;49:289–93.
99. Weiner AL, Vieira L, McKay CA, Bayer MJ. Ketamine abusers presenting to the emergency department: a case series. J Emerg Med. 2000;18(4):447–51.
100. Morgan HL, Turner D, Corlett PR, Corlett PR, Absalom AR, Adapa R, Arana FS, Pigott J, Gardner

J, Everitt J, Haggard P, Fletcher PC. Exploring the impact of ketamine on the experience of illusory body ownership. Biol Psychiatry. 2011;69(1):35–41.
101. Bäckberg M, Beck O, Helander A. Phencyclidine analog use in Sweden–intoxication cases involving 3-MeO-PCP and 4-MeO-PCP from the STRIDA project. Clin Toxicol. 2015;53:856–64.
102. Iversen L, White M, Treble R. Designer psychostimulants: pharmacology and differences. Neuropharmacology. 2014;87:59–65.
103. Mladěnka P, Applová L, Patočka J, Costa VM, Remiao F, Pourová J, Mladěnka A, Karlíčková J, Jahodář L, Vopršalová M, Varner KJ, Štěrba M, TOX-OER and CARDIOTOX Hradec Králové Researchers and Collaborators. Comprehensive review of cardiovascular toxicity of drugs and related agents. Med Res Rev. 2018;38(4):1332–403.
104. Holden R, Jackson MA. Near-fatal hyponatraemic coma due to vasopressin over-secretion after "ecstasy" (3,4-MDMA). Lancet. 1996;347(9007):1052.
105. Hartung TK, Schofield E, Short AI, Parr MJ, Henry JA. Hyponatraemic states following 3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy') ingestion. QJM. 2002;95(7):431–7.
106. Locatelli CA, Buscaglia E, Vecchio S, Prevaldi C, Scaravaggi G, Papa P, Lonati D, Coccini T. Clinical features of paramethoxymethamphetamine (PMMA) poisoning in lethal and non-lethal cases. Clin Toxicol. 2016;54(4):406–7.
107. Vevelstad M, Øiestad EL, Middelkoop G, Hasvold I, Lilleng P, Delaveris GJ, Eggen T, Mørland J, Arnestad M. The PMMA epidemic in Norway: comparison of fatal and non-fatal intoxications. Forensic Sci Int. 2012;219(1–3):151–7.
108. Al-Samarraie MS, Vevelstad M, Nygaard IL, Bachs L, Mørland J. Intoxation with para-methoxymethamphetamine. Tidsskr Nor Laegeforen. 2013;133(9):966–9.
109. Ptaszyńska-Sarosiek I, Wardaszka Z, Sackiewicz A, Okłota M, Niemcunowicz-Janica A. Cases of fatal para methoxy amphetamine (PMA) poisoning in the material of the Forensic Medicine Department, Medical University of Białystok, Poland. Arch Med Sadowej Kryminol. 2009;59(3):190–3.
110. Ling LH, Marchant C, Buckley NA, Prior M, Irvine RJ. Poisoning with the recreational drug para-methoxyamphetamine ("death"). Med J Aust. 2001;174(9):453–5.
111. Richards JR, Derlet RW, Albertson TE, Horowitz BZ, Lange RA. Methamphetamine, "Bath Salts," and other amphetamine-related derivatives: progressive treatment update. Enliven: Toxicol Allied Clin Pharmacol. 2014;1(1):001.
112. Hondebrink L, Nugteren-van Lonkhuyzen JJ, Rietjens SJ, Brunt TM, Venhuis B, Soerdjbalie-Maikoe V, Smink BE, van Riel AJHP, de Vries I. Fatalities, cerebral hemorrhage, and severe cardiovascular toxicity after exposure to the new psychoactive substance 4-fluoroamphetamine: a prospective cohort study. Ann Emerg Med. 2018;71(3):294–305.
113. Wikström M, Holmgren P, Ahlner J. A2 (N-benzylpiperazine) a new drug of abuse in Sweden. J Anal Toxicol. 2004;28:67–70.
114. Monteiro MS, Bastos Mde L, Guedes de Pinho P, Carvalho M. Update on 1-benzylpiperazine (BZP) party pills. Arch Toxicol. 2013;87(6):929–47.
115. Schep LJ, Slaughter RJ, Vale JA, Beasley DM, Gee P. The clinical toxicology of the designer "party pills" benzylpiperazine and trifluoromethylphenylpiperazine. Clin Toxicol. 2011;49(3):131–41.
116. Gee P, Gilbert M, Richardson S, Moore G, Paterson S, Graham P. Toxicity from the recreational use of 1-benzylpiperazine. Clin Toxicol. 2008;46(9):802–7.
117. Briner K, Burkhart JP, Burkholder TM, et al. Aminoalkylbenzofurans as serotonin (5-HT(2C)) agonists. US Patent 7045545 B1 to Eli Lilly and Co., 16 May 2006.
118. Chambers JJ, Kurrasch-Orbaugh DM, Parker MA, Nichols DE. Enantiospecific synthesis and pharmacological evaluation of a series of super-potent, conformationally restricted 5-HT(2A/2C) receptor agonists. J Med Chem. 2001;44(6):1003–10.
119. Locatelli CA, Lonati D, Buscaglia E, Vecchio S, Giampreti A, Petrolini VM, Chiara F, Aloise M, Corsini E, Papa P, Valli A, Andreoni L, Rimondo C, Seri C, Serpelloni G. "Benzofury" poisoning that mimics meningoecephalitis/septicemia. Clin Toxicol. 2013;51:286–7.
120. Personne M, Hulten P. Bromo-dragonfly: a life-threatening designer drug. Clin Tox. 2008;46:379–80.
121. Thorlacius K, Borna C, Personne M. Bromo-dragonfly – life-threatening drug. Can cause tissue necrosis as demonstrated by the first described case. Lakartidningen. 2008;105(16):1199–200.
122. Andreasen MF, Telving R, Birkler RI, Schumacher B, Johannsen M. A fatal poisoning involving Bromo-Dragonfly. Forensic Sci Int. 2009;183(1–3):91–6.
123. Villalobos CA, Bull P, Sáez P, Cassels BK, Huidobro-Toro JP. 4-Bromo-2,5-imethoxyphenethylamine (2C-B) and structurally related phenylethylamines are potent 5-HT2A receptor antagonists in *Xenopus laevis* oocytes. Br J Pharmacol. 2004;141(7):1167–74.
124. Nagai F, Nonaka R, Satoh Hisashi Kamimura K. The effects of nonmedically used psychoactive drugs on monoamine neurotransmission in rat brain. Eur J Pharmacol. 2007;559(2–3):132–7.
125. Sanders B, Lankenau SE, Bloom JJ, Hathazi D. "Research chemicals": tryptamine and phenethylamine use among high-risk youth. Subst Use Misuse. 2008;43(3–4):389–402.
126. Johnson MP, Huang XM, Oberlender R, Nash JF, Nichols DE. Behavioral, biochemical and neurotoxicological actions of the alpha-ethyl homologue of p-chloroamphetamine. Eur J Pharmacol. 1990;191(1):1–10.
127. Papaseit E, Farré M, Pérez-Mañá C, Torrens M, Ventura M, Pujadas M, de la Torre R, González D. Acute

pharmacological effects of 2C-B in humans: an observational study. Front Pharmacol. 2018;9:206.
128. Miyajima M, Matsumoto T, Ito S. 2C-T-4 intoxication: acute psychosis caused by a designer drug. Psychiatry Clin Neurosci. 2008;62(2):243.
129. Huang HH, Bai YM. Persistent psychosis after ingestion of a single tablet of '2C-B'. Prog Neuro-Psychopharmacol Biol Psychiatry. 2011;35(1):293–4.
130. Vilke GM, DeBard ML, Chan TC, Ho JD, Dawes DM, Hall C, Curtis MD, Costello MW, Mash DC, Coffman SR, McMullen MJ, Metzger JC, Roberts JR, Sztajnkrcer MD, Henderson SO, Adler J, Czarnecki F, Heck J, Bozeman WP. Excited Delirium Syndrome (ExDS): defining based on a review of the literature. J Emerg Med. 2012;43(5):897–905.
131. Sacks J, Ray MJ, Williams S, Opatowsky MJ. Fatal toxic leukoencephalopathy secondary to overdose of a new psychoactive designer drug 2C-E ("Europa"). Proc (Bayl Univ Med Cent). 2012;25(4):374–6.
132. Topeff JM, Ellsworth H, Willhite LA, Bangh SA, Edwards EM, Cole JB. A case series of symptomatic patients, including one fatality, following 2C-E exposure. Clin Toxicol. 2011;49:526.
133. Locatelli CA, Lonati D, Giampreti A, Petrolini VM, Papa P, Buscaglia E, Roda E, Coccini T. Clinical features of intoxication with 2C-series phenethylamines. Clin Toxicol. 2016b;54(4):407.
134. Bosak A, LoVecchio F, Levine M. Recurrent seizures and serotonin syndrome following "2C-I" ingestion. J Med Toxicol. 2013;9(2):196–8.
135. Cheng HC, Long JP, Nichols DE, Barfknecht CF. Effects of psychotomimetics on vascular strips: studies of methoxylated amphetamines and optical isomers of 2,5-dimethoxy-4-methylamphetamine and 2,5-dimethoxy-4-bromoamphetamine. J Pharmacol Exp Ther. 1974;188(1):114–23.
136. Rusterholz DB, Spratt JL, Long JP, Kelly TF. Serotonergic and dopaminergic involvement in the mechanism of action of R-(-)-2,5-dimethoxy-4-bromoamphetamine (DOB) in cats. Life Sci. 1978;23(14):1499–506.
137. Bowen JS, Davis GB, Kearney TE, Bardin J. Diffuse vascular spasm associated with 4-bromo-2,5-dimethoxyamphetamine ingestion. JAMA. 1983;249(11):1477–9.
138. Ovaska H, Viljoen A, Puchnarewicz M, Button J, Ramsey J, Holt DW, Dargan PI, Wood DM. First case report of recreational use of 2,5-dimethoxy-4-chloroamphetamine confirmed by toxicological screening. Eur J Emerg Med. 2008;15(6):354–6.
139. Morini L, Bernini M, Vezzoli S, Restori M, Moretti M, Crenna S, Papa P, Locatelli C, Osculati AMM, Vignali C, Groppi A. Death after 25C-NBOMe and 25H-NBOMe consumption. Forensic Sci Int. 2017;279:e1–6.
140. Fantegrossi WE, Murnane KS, Reissig CJ. The behavioral pharmacology of hallucinogens. Biochem Pharmacol. 2008;75(1):17–33.
141. Cozzi NV, Gopalakrishnan A, Anderson LL, Feih JT, Shulgin AT, Daley PF, Ruoho AE. Dimethyltryptamine and other hallucinogenic tryptamines exhibit substrate behavior at the serotonin uptake transporter and the vesicle monoamine transporter. J Neural Transm (Vienna). 2009;116(12):1591–9.
142. Fontanilla D, Johannessen M, Hajipour AR, Cozzi NV, Jackson MB, Ruoho AE. The hallucinogen N,N-dimethyltryptamine (DMT) is an endogenous sigma-1 receptor regulator. Science. 2009;323(5916):934–7. https://doi.org/10.1126/science.1166127.
143. Sogawa C, Sogawa N, Tagawa J, Fujino A, Ohyama K, Asanuma M, Funada M, Kitayama S. 5-Methoxy-N,N-diisopropyltryptamine (Foxy), a selective and high affinity inhibitor of serotonin transporter. Toxicol Lett. 2007;170(1):75–82. Epub 2007 Feb 21
144. Araújo AM, Carvalho F, Bastos Mde L, Guedes de Pinho P, Carvalho M. The hallucinogenic world of tryptamines: an updated review. Arch Toxicol. 2015;89(8):1151–73.
145. Schifano F, Orsolini L, Duccio Papanti G, Corkery JM. Novel psychoactive substances of interest for psychiatry. World Psychiatry. 2015;14(1):15–26. https://doi.org/10.1002/wps.20174.
146. Yoon KS, Lee JM, Kim YH, Suh SK, Cha HJ. Cardiotoxic effects of [3-[2-(diethylamino)ethyl]-1H-indol-4-yl] acetate and 3-[2-[ethyl(methyl)amino] ethyl]-1H-indol-4-ol. Toxicol Lett. 2020;319:40–8.
147. Strassman RJ, Qualls CR. Dose-response study of N, N-dimethyltryptamine in humans. I. Neuroendocrine, autonomic, and cardiovascular effects. Arch Gen Psychiatry. 1994;51(2):85–97.
148. Garbelli E, Petrolini VM, Coccini T, Vecchio S, Papa P, Lonati D, Locatelli CA. Hyperthermia in sympathomimetic/serotonergic substance of abuse poisoning: a case series. Clin Toxicol. 2018;56(6):470.
149. Grunau BE, Wiens MO, Brubacher JR. Dantrolene in the treatment of MDMA-related hyperpyrexia: a systematic review. CJEM. 2010;12:435–42.
150. Hysek C, Schmid Y, Rickli A, Simmler LD, Donzelli M, et al. Carvedilol inhibits the cardiostimulant and thermogenic effects of MDMA in humans. Br J Pharmacol. 2012;166:2277–88.
151. Sprague JE, Moze P, Caden D, Rusyniak DE, Holmes C, Goldstein DS, Mills EM. Carvedilol reverses hyperthermia and attenuates rhabdomyolysis induced by 3,4-methylenedioxymethamphetamine (MDMA, ecstasy) in an animal model. Crit Care Med. 2005;33(6):1311–6.
152. Hoskins MH, Leleiko RM, Ramos JJ, Sola S, Caneer PM, Khan BV. Effects of labetalol on hemodynamic parameters and soluble biomarkers of inflammation in acute coronary syndrome in patients with active cocaine use. J Cardiovasc Pharmacol Ther. 2010;15(1):47–52.
153. Valli A, Lonati D, Locatelli CA, Buscaglia E, Di Tuccio M, Papa P. Analytically diagnosed intoxication by 2-methoxphenidine and flubromazepam mimicking an ischemic cerebral disease. Clin Toxicol. 2017;55(6):611–2. https://doi.org/10.1080/15563650.2017.1286016. Epub 2017 Feb 8.

Part X

Life Style and Activities Influencing Cardiovascular and Cerebral Function

Physical Activity and Cardiovascular Health

54

Cosme Franklim Buzzachera, Luca Correale, and Giulia Liberali

Contents

Abstract

Cardiovascular diseases (CVDs) are a leading cause of death in the world. When combined, ischemic heart disease and all forms of CVDs were the attributed causes of death for an estimated 17.6 million people globally in 2016, or 1 in 4 deaths worldwide. Multiple risk factors are attributed to causing CVDs. Some of the most significant CVD risk factors are age, sex, family history, tobacco smoking, obesity, blood pressure, and diabetes. A sedentary lifestyle, characterized by low rates of physical activity, is also currently recognized as a leading contributor to poor cardiovascular health. A more active lifestyle, therefore, reduces the risk of CVDs, with potential implications in a number of noncardiovascular chronic diseases, such as type 2 diabetes, hypertension, osteoporosis, and breast and colon cancer. Herein we describe the role of a comprehensive exercise program that includes aerobic exercise and weight training as an effective and important strategy for the prevention and management of CVDs.

Keywords

Exercise · Aerobic training · Resistance training · Fitness · Heart · Brain

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*,
https://doi.org/10.1007/978-3-030-28008-6_59

Introduction

Cardiovascular diseases (CVDs) are a leading cause of death in the world. When combined, ischemic heart disease and all forms of CVDs were the attributed causes of death for an estimated 17.6 million people globally in 2016, or 1 in 4 deaths worldwide [1]. In the United States, for example, CVDs were responsible for 840,768 deaths in 2016. Of note, 306,638, or 36.5% of deaths attributed to CVDs, occurred before the age of 75 years, which is below the average US life expectancy of 78.6 years. However, from 2006 to 2016, the US death rate from CVDs decreased by 18.6% [2]. Similar declines have been observed in nearly all regions of the world, particularly in high-income countries including North America, Japan, Australia, New Zealand, and Western Europe [3]. The reasons for the remarkable decline in death rates from CVDs among high-income countries are still unclear but may be related to improvements in health care and, more recently, population-level changes in risk factors [4].

Multiple risk factors are attributed to causing CVDs. Some of the most significant risk factors are age, sex, family history, tobacco smoking, obesity, blood pressure, and diabetes [4, 5]. These risk factors can be split into two categories: nonmodifiable and modifiable risk factors. Nonmodifiable risk factors consist of those conditions that a person cannot alter, whereas modifiable risk factors are conditions that can be altered by making certain lifestyle changes [6]. Among the many modifiable risk factors that predispose to development and progression of CVDs, a sedentary lifestyle, characterized by low rates of physical activity, is currently recognized as a leading contributor to poor cardiovascular health. A more active lifestyle, on the other hand, reduces the risk of CVDs, with a magnitude of risk reduction comparable to that of not smoking [7, 8]. Accordingly, more active individuals tend to develop less CVDs than their sedentary counterparts. If CVDs develop in active individuals, they tend to occur at a later age and be less severe [9]. Retrospective and follow-up studies have also documented the protective effects of physical activity for a number of noncardiovascular chronic diseases, such as type 2 diabetes, hypertension, osteoporosis, and breast and colon cancer [10, 11]. Consistent with this notion, organizations such as the Centers for Disease Control and Prevention (CDC), the American Heart Association (AHA), and the American College of Sports Medicine (ACSM) have reinforced the importance of regular physical activity to cardiovascular and noncardiovascular health [12, 13].

Within the past few decades, cardiorespiratory fitness (CRF) has emerged as an important risk factor for CVDs, independent of traditional risk factors [4, 5]. CRF is a health-related component of physical fitness, defined as the ability of the respiratory, circulatory, and muscular systems to supply oxygen during sustained physical activity [14]. CRF is mostly influenced by nonmodifiable, intrinsic factors (e.g., genetics, environment) [15]. Prior evidence has shown that in individuals with the same CRF, being physically active does not lower mortality risk, suggesting that intrinsic factors drive the association between CRF and risk [16]. However, these findings also reinforce the notion that those individuals who adopted physical activity achieved the same risk reduction as those with an intrinsically high CRF [17], thus highlighting the role of physical activity as a primary modifiable determinant of CRF. In fact, higher rates of cardiovascular events and higher death rates are reported in insufficiently active individuals with low levels of CRF [18, 19]. Additionally, even during midlife, increases in physical activity and CRF, through changes in occupational or recreational activities, are associated with decreases in all-cause and CVD mortality [18, 19]. These findings, along with others [20–22], underscore the fact that fitness and daily activity levels have a strong influence on the occurrence of CVDs and overall mortality.

Benefits of Physical Activity on Cardiovascular Risk Factors

Sixty years ago, the first empirical investigation of what was subsequently termed the exercise hypothesis – physical activity reduces the

incidence of coronary heart disease – was undertaken by Professor Jeremy N. Morris. In a series of studies [23–25], Morris and his associates used quantitative analysis to demonstrate that physical activity protects against coronary heart disease. Specifically, they found that deaths from coronary heart disease might be less common among men engaged in physically active work than in those in sedentary jobs. Although this series of research was pioneering, it was not without its shortcomings. Early statistical methods were limited in their capacity for controlling for intervening variables or demonstrating causality. However, the observations of Morris and colleagues were later confirmed by several other investigators [26]. In fact, physical activity is currently reported to be cardioprotective, an effect that is maintained after controlling for a range of covariates [10].

The pathways underlying the protective effect of physical activity against CVDs are not yet fully understood. For example, some evidence has suggested that regular physical activity may improve coronary endothelial function and may be associated with potentially beneficial changes in hemostatic and inflammatory variables [27, 28]. These pathways warrant further research. Evidence from many scientific studies, however, has shown that reducing the modifiable risk factors for CVDs decreases the chances of having a heart attack or experiencing another form of cardiac event, such as a stroke [9]. Regular physical activity can promote favorable effects on many of the traditional risk factors for CVDs. For example, regular engagement in physical activity may lower CVD risk by affecting the levels of circulating lipoproteins [29]. Previous studies have found that physical activity in terms of structured aerobic exercise is associated with elevated levels of circulating high-density lipoprotein (HDL) and, to a lesser extent, a reduction in triglyceride levels [30, 31]. However, in a more recent study, Kraus et al. [32] found a dose-dependent effect of aerobic exercise not only on circulating HDL and triglyceride levels but also on plasma levels of low-density lipoprotein (LDL) and large particle, very low-density lipoprotein (VLDL). Physical activity can also promote favorable changes in blood pressure (BP) at rest [29]. In fact, a meta-analysis of randomized controlled intervention studies found that regular moderate to vigorous exercise performed 3–5 times per week decreases BP by an average of 3.4/2.4 mmHg [33], which is likely to be related to a reduction in systemic vascular resistance, to which the sympathetic nervous system and the renin-angiotensin system appear to be related [34]. These findings are of paramount importance because even a 1 mmHg population-wide systolic BP reduction is associated with 20.3 and 13.3 fewer heart failure events per 100,000 person-years [35]. Finally, in diabetic patients, regular engagement in physical activity favorably affects the body's ability to use insulin to control glucose levels in the blood [29]. Prior reports have shown that individuals with insulin-dependent and non-insulin-dependent diabetes mellitus present improved sensitivity to insulin and improved glycemic control after acute [36] and chronic exercise [37]. These results are also of interest, since the association between blood lipids and cardiovascular health is heavily influenced by systemic insulin sensitivity [38].

Overweight (i.e., body mass index, BMI, 25 to 29.9 $kg.m^{-2}$) and obesity (i.e., BMI, 30 $kg.m^{-2}$ or greater) are other well-established risk factors for most CVDs [39]. Overweight and obese individuals tend to present a greater prevalence of CVDs in comparison with their leaner counterparts [40]. Data from the Framingham Health Study also demonstrated, after adjustment for other covariates, that approximately 23% of CVDs in men and 15% of CVDs in women were attributable to excess adiposity [39]. Additionally, every 1 $kg.m^{-2}$ increment in BMI was found to elevate the risk of heart failure by 5% in men and 7% in women [41]. These findings are of concern because the prevalence rates of overweight and obesity are rising alarmingly among adults in many industrialized and developing countries [42]. Interestingly, despite the strong relationship between excess adiposity and the development of CVDs, a growing body of evidence supports an "obesity paradox" in patients with CVD. This phenomenon is characterized by a better prognosis in overweight patients with CVD, compared to their leaner counterparts [43]. In addition, the worst outcomes are reported in underweight

CVD patients, followed by those with normal weight or overweight [44]. The exact mechanisms for the "obesity paradox" in CVDs are incompletely understood; however, prior evidence suggests that both CRF and muscle strength are the major determinants of the prognostic implications of overweight and obesity in CVD [45]. Hence, regular physical activity and structured exercise training, with potential implications in CRF and muscle strength, constitute a fundamental aspect of non-pharmacological management of patients with or at risk for CVDs, regardless of their BMI.

Dietary patterns are associated with mortality from all-causes and CVDs [46]. There is a large body of evidence to support that diets rich in fruits, vegetables, whole grain breads, high fibre cereals, fish, and low-fat dairy products, as well as diets low in saturated fats and sodium, can reduce the risk of developing CVDs [6]. However, whether regular physical activity and structured exercise training affect dietary patterns is controversial. Limited studies are available, and results are inconsistent [47, 48]. For example, in a recent study, Shaw et al. [49] found that 16 weeks of either aerobic training or combined aerobic plus weight training significantly reduced the amount of total kilocalories, carbohydrates, proteins, and fats consumed. No changes were found in self-reported dietary intake in the weight training or non-exercising control groups [50]. In contrast, a previous study by Willis et al. [51] found that 32 weeks of aerobic training, weight training, or their combination did not modify the self-reported energy intake in a group of previously sedentary, overweight, or obese adults. Inconsistencies between physical activity, exercise, and other modifiable risk factors for CVDs, such as tobacco smoking and alcohol use, have also been noted in the literature [52–54]. It is noteworthy, however, that although the effect of a structured exercise program on any single CVD risk factor may generally be small, the effect of continued, long-term exercise training on cardiovascular health, when combined with multiple lifestyle modifications, can be dramatic.

Although it is well known that regular physical activity protects against CVDs and related complications [9], unfortunately, most adults do not meet the minimum recommended levels of exercise participation [55]. In fact, physical inactivity continues to be a major public health problem in many industrialized and developing countries. According to the World Health Organization [56], approximately 1.9 million people worldwide die each year from diseases related to physical inactivity. Additionally, approximately 19 million disability-adjusted life years are lost annually because of physical inactivity. Although several public health strategies have been adopted to reduce the prevalence of physical inactivity, the proportion of people meeting the current recommendation of accumulating $\geq$30 min of moderate physical activity at least five times a week or $\geq$20 min of vigorous physical activity at least three times a week has remained essentially unchanged over the last decades [55]. In addition, approximately 50% of individuals who initiate an exercise program drop out within the first few months of participation [57]. Identification of potential factors that contribute to physical inactivity has been one of the greatest challenges in exercise research in recent years.

How Much Physical Activity for Cardiovascular Health?

Aerobic Training

Physical activity in terms of structured exercise for the prevention and management of CVDs should focus on aerobic (or endurance/cardiovascular) modes of exercise. Aerobic exercise uses large muscle groups in a rhythmic and continuous fashion and is associated with a myriad of health benefits in patients with or at risk for CVDs, including improved lipid profile and blood glucose control, reduced blood pressure at rest, and increased overall well-being [29]. In overweight and obese patients, for example, aerobic exercise may lead to expenditure of a considerable amount of energy in a given period of time, which in turn may be useful for achieving the recommended target of 2000 kcal.wk.$^{-1}$ [58]. Traditionally, aerobic exercise has been categorized as either weight bearing or non-weight bearing. Walking

is a typical example of a weight-bearing activity that is currently considered one of the best forms of exercise for several reasons, including safety and all individuals having experience with the activity; it is also available to most individuals and does not require special facilities [59]. However, some patients with or at risk for CVDs have preexisting clinical conditions that could prevent certain modes of activities, such as walking (for more details, see [60]). In this scenario, activities such as stationary cycling, recumbent cycling, or water activities should be selected. It is therefore recommended that physicians include aerobic training as an important part of exercise programs for patients with or at risk for CVDs.

To achieve the benefits associated with aerobic training, individuals need to participate in adequate levels of physical activity. Thus, in 1996, the US Surgeon General's Report on Physical Activity and Health provided a springboard for the largest government effort to date to promote physical activity and exercise among Americans [61]. This historic turning point redefined physical activity and exercise as key elements of health promotion and disease prevention. The US Surgeon General's Report stated that the favorable effects of physical activity will generally occur by engaging in a minimum of 30 min/day of moderate aerobic activity. These moderate activities should ideally last at least 10 min and be spread throughout the week [61]. However, although this traditional recommendation for the amount of physical activity is useful for the majority of sedentary adults [58], research has suggested that greater amounts may be needed for patients with excess body weight [62]. Accordingly, in 2008, the Physical Activity Guidelines for Americans [63] recommended a target range that should be achieved of not only 150 to 300 min/week of moderate-intensity physical activity but also 75 to 150 min/week of vigorous physical activity, or an equivalent volume from a combination of moderate and vigorous physical activity. Although the associations of non-structured physical activity with favorable health outcomes begin when adopting very modest amounts, meeting the 2008 Physical Activity Guidelines for Americans reduces mortality and CVD risk to about 75% of the maximal benefit [64]. Interestingly, although additional physical activity continues to reduce the risk even more, greater amounts of physical activity are required to obtain small health benefits [64].

When prescribing an exercise program, it is helpful for physicians to understand some basic concepts of exercise. For example, intensity and duration components must be manipulated so that the intensity is low (or high) enough to allow a suitable duration to promote health benefits [65]. Health benefits of physical activity can be promoted when performing aerobic exercise with low intensity and long duration or exercise with moderate to high intensity and short duration. Less intense, shorter bouts (<10 min), with more rest periods, should be prescribed for most cardiac, frail, and older patients [63]. Similarly, for many overweight adults who are engaging in an exercise program, the intensity must not be high enough to cause improvements in CRF, because the initial focus should be on weight maintenance and loss and therefore energy expenditure [58]. As the exercise program progresses and the individual is able to better tolerate the exercise session, moderate intensities between 40 and 59% of heart rate reserve (HRR; maximum heart rate minus resting heart rate), corresponding to a rating of perceived exertion (RPE) of 11–13 on a 6–20 scale [66], should be encouraged [63]. Moderate activities are any activity that is similar in intensity to brisk walking and can include other forms of occupational or recreational tasks that are dynamic in nature and of similar intensity, such as bicycling, swimming, vacuuming, and gardening [9]. Higher-intensity exercise bouts above 60%HRR could also be prescribed under the supervision of a health professional [67, 68]. There is growing and robust evidence that exercise protocols alternating between periods of vigorous activities and periods of rest or recovery, termed as "high-intensity interval training" (HIIT), show similar or greater efficacy compared with traditional, low- to moderate-intensity continuous aerobic exercise training across a range of cardiovascular and metabolic outcomes, in both healthy and diseased patients [69]. Hence, patients with or at risk for CVDs who have been

participating in regular exercise may consider raising the intensity to elicit higher levels of physical exertion. However, the prescription of vigorous-intensity activities is likely to be a contributing factor to nonadherence to exercise programs. Considerable evidence exists that people are more likely to adhere to low-intensity activities than high-intensity activities [70, 71]; thus, physicians are not always encouraged to "push" their patients in order to avoid premature exercise dropout.

Resistance Training

Until 1990, weight (or resistance) training was not a component of the recommended guidelines for exercise training from either the AHA or the ACSM. However, in 1990, the ACSM first recognized weight training as an important part of a comprehensive exercise program for healthy adults of all ages [72]. Currently, weight training is established as a safe and effective method of exercise for healthy and diseased adults [73, 74]. When appropriately prescribed and monitored, weight training has favorable effects on muscle mass, which may in turn increase 24-h energy expenditure [75]. These beneficial effects on muscle structure and function may also be advantageous for improving the ability to perform activities of daily living in the majority of cardiac, frail, and older patients, who benefit substantially in terms of quality of life [76]. Additionally, weight training can be beneficial in the prevention and management of noncardiovascular chronic diseases, including but not limited to obesity, type 2 diabetes, hypertension, osteoporosis, and certain types of cancer [74]. The addition of weight training to a comprehensive exercise program, therefore, may promote benefits for reasons other than the impact of this form of exercise on muscular development. On 2–3 days/week, adults are encouraged to perform a single set of eight to ten different exercises that train the major muscle groups, although greater frequencies of training and more sets are associated with small but significant gains [77]. A repetition range of 8 to 12 is recommended for healthy, young adults, while 10 to 15 repetitions at a low relative weight are encouraged for older and diseased adults [74]. Finally, neuromotor exercise involving balance, agility, and coordination is also recommended in most circumstances [73].

Is Physical Activity Safe?

The risk of having a cardiac-related complication (e.g., a heart attack or serious heart rhythm disorder) during physical activity is extremely small. For adults without existing heart disease, for example, the risk of a major or fatal cardiovascular event is estimated to be 1 in 400,000–800,000 h of exercise. For patients with existing heart disease, an event can occur an average of once in 62,000 h of exercise [78]. Of note, the risk of having a cardiac-related complication is still significantly lower among regular exercisers [13]. Thus, the benefits of physical activity for cardiovascular and noncardiovascular health clearly far outweigh the risks. Although the safety of physical activity in terms of structured exercise in apparently healthy adults is well established, proper preliminary screening, appropriate prescriptive guidelines, and careful supervision are important. Patients with existing heart disease, however, should proceed with exercise training with caution and closely monitor warning signs and symptoms that may indicate a problem [9].

Conclusions

Multiple risk factors are attributed to causing CVDs. A sedentary lifestyle, characterized by low rates of physical activity, is currently recognized as a leading contributor to poor cardiovascular health. A more active lifestyle, therefore, reduces the risk of CVDs, with potential implications in a number of noncardiovascular chronic diseases, such as type 2 diabetes, hypertension, osteoporosis, and breast and colon cancer. Mild-to-moderate aerobic training is of paramount importance for the prevention and management of CVDs. The addition of weight training to a comprehensive exercise program, however, may

increase some of the exercise-related health benefits in patients with or at risk for CVDs, including improved lipid profile and blood glucose control, reduced blood pressure at rest, and increased overall well-being. As both healthy and diseased adults are often predisposed to drop out of an exercise program within the first few months of participation, exercise interventions that may lead them to feel better should be taken into consideration by health professionals.

References

1. GBD 2016 Causes of Death Collaborators. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2017;390:1151–210. https://doi.org/10.1016/S0140-6736(17)32152-9.
2. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, et al. Heart disease and stroke statistics – 2019 update: a report from the American Heart Association. Circulation. 2019;139:e56–e528. https://doi.org/10.1161/CIR.0000000000000659.
3. Roth GA, Huffman MD, Moran AE, Feigin V, Mensah GA, Naghavi M, et al. Global and regional patterns in cardiovascular mortality from 1990 to 2013. Circulation. 2015;132:1667–78. https://doi.org/10.1161/CIRCULATIONAHA.114.008720.
4. Ford ES, Ajani UA, Croft JB, Critchley JA, Labarthe DR, Kottke TE, et al. Explaining the decrease in U.S. deaths from coronary disease, 1980–2000. N Engl J Med. 2007;356:2388–98. https://doi.org/10.1056/NEJMsa053935.
5. Mensah GA, Wei GS, Sorlie PD, Fine LJ, Rosenberg Y, Kaufmann PG, et al. Decline in cardiovascular mortality: possible causes and implications. Circ Res. 2017;120:366–80. https://doi.org/10.1056/NEJMsa053935.
6. Buttar HS, Li T, Ravi N. Prevention of cardiovascular diseases: role of exercise, dietary interventions, obesity and smoking cessation. Exp Clin Cardiol. 2005;10:229–49.
7. Manson JE, Greenland P, LaManson JE, Greenland P, LaCroix AZ, Stefanick ML, et al. Walking compared with vigorous exercise for the prevention of cardiovascular events in women. N Engl J Med. 2002;347:716–25. https://doi.org/10.1056/NEJMoa021067.
8. Blair SN, Kampert JB, Kohl HW 3rd, Barlow CE, Macera CA, Paffenbarger RS Jr, et al. Influences of cardiorespiratory fitness and other precursors on cardiovascular disease and all-cause mortality in men and women. JAMA. 1996;276:205–10.
9. Myers J. Exercise and cardiovascular health. Circulation. 2003;107:e2–5. https://doi.org/10.1161/01.CIR.0000048890.59383.8D.
10. Lee IM, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT, et al. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. Lancet. 2012;380:219–29. https://doi.org/10.1016/S0140-6736(12)61031-9.
11. Batty GD, Lee IM. Physical activity and coronary heart disease. BMJ. 2004;328:1089–90. https://doi.org/10.1136/bmj.328.7448.1089.
12. Pate RR, Pratt MP, Blair SN, Haskell WL, Macera CA, Bouchard C, et al. Physical activity and public health: a recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. JAMA. 1995;273:402–7. https://doi.org/10.1001/jama.273.5.402.
13. Fletcher GF, Ades PA, Kligfield P, Arena R, Balady GJ, Bittner VA, et al. Exercise standards for testing and training: a scientific statement from the American Heart Association. Circulation. 2013;128:873–934. https://doi.org/10.1161/CIR.0b013e31829b5b44.
14. Bouchard C, Ping A, Rice T, Skinner JS, Wilmore JH, Gagnon J, et al. Familial aggregation of VO(2max) response to exercise training: results from HERITAGE family study. J Appl Physiol. 1999;87:1003–8. https://doi.org/10.1152/jappl.1999.87.3.1003.
15. Bassett DR Jr, Howley ET. Limiting factors for maximum oxygen uptake and determinants of endurance performance. Med Sci Sports Exerc. 2000;32:70–84. https://doi.org/10.1097/00005768-200001000-00012.
16. Davidson T, Vainshelboim B, Kokkinos P, Myers J, Ross R. Cardiorespiratory fitness versus physical activity as predictors of all-cause mortality in men. Am Heart J. 2018;196:156–62. https://doi.org/10.1016/j.ahj.2017.08.022.
17. de Lannoy L, Sui X, Blair SN, Ross R. All-cause mortality risk among active and inactive adults matched for cardiorespiratory fitness. Eur J Prev Cardiol. 2019;26:554–6. https://doi.org/10.1016/j.ahj.2017.08.022.
18. Blair SN, Kohl HW 3rd, Paffenbarger RS Jr, Clark DG, Cooper KH, Gibbons LW. Physical fitness and all-cause mortality: A prospective study of healthy men and women. JAMA. 1989;262:2395–401. https://doi.org/10.1001/jama.262.17.2395.
19. Paffenbarger RS Jr, Hyde RT, Wing AL, Lee IM, Jung DL, Kampert JB. The association of changes in physical-activity level and other lifestyle characteristics with mortality among men. N Engl J Med. 1993;328:538–45. https://doi.org/10.1056/NEJM199302253280804.
20. Yu S, Yarnell JW, Sweetnam PM, Murray L. What level of physical activity protects against premature cardiovascular death? Caerphilly Stud Heart. 2003;89:502–6. https://doi.org/10.1136/heart.89.5.502.
21. Oguma Y, Shinoda-Tagawa T. Physical activity decreases cardiovascular disease risk in women: review and meta-analysis. Am J Prev Med. 2004;26:407–18. https://doi.org/10.1016/j.amepre.2004.02.007.
22. Stevens J, Cai J, Evenson KR, Thomas R. Fitness and fatness as predictors of mortality from all causes and

from cardiovascular disease in men and women in the lipid research clinics study. Am J Epidemiol. 2002;156:832–41. https://doi.org/10.1093/aje/kwf114.
23. Morris JN, Crawford MD. Coronary heart disease and physical activity of work: evidence of a national necropsy survey. Br Med J. 1958;2:1485–96. https://doi.org/10.1136/bmj.2.5111.1485.
24. Morris JN, Heady JA, Raffle PAB, Roberts CG, Parks JW. Coronary heart disease and physical activity of work. Lancet. 1953;2:1053–7, 1111–1120. https://doi.org/10.1016/s0140-6736(53)90665-5.
25. Morris JN, Kagan A, Pattison DC, Gardner MJ. Incidence and prediction of ischaemic heart-disease in London busmen. Lancet. 1966;2:553–9. https://doi.org/10.1016/s0140-6736(66)93034-0.
26. Paffenbarger RS Jr, Blair SN, Lee IM. A history of physical activity, cardiovascular health and longevity: the scientific contributions of Jeremy N. Morris Int J Epidemiol. 2001;30:1184–92. https://doi.org/10.1093/ije/30.5.1184.
27. Hambrecht R, Wolf A, Gielen S, Linke A, Hofer J, Erbs S, et al. Effect of exercise on coronary endothelial function in patients with coronary artery disease. N Engl J Med. 2000;342:454–60. https://doi.org/10.1056/NEJM200002173420702.
28. Wannamethee SG, Lowe GDO, Whincup PH, Rumley A, Walker M, Lennon L. Physical activity and hemostatic and inflammatory variables in elderly men. Circulation. 2002;105:1785–90. https://doi.org/10.1161/hc1502.107117.
29. Nystoriak MA, Bhatnagar A. Cardiovascular effects and benefits of exercise. Front Cardiovasc Med. 2018;5:135. https://doi.org/10.3389/fcvm.2018.00135.
30. Haskell WL. The influence of exercise on the concentrations of triglyceride and cholesterol in human plasma. Exerc Sport Sci Rev. 1984;12:205–44. https://doi.org/10.1249/00003677-198401000-00009.
31. Leon AS, Sanchez OA. Response of blood lipids to exercise training alone or combined with dietary intervention. Med Sci Sports Exerc. 2001;33:S502–15. https://doi.org/10.1097/00005768-200106001-00021.
32. Kraus WE, Houmard JA, Duscha BD, Knetzger KJ, Wharton MB, McCartney JS, et al. Effects of the amount and intensity of exercise on plasma lipoproteins. N Engl J Med. 2002;347:1483–92. https://doi.org/10.1056/NEJMoa020194.
33. Fagard RH. Exercise characteristics and the blood pressure response to dynamic physical training. Med Sci Sports Exerc. 2001;33:S484–92. https://doi.org/10.1097/00005768-200106001-00018.
34. Cornelissen VA, Fagard RH. Effects of endurance training on blood pressure, blood pressure-regulating mechanisms, and cardiovascular risk factors. Hypertension. 2005;46:667–75. https://doi.org/10.1161/01.HYP.0000184225.05629.51.
35. Hardy ST, Loehr LR, Butler KR, Chakladar S, Chang PP, Folsom AR, et al. Reducing the blood pressure-related burden of cardiovascular disease: impact of achievable improvements in blood pressure prevention and control. J Am Heart Assoc. 2015;4:e002276. https://doi.org/10.1161/JAHA.115.002276.
36. Newsom SA, Everett AC, Hinko A, Horowitz JF. A single session of low-intensity exercise is sufficient to enhance insulin sensitivity into the next day in obese adults. Diabetes Care. 2013;36:2516–22. https://doi.org/10.2337/dc12-2606.
37. Trovati M, Carta Q, Cavalot F, Vitali S, Banaudi C, Lucchina PG, et al. Influence of physical training on blood glucose control, glucose tolerance, insulin secretion, and insulin action in non-insulin-dependent diabetic patients. Diabetes Care. 1984;7:416–20. https://doi.org/10.2337/diacare.7.5.416.
38. Ginsberg HN. Insulin resistance and cardiovascular disease. J Clin Invest. 2000;106:453–8. https://doi.org/10.1172/JCI10762.
39. Wilson PWF, D'Agostino RB, Sullivan L, Parise H, Kannel WB. Overweight and obesity as determinants of cardiovascular risk: the Framingham experience. Arch Intern Med. 2002;162:1867–72. https://doi.org/10.1001/archinte.162.16.1867.
40. Rabkin SW, Mathewson FA, Hsu PH. Relation of body weight to development of ischemic heart disease in a cohort of young North American men after a 26-year observation period: the Manitoba study. Am J Cardiol. 1977;39:452–8. https://doi.org/10.1016/s0002-9149(77)80104-5.
41. Kenchaiah S, Evans JC, Levy D, Wilson PWF, Benjamin EJ, Larson MG, et al. Obesity and the risk of heart failure. N Engl J Med. 2002;347:305–13. https://doi.org/10.1056/NEJMoa020245.
42. Chooi YC, Ding C, Magkos F. The epidemiology of obesity. Metabolism. 2019;92:6–10. https://doi.org/10.1016/j.metabol.2018.09.005.
43. Lavie CJ, De Schutter A, Parto P, Jahangir E, Kokkinos PF, Ortega FB, et al. Obesity and prevalence of cardiovascular diseases and prognosis: the obesity paradox updated. Prog Cardiovasc Dis. 2016;58:537–47. https://doi.org/10.1016/j.pcad.2016.01.008.
44. Oktay AA, Lavie CJ, Kokkinos PF, Parto P, Pandey A, Ventura HO. The interaction of cardiorespiratory fitness with obesity and the obesity paradox in cardiovascular disease. Prog Cardiovasc Dis. 2017;60:30–44. https://doi.org/10.1016/j.pcad.2017.05.005.
45. Goel K, Thomas RJ, Squires RW, Coutinho T, Trejo-Gutierrez JF, Somers VK, et al. Combined effect of cardiorespiratory fitness and adiposity on mortality in patients with coronary artery disease. Am Heart J. 2011;161:590–7. https://doi.org/10.1016/j.ahj.2010.12.012.
46. Haveman-Nies A, de Groot LPGM, Burema J, Cruz JAA, Osler M, van Staveren WA. Dietary quality and lifestyle factors in relation to 10-year mortality in older Europeans: the SENECA study. Am J Epidemiol. 2002;156:962–8. https://doi.org/10.1093/aje/kwf144.
47. Elder SJ, Roberts SB. The effects of exercise on food intake and body fatness: a summary of published studies. Nutr Rev. 2007;65:1–19. https://doi.org/10.1111/j.1753-4887.2007.tb00263.x.

48. Kerksick CM, Wismann-Bunn J, Fogt D, Thomas AR, Taylor L, Campbell BI, Wilborn CD, et al. Changes in weight loss, body composition and cardiovascular disease risk after altering macronutrient distributions during a regular exercise program in obese women. Nutr J. 2010;9:59. https://doi.org/10.1186/1475-2891-9-59.
49. Shaw BS, Shaw I, Brown GA. Self-reported dietary intake following endurance, resistance and concurrent endurance and resistance training. J Sports Sci Med. 2008;7:255–9.
50. Ambler C, Eliakim A, Brasel JA, Lee WN, Burke G, Cooper DM. Fitness and the effect of exercise training on the dietary intake of healthy adolescents. Int J Obes Relat Metab Disord. 1998;22:354–62. https://doi.org/10.1038/sj.ijo.0800595.
51. Willis LH, Slentz CA, Bateman LA, Shields T, Piner LW, Bales CW, et al. Effects of aerobic and/or resistance training on body mass and fat mass in overweight or obese adults. J Appl Physiol. 2012;113:1831–7. https://doi.org/10.1152/japplphysiol.01370.2011.
52. Ussher MH, Taylor AH, Faulkner GE. Exercise interventions for smoking cessation. Cochrane Database Syst Rev. 2014;8:CD002295. https://doi.org/10.1002/14651858.CD002295.pub5.
53. Auer R, Vittinghoff E, Kiefe C, Reis JP, Rodondi N, Khodneva YA, et al. Changes in in physical activity after smoking cessation: the coronary artery risk development in young adults (CARDIA) study. Addiction. 2014;109:1172–83. https://doi.org/10.1111/add.12561.
54. Georgakouli K, Manthou E, Georgoulias P, Ziaka A, Fatouros IG, Mastorakos G, et al. Exercise training reduces alcohol consumption but does not affect HPA-axis activity in heavy drinkers. Physiol Behav. 2017;179:276–83. https://doi.org/10.1016/j.physbeh.2017.07.003.
55. Hallal PC, Andersen LB, Bull FC, Guthold R, Haskell W, Ekelund U, et al. Global physical activity levels: surveillance progress, pitfalls, and prospects. Lancet. 2012;380:247–57. https://doi.org/10.1016/S0140-6736(12)60646-1.
56. World Health Organization. A global strategy for diet, physical activity, and health. Geneva: Technical Report Series; 2004.
57. Dishman RK, Buckworth J. Increasing physical activity: a quantitative synthesis. Med Sci Sports Exerc. 1996;28:706–19. https://doi.org/10.1097/00005768-199606000-00010.
58. Jakicic JM, Otto AD. Physical activity considerations for the treatment and prevention of obesity. Am J Clin Nutr. 2005;82:S226–9. https://doi.org/10.1093/ajcn/82.1.226S.
59. DaSilva SG, Guidetti L, Buzzachera CF, Elsangedy HM, Krinski K, De Campos W, et al. Psychophysiological responses to self-paced treadmill and overground exercise. Med Sci Sports Exerc. 2011;43:1114–24. https://doi.org/10.1249/MSS.0b013e318205874c.
60. Briffa TG, Maiorana A, Sheerin NJ, Stubbs AG, Oldenburg BF, Sammel NL, et al. Physical activity for people with cardiovascular disease: recommendations of the National Heart Foundation of Australia. Med J Aust. 2006;184:71–5. https://doi.org/10.1249/MSS.0b013e318205874c.
61. U.S. Public Health Service, Office of the Surgeon General. Physical activity and health: A report of the Surgeon General. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion; 1996.
62. Jakicic JM, Marcus BH, Gallagher KI, Napolitano M, Lang W. Effect of exercise duration and intensity on weight loss in overweight, sedentary women: a randomized trial. JAMA. 2003;290:1323–30. https://doi.org/10.1001/jama.290.10.1323.
63. Physical Activity Guidelines Advisory Committee. Physical activity guidelines advisory committee scientific report. Washington: U.S. Department of Health and Human Services; 2008.
64. Kraus WE, Powell KE, Haskell WL, Janz KF, Campbell WW, Jakicic JM, et al. Physical activity, all-cause and cardiovascular mortality, and cardiovascular disease. Med Sci Sports Exerc. 2019;51:1270–81. https://doi.org/10.1249/MSS.0000000000001939.
65. Buzzachera CF, Meucci M, Baldari C. Physical activity and training prescription. In: Lenzi A, Migliaccio S, Donini LM, editors. Multidisciplinary approach to obesity: from assessment to treatment. Switzerland: Springer International Publishing; 2015. https://doi.org/10.1007/978-3-319-09045-0.
66. Borg GA. Psychophysical bases of perceived exertion. Med Sci Sports Exerc. 1982;14:377–81.
67. Currie KD, Dubberley JB, McKelvie RS, MacDonald MJ. Low-volume, high-intensity interval training in patients with CAD. Med Sci Sports Exerc. 2013;45:1436–42. https://doi.org/10.1249/MSS.0b013e31828bbbd4.
68. Follador L, Alves RC, Ferreira SDS, Buzzachera CF, Andrade VFS, Garcia EDS, et al. Physiological, perceptual, and affective responses to six high-intensity interval training protocols. Percept Mot Skills. 2018;125:329–50. https://doi.org/10.1177/0031512518754584.
69. Wewege MA, Ahn D, Yu J, Liou K, Keech A. High-intensity interval training for patients with cardiovascular disease: is it safe? A systematic review. J Am Heart Assoc. 2018;7:e009305. https://doi.org/10.1161/JAHA.118.009305.
70. Perri MG, Anton SD, Durning PE, Ketterson TU, Sydeman SJ, Berlant NE, et al. Adherence to exercise prescriptions: effects of prescribing moderate versus higher levels of intensity and frequency. Health Psychol. 2002;21:452–8. https://doi.org/10.1037/0278-6133.21.5.452.
71. Sallis JF, Haskell WL, Fortmann SP, Vranizan KM, Taylor CB, Solomon DS. Predictors of adoption and maintenance of physical activity in a community sample. Prev Med. 1986;15:331–41. https://doi.org/10.1016/0091-7435(86)90001-0.
72. American College of Sports Medicine position stand. The recommended quantity and quality of exercise for

developing and maintaining cardiorespiratory and muscular fitness in healthy adults. Med Sci Sports Exerc. 1990;22:265–74.
73. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. Med Sci Sports Exerc. 2011;43:1334–59. https://doi.org/10.1249/MSS.0b013e318213fefb.
74. Williams MA, Haskell WL, Ades PA, Amsterdam EZ, Bittner V, Franklin BA, et al. Resistance exercise in individuals with and without cardiovascular disease: 2007 update: a scientific statement from the American Heart Association Council on clinical cardiology and council on nutrition, physical activity, and metabolism. Circulation. 2007;116(5):572–84. https://doi.org/10.1161/CIRCULATIONAHA.107.185214.
75. Pratley R, Nicklas B, Rubin M, Miller J, Smith A, Smith M, et al. Strength training increases resting metabolic rate and norepinephrine levels in healthy 50- to 65-yr-old men. J Appl Physiol. 1994;76:133–7. https://doi.org/10.1152/jappl.1994.76.1.133.
76. Hunter GR, Wetzstein CJ, Fields DA, Brown A, Bamman MM. Resistance training increases total energy expenditure and free-living physical activity in older adults. J Appl Physiol. 2000;89:977–84. https://doi.org/10.1152/jappl.2000.89.3.977.
77. Feigenbaum MS, Pollock ML. Strength training: rationale for current guidelines for adult fitness programs. Physician Sports Med. 1997;25:44–64. https://doi.org/10.3810/psm.1997.02.1137.
78. Franklin BA, Bonzheim K, Gordon S, Timmis GC. Safety of medically supervised outpatient cardiac rehabilitation exercise therapy: a 16-year follow-up. Chest. 1998;114:902–6. https://doi.org/10.1378/chest.114.3.902.

Nutrition and Cardiovascular Disease 55

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Contents

Abstract

Cardiovascular diseases (CVDs) are a leading cause of mortality internationally, accounting for approximately one third of all deaths. Multiple risk factors are attributed to causing CVDs. An unhealthy dietary pattern, characterized by regular choices of potentially harmful foods and beverages, is currently recognized as a leading contributor to poor cardiovascular health. Poor diet was the attributed cause of CVD death for approximately 10 million people worldwide in 2017, in part as a result of its effects on other major risk factors. Healthy dietary practices, therefore, reduce the risk of CVDs, with potential implications in all-cause and CVD mortality. Herein we summarize the evidence of associations between different dietary patterns and CVD risk and discuss some of the most challenging issues about diet-disease relationship that could be considered for further research.

Keywords

Nutrition · Food · Mediterranean diet · Dash diet · Ketogenic diet · Heart · Brain

Introduction

Cardiovascular diseases (CVDs) are a leading cause of mortality internationally, accounting for approximately one third of all deaths [1]. When

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*,
https://doi.org/10.1007/978-3-030-28008-6_58

combined, ischemic heart disease and all forms of CVDs were the attributed causes of death for an estimated 17.7 million people globally in 2017 [1]. The current epidemic of CVDs is largely explained by multiple nonmodifiable and modifiable risk factors. Nonmodifiable risk factors consist of those conditions that a person cannot alter, such as age, sex, ethnicity, and family history. Modifiable risk factors, in turn, are conditions that can be altered by making certain lifestyle changes, including sedentarism and physical inactivity, tobacco smoking, excessive alcohol consumption, obesity, hypercholesterolemia, high blood pressure, and diabetes [2]. Although the effect of an individual lifestyle change on any single CVD risk factor may generally be modest, the effect of combined healthy lifestyle choices on cardiovascular health can be dramatic [3, 4]. A recent meta-analysis revealed that adherence to multiple healthy lifestyle behaviors simultaneously, such as eating a prudent diet, exercising regularly, managing weight, and not smoking, was associated with a 66% reduced CVD risk compared with adopting none or only one behavior. Importantly, a clear dose-response effect for adherence to an increasing number of healthy lifestyle behaviors and CVD risk was observed [5]. Hence, although traditional pharmacological agents, including lipid-lowering and antihypertensive medications, successfully reduce cardiovascular events, the overall reduction in risk is relatively modest and could be greatly improved by the addition of lifestyle modifications.

Among the many modifiable risk factors that predispose to CVDs development and progression, an unhealthy dietary pattern, characterized by regular choices of potentially harmful foods and beverages, is currently recognized as a leading contributor to poor cardiovascular health [6]. In fact, poor diet was the attributed cause of CVD death for approximately 10 million people worldwide in 2017 [7], in part as a result of its effects on other major risk factors. Poor dietary habits are therefore responsible for more deaths than any other CVD risk factor, including tobacco smoking. However, unlike many other risk factors, unhealthy dietary patterns affected people regardless of age, sex, and sociodemographic development of their place of residence [7]. These findings, along with others [8, 9], underscore the need for improving diet at the global, regional, and national level. While there have been modest improvements in diet quality over the past few years [9], addressing poor dietary habits is still a priority to reduce the global burden of CVDs. The aim of this chapter is therefore to summarize the evidence of associations between different dietary patterns and CVD risk and to discuss some of the most challenging issues about diet-disease relationship that could be considered for further research.

Dietary Patterns and Nutrients and Its Association with CVDs

The cardiovascular impact of unhealthy dietary patterns has been extensively debated over the past few decades [6]. This concept of relating poor dietary habits to CVDs, however, began as early as 1950s with some of the prospective studies at that time. Professor John W. Gofman and his colleagues at the University of California began to entertain the notion that certain classes of lipoproteins were related to atherosclerotic heart disease and implicated dietary fat as a factor in this relationship [10]. At about the same time, Professor Ancel Keys at the University of Minnesota found a significant association between fat and saturated fat intake and heart disease mortality [11, 12]. Keys and his associates noted that the poor population of small towns of southern Italy was, against all predictions, much healthier than the wealthy citizens of New York and relatives who had emigrated to the United States in earlier decades. Specifically, they noted that the inhabitants from the southern Italy had very low levels of blood cholesterol and low incidence of heart disease [12], which may be due primarily to their dietary habits [13]. The observations of John W. Gofman and Ancel Keys were later confirmed by several other investigators [14]. However, although this series of research was pioneering, it was not without its shortcomings. Early research initiatives focused on the cardiovascular impact of dietary components in isolation, which can result

in erroneous conclusions. CVDs, for instance, do not arise simply from excessive saturated fat in the diet but rather from a complex interaction of multiple nutritional factors directly linked to the excessive consumption of potentially harmful foods, such as dairy products, refined cereals, refined sugars, refined vegetable oils, fatty meats, salt, and combinations of these foods [15]. Unfortunately, this reductionist approach is still evident in many dietary guidelines [16–18], where recommendations are made for saturated fat, added sugar, sodium, and dietary cholesterol, because these are overconsumed by many people and are associated with increased risk for CVDs. It is noteworthy, however, that most researchers are currently returning to a more holistic view of nutrition by, for example, considering dietary patterns rather than dietary components in isolation [19]. Future dietary guidelines should therefore emphasize dietary pattern-based approaches that are imperative for successful CVD prevention [20].

Emerging research supports the notion that the potential gain accrued by dietary interventions to reduce CVD risk is unique to each individual. Consequently, future dietary guidelines should also incorporate more individualized advice [20]. However, current scientific evidence confirms that dietary habits are a function of multiple determinants [21]. In fact, the influences on food choices are complex and not completely understood. At the individual level, dietary habits are determined not simply by personal preferences but also by familial norms, nutritional and cooking knowledge and skills, and health status [22]. Related psychological attributes, such as attitudes toward food and health, incentives, motivation, and values, also influence individuals' dietary habits [21]. Similarly, other lifestyle characteristics, such as sedentarism and physical inactivity [23], excessive alcohol consumption [24], and poor sleep [25], have been positively associated with unfavorable dietary patterns. Dietary habits are also determined by both sociocultural and environmental factors. The sociocultural factors most cited in the literature include education, cultural norms, social pressures, social class, social networks, and race/ethnicity [22]. The environment attributes, in turn, mainly include accessibility (e.g., food availability, cost, convenience), industry advertising and marketing, and the local (e.g., residential, school, workplace) food environment. Each of these individual, sociocultural, and environmental determinants represent a potential barrier, but also a promising opportunity for encouraging healthy dietary practices [26]. Food choices, therefore, must not only be supported by clinical behavior change efforts but must also be reinforced by health systems reforms, novel technologies, and robust policy strategies targeting economic incentives, schools and workplaces, neighborhood environments, and the entire food system [27].

Popular Dietary Patterns and Cardiovascular Health

Over the past few decades, the impact of CVDs on a population has been drastic and remains a major health concern even today. Poor lifestyle behaviors, including suboptimal diet, largely contribute to the enormous burden of CVDs worldwide [3]. Retrospective and follow-up studies have confirmed that suboptimal diet is a leading contributor to poor cardiovascular health [6], in part as a result of its effects on other major CVD risk factors, such as excess weight, high blood pressure, diabetes, and dyslipidemia [2]. The identification of nutrients, foods, and dietary patterns that can improve cardiovascular health is therefore a priority. In fact, researchers and health professionals are currently focused on identifying diets with the highest level of scientific evidence to guide clinical decision making. Some diets have been rigorously studied and shown to be effective in promoting cardiovascular health, while other diets, although marketed as providing cardiovascular benefits, lack conclusive scientific evidence on their effectiveness. A well-established example is the now popular and world-famous Mediterranean diet, which is based upon the eating habits of people living around the Mediterranean Sea. The Mediterranean diet, characterized by moderate energy intake, high consumption of olive oil, fish, legumes, nuts, whole grains, fruits, and vegetables, fewer red meats and processed meats, and

a regular but moderate consumption of red wine, is associated with decreases in all-cause and CVD mortality [28, 29]. The cardiovascular impact of the Mediterranean diet, along with other less popular dietary interventions, will therefore be the focus of this section. The Western diet, characterized by a high intake of red meats, fat dairy products, refined grains and sugars, and commonly associated with poor cardiovascular outcomes, will not be discussed because it is not a topic of significant controversy (see Ref. [16] for more details).

Low-Carbohydrate, Low-Fat, and High-Protein Diets

A multitude of studies have been published on the relationship between CVD risk and dietary intervention [30]. Some of these diets can demand the modulation of macronutrients (e.g., low- carbohydrate, high-protein, and low-fat diets), while others are mainly focused on dietary patterns (e.g., Mediterranean, DASH, Nordic, vegetarian, and portfolio dietary models) [31]. For example, dietary interventions that have demonstrated cardiovascular benefits in people with or at risk for CVDs present a carbohydrate content lower than 50% of daily energy content [32]. It is noteworthy, however, that carbohydrate supplies about 55% of the energy in the typical Western diet, ranging from 200 to 300 g.day^{-1} in relation to a person's overall caloric intake. Low-carbohydrate diets typically restrict carbohydrate intake to 50–130 g daily, or up to 45% of total calories [34], and thus are growing in interest and popularity among researchers and health professionals [33]. Low-carbohydrate diets were often associated with favorable effects on body weight and other major CVD risk factors, such as high blood pressure, diabetes, and dyslipidemia [35, 36]. However, a recent umbrella review summarizing evidence from 80 studies on popular dietary interventions, including low-carbohydrate diets, found contrasting evidence, leaving the debate still open. Compared with low-fat diets and other traditional dietary regimens, low-carbohydrate diets elicited greater changes in body weight, particularly in response to short-term interventions (<6 months) and very low-carbohydrate ketogenic diets. When the follow-up period or the amount of carbohydrates increased, however, the favorable effect was mitigated. Limited or no evidence was also for the effectiveness of low-carbohydrate diets on other outcomes of interest, such as glycemic profile, blood pressure, and lipid profile, with potentially negative effects on both total and LDL serum cholesterol [31]. The detrimental effects of low-carbohydrate diets on certain lipid fractions may be attributed, at least in part, to the fact that people on low-carbohydrate diets are predisposed to eat less vegetable and fruits rich in micronutrients and fiber, and more animal-derived food [31]. This hypothesis is of interest, since prolonged consumption of diets low in carbohydrates and high in animal fat and protein is associated with an increase in all-cause and CVD mortality [37]. Therefore, there is currently insufficient evidence to recommend the use of low-carbohydrate diets to improve cardiovascular health; however, in individuals who choose to follow a low-carbohydrate diet, high leafy green vegetable and increased plant-based protein consumption should be strongly encouraged [38].

In recent years, there has been considerable interest in the utility of very low-calorie ketogenic diet (VLCKD) as a potential dietary intervention to improve cardiovascular health. Basically, VLCKD are known for being very low in carbohydrates, usually less than 50 g.day^{-1}, associated with extreme calorie restriction (i.e., 700–800 kcal) [39]. In humans, VLCKD has been suggested to be more effective than very low-calorie non-ketogenic diet to induce weight loss due to dietary ketosis. The combination of caloric restriction and very low carbohydrate intake may maintain a mild level of ketosis, and particularly influence appetite signal [40]. A recent systematic review and meta-analysis summarized the best available evidence from 12 studies on the efficacy and safety of VLCKD in overweight and obesity management. VLCKD proved to be a reliable option to achieve a significant weight loss in those patients. Results were obtained early during the ketogenic phase and were stable over a follow-up of up to 2 years. In addition, VLCKD was

associated with significant improvements in traditional risk CVD factors, including hypertension, dyslipidemia, diabetes mellitus type 2, and non-alcoholic fatty liver disease [41]. The safety profile is generally reassuring, but, given the restriction in calories and micronutrients, it should be only considered in properly selected patients, under strict medical supervision and as a part of a multicomponent strategy, as well as any very-low-calorie not ketogenic diet [42]. Hence, further studies evaluating long-term cardiovascular outcomes are warranted before a VLCKD can be endorsed.

A lower consumption of dietary fat is often recommended in the context of weight management because of its harmful impacts on energy balance [6]. Low-fat dietary regimens typically restrict fat intake from 10% to 30% of total energy [31], which can be achieved by choosing low-fat meats, vegetables, low-fat dairy products, and lowering food containing trans fatty acids [43]. Low-fat diets are also well accepted in clinical guidelines on CVD prevention and management [14]. More recently, however, low-fat diets have not been advocated to lower the risk for CVDs [44–46]. In fact, a previous study in 148 obese adults (range BMI 30–45 $kg.m^{-2}$) aged 22–75 years found that participants using a low-fat diet with a fat intake restricted to less than 30% lost less weight than those using a low-carbohydrate diet (mean difference in change, −3.5 kg). The low-fat diet was also less effective for CVD risk factor reduction, such as increased HDL serum cholesterol and reduced serum triglyceride, than the low-carbohydrate diet [46]. Additionally, a recent study in 48,835 postmenopausal women aged 50–79 years found that participants using a very low-fat dietary regimen with a fat intake restricted to less than 20% reported similar risk of ischemic heart disease and other forms of CVDs in comparison with those using a conventional diet [45]. Some of these results have been confirmed by systematic reviews using meta-analyses [31, 47, 48]. Finally, an alternative macronutrient alteration is increased protein intake. High-protein diets are commonly defined as protein content greater than 20–35% of total energy [49, 50]. A typical high-protein diet increases the protein intake, and controversy exists about the amount and type of protein consumed [51]. However, although high-protein dietary regimens are popular for weight loss, their cardiovascular effects have not been well-studied. Some studies [52, 53], but not all [54, 55], have confirmed that high-protein diets enhance weight loss compared with lower-protein diets in the short term (within 6 months). For example, a previous study in 13 obese adults (mean BMI 31 $kg.m^{-2}$) with hyperinsulinemia found that participants using a high-protein diet (45% protein) lost more weight than those using a low-protein diet (12% protein; -8.3 ± 0.7 kg vs. -6.0 ± 0.6 kg) [52]. Possible mechanisms include an increased satiety, decreased subsequent energy intake, and carbohydrate displacement with higher-protein diets [56]. However, high-protein dietary regimens, used on a regular basis and without consideration of the source of proteins, are associated with increased risk of CVD [57]. High-protein diets, therefore, do not align with the low-protein recommendations endorsed by researchers and health professionals.

Mediterranean Diet, DASH Diet, and Other Dietary Regimens

The relationship between nutrients, foods, dietary patterns, and cardiovascular health has been of scientific and clinical interest for decades. The study of the overall quality of the whole dietary pattern, however, represents the current state of the art in the investigation of the nutritional determinants of cardiovascular health [30]. A well-established example of dietary patterns is the Mediterranean diet, which is based upon the eating habits of people living around the Mediterranean Sea. The Mediterranean diet has been rigorously studied, especially during the last few decades, and was shown to be effective in promoting cardiovascular benefits [28]. The main characteristics of the Mediterranean diet are a low consumption of red meats and processed meats, with an abundant consumption of olive oil, legumes, nuts, whole grains, fruits, and vegetables. Fish and shellfish are important sources of

protein, while red wine is the main source of alcohol among persons in the traditional Mediterranean diet. The moderate consumption of red wine during meals, along with the abundant use of extra-virgin olive oil, through salads, vegetables, and legumes, makes this diet highly nutritious and palatable [58]. Both red wine and extra-virgin olive oil are concentrated sources of bioactive polyphenols with postulated cardioprotective effects [59, 60]. More importantly, the Mediterranean diet has often been associated with lower risk for mortality from CVD and all-causes [30]. In a landmark observational study, Trichopoulou et al. [28] found that a higher adherence to the traditional Mediterranean diet was associated with a reduction in total mortality, with an inverse association between death from CVD causes and adherence to the diet. These results have been well described by multiple observational studies and confirmed by several systematic reviews [31, 61–63]. The Mediterranean diet, therefore, appears to be an effective and important nutritional strategy for the prevention and management of CVDs.

There is also a growing body of evidence to support the cardiovascular benefits of the popular and world-famous DASH diet. The Dietary Approach to Stop Hypertension (DASH) diet is typically characterized by an abundant consumption of fruits, vegetables, legumes, nuts, whole grains, low-fat dairy products, fish, and poultry. This diet also comprises a reduced intake of red meat and processed meat, refined grains and sugars, saturated fat, cholesterol, and sodium [64]. Traditionally, the DASH diet is recommended to lower blood pressure, a well-established CVD risk factor [3]. In a pioneer study conducted from 1994 to 1996 of 459 adults not taking antihypertensives, Appel et al. [65] found a significant decrease in both systolic and diastolic blood pressures (−5.5 and −3.0 mmHg, respectively) after 8 weeks feeding a "combination" diet (hereafter referred to as the DASH diet). In hypertensive participants ($n = 133$), however, the effects of the "combination" diet were even more pronounced (−11.4 and −5.5 mmHg, respectively, for systolic and diastolic blood pressures) [65]. Adding sodium restriction to the DASH diet further reduced the blood pressure [66]. Whether the DASH diet would affect other major CVD risk factors is still uncertain. A recent umbrella review summarizing evidence from 80 studies found contrasting evidence, with weak evidence of an effect on cardiovascular outcomes. The DASH diet reported suggestive evidence of a beneficial effect on weight and blood pressure, and weak evidence for BMI and total cholesterol [31]. More importantly, however, higher adherence rates to the DASH diet were associated with decreases in all-cause and CVD mortality [67–69]. Together, these data provide support for the concept that the original DASH diet may be appropriate for patients with or at risk for CVDs.

While both Mediterranean and DASH diets have been promoted for more than 20 years to reduce CVD risk, recently there has been a proliferation of new dietary regimens that promise successfully reduction cardiovascular events. The marketing strategies of diet promoters have led researchers, health professionals, and consumers to consider the benefits and risks of these diets for cardiovascular health [6]. An example is the Nordic diet, which has been studied in epidemiological investigations and randomized trials, especially during the last decade [70]. The Nordic diet, characterized by a moderate consumption of oily fish (salmon and mackerel), vegetables, roots, legumes, fruits, berries, whole grains, and cereals (oat, rye, and barley), was shown to be effective in promoting cardiovascular benefits [71]. In a pioneer study, Adamson et al. [72] found a significant decrease in body weight (-3.0 ± 1.8 kg), total cholesterol (-0.9 ± 0.7 mmol.L^{-1}), serum LDL (-0.8 ± 0.6 mmol.L^{-1}), and systolic blood pressure (-6.5 ± 13.1 mmHg) after 6 weeks feeding a Nordic diet. More importantly, adherence to the Nordic diet, assessed with food frequency questionnaire, was associated with lower risk of all-cause and CVD mortality in two large cohort studies [73, 74]. However, a recent cohort study with 2019 adults with mean age of 61 years did not found a significant association between adherence to the Nordic diet and a reduction of risk of coronary heart disease [75]. The reasons for these contrasting results are not immediately clear and are likely a fertile area for further research. The

cardiovascular impact of other dietary regimens, such as the vegetarian diet, has also been debated over the past few years [70]. The vegetarian diet typically substitutes meat, seafood, and poultry with the consumption of soy products, legumes, nuts, and whole grains. Vegetarian diets were associated with a myriad of health benefits, including reduced body weight, serum LDL, and systolic blood pressure in addition to reduced risk for CVD [76]. Additionally, vegetarian diets reduced significantly the risk of incidence and mortality from CVDs [77]. However, other large, single center studies have failed to corroborate these results [78, 79]. Further studies are warranted to confirm or refute the present findings.

Conclusion

The treatment of multidimensional diseases such as CVD requires well-established evidence- based approaches. Healthy dietary approaches are advocated to reduce the risk of CVDs, with potential implications in all-cause and CVD mortality. Among all the dietary regimens evaluated, Mediterranean diet had the strongest and most consistent evidence, with no related adverse effects. Suggestive evidence of an improvement in body weight and CVD risk was also reported for DASH diet. Low-carbohydrate, low-fat, and high-protein, on the other hand, appear not to promote cardiovascular benefits. The current findings underscore the strengths and limitations of most popular and world-famous dietary interventions, suggesting that the best results, in terms of cardiovascular health, are obtained with favorable dietary patterns such as Mediterranean diet.

References

1. GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018;392:1736–88. https://doi.org/10.1016/S0140-6736(18)32203-7.
2. Buttar HS, Li T, Ravi N. Prevention of cardiovascular diseases: role of exercise, dietary interventions, obesity and smoking cessation. Exp Clin Cardiol. 2005;10:229–49.
3. Myers J. Exercise and cardiovascular health. Circulation. 2003;107:e2–5. https://doi.org/10.1161/01.CIR.0000048890.59383.8D.
4. Stampfer MJ, Hu FB, Manson JE, Rimm EB, Willett WC. Primary prevention of coronary heart disease in women through diet and lifestyle. N Engl J Med. 2000;343:16–22. https://doi.org/10.1056/NEJM200007063430103.
5. Barbaresko J, Rienks J, Nöthlings U. Lifestyle indices and cardiovascular disease risk: a meta-analysis. Am J Prev Med. 2018;155:555–64. https://doi.org/10.1016/j.amepre.2018.04.046.
6. Tapsell LC, Neale EP, Probst Y. Dietary patterns and cardiovascular disease: insights and challenges for considering food groups and nutrient sources. Curr Atheroscler Rep. 2019;21:9. https://doi.org/10.1007/s11883-019-0770-1.
7. GBD 2017 Diet Collaborators. Health effects of dietary risks in 195 Countries, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2019;393:1958–72. https://doi.org/10.1016/S0140-6736(19)30041-8.
8. Micha R, Kalantarian S, Wirojratana P, Byers T, Denaei G, Elmadfa I, et al. Estimating the global and regional burden of suboptimal nutrition on chronic disease: methods and inputs to the analysis. Eur J Clin Nutr. 2012;66:119–29. https://doi.org/10.1038/ejcn.2011.147.
9. Imamura F, Micha R, Khatibzadeh S, Fahimi S, Shi P, Powles J, et al. Dietary quality among men and women in 187 countries in 1990 and 2010: a systematic assessment. Lancet Glob Health. 2015;3:e132–42. https://doi.org/10.1016/S2214-109X(14)70381-X.
10. Gofman JW, Lindgren F. The role of lipids and lipoproteins in atherosclerosis. Science. 1950;111:166–71. https://doi.org/10.1126/science.111.2877.166.
11. Keys A, Mickelsen O, Miller EV, Chapman CB. The relation in man between cholesterol levels in the diet and in the blood. Science. 1950;112:79–81. https://doi.org/10.1126/science.112.2899.79.
12. Keys A. Coronary heart disease in seven countries. Circulation. 1970;41:1–211.
13. Keys A, Menotti A, Karvonen MJ, Aravanis C, Blackburn H, Buzina R, et al. The diet and 15-year death rate in the seven countries study. Am J Epidemiol. 1986;124:903–15. https://doi.org/10.1093/oxfordjournals.aje.a114480.
14. Eckel RH, Jakicic JM, Ard JD, De Jesus JM, Miller NH, Hubbard VS, et al. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63:2960–84. https://doi.org/10.1161/01.cir.0000437740.48606.d1.
15. Cordain L, Boyd Eaton S, Sebastian A, Mann N, Lindeberg S, Watkins BA, et al. Origins and evolution of the Western diet: health implications for the 21st century. Am J Clin Nutr. 2005;81:341–54. https://doi.org/10.1093/ajcn.81.2.341.

16. National Health and Medical Research Council. Australian dietary guidelines. Canberra: National Health and Medical Research Council; 2013.
17. Government of Canada. Eating well with Canada's food guide. Ontario: Health Canada; 2011.
18. Public Health England. Eatwell Guide Public Health England in association with the Welsh government, Food Standards Scotland and the Food Standards Agency in Northern Ireland. 2016.
19. Fardet A, Rock E. Toward a new philosophy of preventive nutrition: from a reductionist to a holistic paradigm to improve nutritional recommendations. Adv Nutr. 2014;5:430–46. https://doi.org/10.3945/an.114.006122.
20. Nettleton JA, Brouwer IA, Geleijnse JM, Hornstra G. Saturated fat consumption and risk of coronary heart disease and ischemic stroke: a science update. Ann Nutr Metab. 2017;70:26–33. https://doi.org/10.1159/000455681.
21. Van't Riet J, Sijtsema SJ, Dagevos H, De Bruijn GJ. The importance of habits in eating behaviour. An overview and recommendations for future research. Appetite. 2011;57:585–96. https://doi.org/10.1016/j.appet.2011.07.010.
22. Brug J. Determinants of healthy eating: motivation, abilities and environmental opportunities. Fam Pract. 2008;25:i50–5. https://doi.org/10.1093/fampra/cmn063.
23. Charreire H, Kesse-Guyot E, Bertrai S, Simon C, Chaix B, Weber C, Touvier M, et al. Associations between dietary patterns, physical activity (leisure-time and occupational) and television viewing in middle-aged French adults. Br J Nutr. 2011;105:902–10. https://doi.org/10.1017/S000711451000440X.
24. Fawehinmi TO, Ilomäki J, Voutilainen S, Kauhanen J. Alcohol consumption and dietary patterns: the FinDrink study. PLoS One. 2012;7:e38607. https://doi.org/10.1371/journal.pone.0038607.
25. Grandner MA, Jackson N, Gerstner JR, Knutson KL. Dietary nutrients associated with short and long sleep duration: data from a nationally representative sample. Appetite. 2013;64:71–80. https://doi.org/10.1016/j.appet.2013.01.004.
26. Nugent R. Bringing agriculture to the table. Chicago: Chicago Council on Global Affairs; 2011.
27. Mozaffarian D. Dietary policy priorities for cardiovascular disease, diabetes, and obesity: a comprehensive review. Circulation. 2016;133:187–225. https://doi.org/10.1161/CIRCULATIONAHA.115.018585.
28. Trichopoulou A, Costacou T, Bamia C, Trichopoulos D. Adherence to a Mediterranean diet and survival in a Greek population. N Engl J Med. 2003a;348:2599–608. https://doi.org/10.1056/NEJMoa025039.
29. Fung TT, Rexrode KM, Mantzoros CS, Manson JE, Willett WC, Hu FB. Mediterranean diet and incidence of and mortality from coronary heart disease and stroke in women. Circulation. 2009;119:1093–100. https://doi.org/10.1161/CIRCULATIONAHA.108.816736.
30. Tapsell LC, Neale EP, Satija A, Hu FB. Foods, nutrients, and dietary patterns: interconnections and implications for dietary guidelines. Adv Nutr. 2016;7:445–54. https://doi.org/10.3945/an.115.011718.
31. Dinu M, Pagliai G, Angelino D, Rosi A, Dall'Asta M, Bresciani L, et al. Effects of popular diets on anthropometric and cardiometabolic parameters: an umbrella review of meta-analyses of randomized controlled trials. Adv Nutr. 2020. https://doi.org/10.1093/advances/nmaa006.
32. Dong T, Guo M, Zhang P, Sun G, Chen B. The effects of low-carbohydrate diets on cardiovascular risk factors: a meta-analysis. PLoS One. 2020;15:e0225348. https://doi.org/10.1371/journal.pone.0225348.
33. Hite AH, Berkowitz VG, Berkowitz K. Low-carbohydrate diet review: shifting the paradigm. Nutr Clin Pract. 2011;26:300–8. https://doi.org/10.1177/0884533611405791.
34. Giugliano D, Maiorino MI, Bellastella G, Esposito K. More sugar? No, thank you! The elusive nature of low carbohydrate diets. Endocrine. 2018;61:383–7. https://doi.org/10.1007/s12020-018-1580-x.
35. Nordmann AJ, Nordmann A, Briel M, Keller U, Yancy WS Jr, Brehm BJ, et al. Effects of low carbohydrate vs. low-fat diets on weight loss and cardiovascular risk factors: a meta-analysis of randomized controlled trials. Arch Intern Med. 2006;166:285–93. https://doi.org/10.1001/archinte.166.3.285.
36. Santos FL, Esteves SS, da Costa PA, Yancy WS Jr, Nunes JP. Systematic review and meta-analysis of clinical trials of the effects of low carbohydrate diets on cardiovascular risk factors. Obes Rev. 2012;13:1048–66. https://doi.org/10.1111/j.1467-789X.2012.01021.x.
37. Trichopoulou A, Psaltopoulou T, Orfanos P, Hsieh CC, Trichopoulos D. Low-carbohydrate- high-protein diet and long-term survival in a general population cohort. Eur J Clin Nutr. 2007;61:575–81. https://doi.org/10.1038/sj.ejcn.1602557.
38. Pallazola VA, Davis DM, Whelton SP, Cardoso R, Latina JM, Michos ED, et al. A clinician's guide to healthy eating for cardiovascular disease prevention. Mayo Clin Proc Innov Qual Outcomes. 2019;3:251–67. https://doi.org/10.1016/j.mayocpiqo.2019.05.001.
39. Kirkpatrick CF, Bolick JP, Kris-Etherton PM, Sikand G, Aspry KE, Soffer DE, et al. Review of current evidence and clinical recommendations on the effects of low-carbohydrate and very-low- carbohydrate (including ketogenic) diets for the management of body weight and other cardiometabolic risk factors: a scientific statement from the National Lipid Association Nutrition and Lifestyle Task Force. J Clin Lipidol. 2019;13:689–711. https://doi.org/10.1016/j.jacl.2019.08.003.
40. Sumithran P, Prendergast L, Delbridge E, et al. Ketosis and appetite-mediating nutrients and hormones after weight loss. Eur J Clin Nutr. 2013;67:759–64. https://doi.org/10.1038/ejcn.2013.90.
41. Castellana M, Conte E, Cignarelli A, Perrini S, Giustina A, Giovanella L, et al. Efficacy and safety of very low-calorie ketogenic diet (VLCKD) in patients

with overweight and obesity: a systematic review and meta-analysis. Rev Endocr Metab Disord. 2019. https://doi.org/10.1007/s11154-019-09514-y.
42. Trimboli P, Castellana M, Bellido D, Casanueva FF. Confusion in the nomenclature of ketogenic diets blurs evidence. Rev Endocr Metabol Disord. 2020. https://doi.org/10.1007/s11154-020-09546-9.
43. Lichtenstein AH, Appel LJ, Brands M, Carnethon M, Daniels S, Franch HA, et al. Diet and lifestyle recommendations revision 2006: a scientific statement from the American Heart Association Nutrition Committee. Circulation. 2006;114:82–96. https://doi.org/10.1161/CIRCULATIONAHA.106.176158.
44. Howard BV, Van Horn L, Hsia J, Manson JA, Stefanick ML, Wassertheil-Smoller S, et al. Low- fat dietary pattern and risk of cardiovascular disease: the Women's Health Initiative randomized controlled dietary modification trial. JAMA. 2006;295:655–66. https://doi.org/10.1001/jama.295.6.655.
45. Prentice RL, Aragaki AK, Van Horn L, Thomson CA, Beresford SA, Robinson J, et al. Low-fat dietary pattern and cardiovascular disease: results from the Women's Health Initiative randomized controlled trial. Am J Clin Nutr. 2017;106:35–43. https://doi.org/10.3945/ajcn.117.153270.
46. Bazzano LA, Hu T, Reynolds K, Yao L, Bunol C, Liu Y, et al. Effects of low-carbohydrate and low-fat diets: a randomized trial. Ann Intern Med. 2014;161:309–18. https://doi.org/10.7326/M14-0180.
47. Hooper L, Summerbell CD, Thompson R, Sills D, Roberts FG, Moore H, et al. Reduced or modified dietary fat for preventing cardiovascular disease. Cochrane Database Syst Rev. 2011;7:CD002137. https://doi.org/10.1002/14651858.CD002137.pub2.
48. Tobias DK, Chen M, Manson JE, Ludwig D, Willett W, Hu FB. Effect of low-fat diet interventions versus other diet interventions on long-term weight change in adults: a systematic review and meta-analysis. Lancet Diabetes Endocrinol. 2015;3:968–79. https://doi.org/10.1016/S2213-8587(15)00367-8.
49. Dong YJ, Zhang ZL, Wang PY, Qin LQ. Effects of high-protein diets on body weight, glycaemic control, blood lipids and blood pressure in type 2 diabetes: meta-analysis of randomised controlled trials. Br J Nutr. 2013;110:781–9. https://doi.org/10.1017/S0007114513002055.
50. Schwingshackl L, Hoffmann G. Long-term effects of low-fat diets either low or high in protein on cardiovascular and metabolic risk factors: a systematic review and meta-analysis. Nutr J. 2013;12:48. https://doi.org/10.1186/1475-2891-12-48.
51. Appel LJ. The effects of protein intake on blood pressure and cardiovascular disease. Curr Opin Lipidol. 2003;14:55–9. https://doi.org/10.1097/00041433-200302000-00010.
52. Baba NH, Sawaya S, Torbay N, Habbal Z, Azar S, Hashim SA. High protein vs high carbohydrate hypoenergetic diet for the treatment of obese hyperinsulinemic subjects. Int J Obes Relat Metab Disord. 1999;23:1202–6. https://doi.org/10.1038/sj.ijo.0801064.
53. Worthington BS, Taylor LE. Balanced low-calorie vs. high-protein-low-carbohydrate reducing diets: I. Weight loss, nutrient intake, and subjective evaluation. J Am Diet Assoc. 1974;64:47–51.
54. Layman DK, Boileau RA, Erickson DJ, Painter JE, Shiue H, Sather C, et al. A reduced ratio of dietary carbohydrate to protein improves body composition and blood lipid profiles during weight loss in adult women. J Nutr. 2003;133:411–7. https://doi.org/10.1093/jn/133.2.411.
55. Whitehead JM, McNeill G, Smith JS. The effect of protein intake on 24-h energy expenditure during energy restriction. Int J Obes Relat Metab Disord. 1996;20:727–32. https://doi.org/10.1093/jn/133.2.411.
56. Hu FB. Protein, body weight, and cardiovascular health. Am J Clin Nutr. 82:242S–7S. https://doi.org/10.1093/ajcn/82.1.242S.
57. Lagiou P, Sandin S, Lof M, Trichopoulos D, Adami HO, Weiderpass E. Low carbohydrate-high protein diet and incidence of cardiovascular diseases in Swedish women: prospective cohort study. BMJ. 2012;344:e4026. https://doi.org/10.1136/bmj.e4026.
58. Martínez-González MA, Gea A, Ruiz-Canela M. The Mediterranean diet and cardiovascular health. Circ Res. 2019;124:779–98. https://doi.org/10.1161/CIRCRESAHA.118.313348.
59. Schwingshackl L, Hoffmann G. Mediterranean dietary pattern, inflammation and endothelial function: a systematic review and meta-analysis of intervention trials. Nutr Metab Cardiovasc Dis. 2014;24:929–39. https://doi.org/10.1016/j.numecd.2014.03.003.
60. Guo X, Tresserra-Rimbau A, Estruch R, Martínez-González MA, Medina-Remón A, Castañer O, et al. Effects of polyphenol, measured by a biomarker of total polyphenols in urine, on cardiovascular risk factors after a long-term follow-up in the PREDIMED study. Oxidative Med Cell Longev. 2016;2016:2572606. https://doi.org/10.1155/2016/2572606.
61. Lopez-Garcia E, Rodriguez-Artalejo F, Li TY, Fung TT, Li S, Willett WC, et al. The Mediterranean-style dietary pattern and mortality among men and women with cardiovascular disease. Am J Clin Nutr. 2014;99:172–80. https://doi.org/10.3945/ajcn.113.068106.
62. Becerra-Tomás N, Blanco Mejía S, Viguiliouk E, Khan T, Kendall CWC, Kahleova H, et al. Mediterranean diet, cardiovascular disease and mortality in diabetes: a systematic review and meta-analysis of prospective cohort studies and randomized clinical trials. Crit Rev Food Sci Nutr. 2019; 1–21. https://doi.org/10.1080/10408398.2019.1565281.
63. Grosso G, Marventano S, Yang J, Micek A, Pajak A, Scalfi L, et al. A comprehensive meta-analysis on evidence of Mediterranean diet and cardiovascular disease: are individual components equal? Crit Rev Food Sci Nutr. 2017;57:3218–32. https://doi.org/10.1080/10408398.2015.1107021.

64. Soltani S, Chitsazi MJ, Salehi-Abargouei A. The effect of dietary approaches to stop hypertension (DASH) on serum inflammatory markers: a systematic review and meta-analysis of randomized trials. Clin Nutr. 2018;37:542–50. https://doi.org/10.1016/j.clnu.2017.02.018.
65. Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM, et al. A clinical trial of the effects of dietary patterns on blood pressure: DASH collaborative research group. N Engl J Med. 1997;336:1117–24. https://doi.org/10.1056/NEJM199704173361601.
66. Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. N Engl J Med. 2001;344:3–10. https://doi.org/10.1056/NEJM200101043440101.
67. Levitan EB, Lewis CE, Tinker LF, Eaton CB, Ahmed A, Manson JE, et al. Mediterranean and DASH diet scores and mortality in women with heart failure: the Women's Health Initiative. Circ Heart Fail. 2013;6:1116–23. https://doi.org/10.1161/CIRCHEARTFAILURE.113.000495.
68. Jones NRV, Forouhi NG, Khaw KT, Wareham NJ, Monsivais P. Accordance to the dietary approaches to stop hypertension diet pattern and cardiovascular disease in a British, population-based cohort. Eur J Epidemiol. 2018;33:235–44. https://doi.org/10.1007/s10654-017-0354-8.
69. Salehi-Abargouei A, Maghsoudi Z, Shirani F, Azadbakht L. Effects of dietary approaches to stop hypertension (DASH)-style diet on fatal or nonfatal cardiovascular diseases – incidence: a systematic review and meta-analysis on observational prospective studies. Nutrition. 2013;29:611–8. https://doi.org/10.1016/j.nut.2012.12.018.
70. Ravera A, Carubelli V, Sciatti E, Bonadei I, Gorga E, Cani D, et al. Nutrition and cardiovascular disease: finding the perfect recipe for cardiovascular health. Nutrients. 2016;8:363. https://doi.org/10.3390/nu8060363.
71. Adamsson V, Reumark A, Cederholm T, Vessby B, Risérus U, Johansson G. What is a healthy Nordic diet? Foods and nutrients in the NORDIET study. Food Nutr Res 2012; 56. https://doi.org/10.3402/fnr.v56i0.18189.
72. Adamsson V, Reumark A, Fredriksson IB, Hammarstrom E, Vessby B, Johansson G, et al. Effects of a healthy Nordic diet on cardiovascular risk factors in hypercholesterolaemic subjects: a randomized controlled trial (NORDIET). J Intern Med. 2011;269:150–9. https://doi.org/10.1111/j.1365-2796.2010.02290.x.
73. Olsen A, Egeberg R, Halkjaer J, Christensen J, Overvad K, Tjonneland A. Healthy aspects of the Nordic diet are related to lower total mortality. J Nutr. 2011;141:639–44. https://doi.org/10.3945/jn.110.131375.
74. Roswall N, Sandin S, Lof M, Skeie G, Olsen A, Adami HO, et al. Adherence to the healthy Nordic food index and total and cause-specific mortality among Swedish women. Eur J Epidemiol. 2015;30:509–17. https://doi.org/10.1007/s10654-015-0021-x.
75. Puaschitz NG, Assmus J, Strand E, Karlsson T, Vinknes KJ, Lysne V, et al. Adherence to the healthy Nordic Food Index and the incidence of acute myocardial infarction and mortality among patients with stable angina pectoris. J Hum Nutr Diet. 2019;32:86–97. https://doi.org/10.1111/jhn.12592.
76. Wang F, Zheng J, Yang B, Jiang J, Fu Y, Li D. Effects of vegetarian diets on blood lipids: a systematic review and meta-analysis of randomized controlled trials. J Am Heart Assoc. 2015;4:e002408. https://doi.org/10.1161/JAHA.115.002408.
77. Dinu M, Abbate R, Gensini GF, Casini A, Sofi F. Vegetarian, vegan diets and multiple health outcomes: a systematic review with meta-analysis of observational studies. Crit Rev Food Sci Nutr. 2017;57:3640–9. https://doi.org/10.1080/10408398.2016.1138447.
78. Key TJ, Fraser GE, Thorogood M, et al. Mortality in vegetarians and nonvegetarians: Detailed findings from a collaborative analysis of 5 prospective studies. Am J Clin Nutr. 1999;70:516S–24S. https://doi.org/10.1093/ajcn/70.3.516s.
79. Appleby PN, Crowe FL, Bradbury KE, Travis RC, Key TJ. Mortality in vegetarians and comparable nonvegetarians in the United Kingdom. Am J Clin Nutr. 2016;103:218–30. https://doi.org/10.3945/ajcn.115.119461.

Cardiovascular and Emotional Effects of Music

56

Laura Fusar-Poli and Cecilia Guiot

Contents

Abstract

Music represents a form of nonverbal language that does not encounter any limit across time, space, and cultures. Since antiquity the healing power of music on the human soul and body has been investigated and exploited by philosophers, scientists, magicians, and priestesses. Music can act both at a psychological level, evoking specific emotional states, and at a corporeal level, inducing physiological changes in different systems of the human body.

The first part of the present chapter has been focused on the emotions evoked by music and provides an analysis of the modifications induced by the musical experience in the neural, endocrinological, and autonomic nervous systems. In the second section, we have attempted to explain why, even in modern times, music can be considered a real therapeutic tool for several neuropsychiatric disorders and cardiovascular diseases. A detailed summary of the most recent literature on the topic has been presented.

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*,
https://doi.org/10.1007/978-3-030-28008-6_56

Keywords

Music · Emotion · Heart · Brain · Psychiatry · Cardiology · Oxytocin · Cortisol · Amygdala

Introduction

The nonverbal language of music is a creative form of art existing across all cultures around the world [1]. People have been making music for at least 35,000 years [2], and no human culture has yet been identified that does not practice some recognizably musical activity.

The notion of music as therapy is based on ancient cross-cultural beliefs that music can have a "healing" effect on mind and body. In the antiquity, the relationship between music, mind, and body was mainly related to the field of magic. Since illnesses were thought to be caused by divine interference as curses or punishment, or by diabolical forces, healing could only come from the divine realm, and music represented the means to access that realm. One can think, for example, of King Saul, who was tormented by an evil spirit, and relief came to him when David played the lyre (Sam 16, 14–23). According to intellectuals from Ancient Greece, such as Pythagoras, Asclepiades, Aristoteles, and Plato, music could be used to reflect and project the harmony of the cosmos onto the mind to create or reestablish the inner harmony. This process was not only considered valuable as therapy but also for educational purposes to strengthen character and virtue [3–5].

In contemporary society, little has changed: music continues to be used to promote health and well-being in clinical settings, such as for pain management, relaxation, psychotherapy, and personal growth. The present chapter is aimed at analyzing the effects of music on mental and cardiovascular functioning. In the first part, we will present the concept of music-evoked emotions and the modifications induced in the central and peripheral nervous system and consequently in the cardiovascular and endocrinological activity. Secondly, we will present the growing body of literature addressing evidence-based music interventions through peer-reviewed scientific experiments, focusing in particular on its clinical use in neuropsychiatric and cardiovascular diseases.

Music and Emotions

Emotions: Definition and Theories

The term *emotion* is used to refer to a quite brief but intense affective reaction that usually involves several sub-components which can be more or less "synchronized" (e.g. subjective feeling, physiological arousal, expression, action tendency, and regulation). Emotions are focused on specific objects and usually last minutes or hours [6]. Notably, emotions differ from *mood*, which is intended as an affective state with lower intensity, without a clear "object," and lasting longer than emotions. The subjective experience of emotions or mood is what we call a *feeling* [6].

Although the occurrence of emotions in animals was recognized since the time of Ancient Greeks, it was Charles Darwin who firstly provided the theoretical framework for biological studies of emotions. Darwin presented his views on emotions in *The Expression of the Emotions in Man and Animals* (1872) [7] in which he collected all his anthropological works, clinical observations, and experimental research on humans and animals [8]. Nowadays, many scholars still agree that humans share an innate set of basic emotions which are recognizable regardless of cultures and species. These basic emotions are described as *discrete* because they are believed to be distinguishable simply observing an individual's facial expression, and could be identified as anger, disgust, fear, happiness, sadness, and surprise [9]. In contrast with the discrete model of emotions, the *dimensional* models affirm that emotions cannot be considered as clear separated "blocks"; contrariwise, affective states could be further dissociated in several continuous dimensions, such as valence, arousal, or intensity. One of the first dimensional models of emotion was theorized by Wilhelm Wundt (1905) and was centered around the three dimensions of pleasure (*positive* vs. *negative*), inhibition (*calm* vs. *excited*), and tension (*relaxed* vs. *tense*) [10]. The most recent two-dimensional

model – often referred to as "circumplex" model – encompasses the orthogonal dimensions of valence and arousal [11] and is however most commonly employed in music research.

Somatic theories of emotion claim that bodily responses, rather than cognitive interpretations, are essential to emotions. For instance, William James and Carl Lange argued that emotional experiences perceived in the brain were secondary to stimuli trigger activity in the autonomic nervous system. As James wrote, "the perception of bodily changes, as they occur, is the emotion"; the author further claimed that "we feel sad because we cry, angry because we strike, afraid because we tremble, and either we cry, strike, or tremble because we are sorry, angry, or fearful, as the case may be" [12]. Cannon and Bard agreed with their predecessors that physiological responses played a crucial role in emotions, but did not believe that they could explain the subjective emotional experiences alone. Their work instead suggests that emotions could be experienced even when the body does not reveal a physiological reaction; in other cases, physiological reactions to different emotions can be extremely similar. Therefore, the emotion and the physical response occur simultaneously and independently [13, 14].

The two-factor theory, elaborated by Schachter (1962), draws on elements of both James-Lange theory and Cannon-Bard theory, proposing that physiological arousal occurs in first place, but that the physical reaction might be similar for different emotions. The two-factor model was based on the earlier work of Gregorio Marañón, a Spanish physician who, after injecting patients with adrenaline, found that most of them felt something even in absence of an actual emotion-evoking stimulus: in fact, the patients were unable to interpret their physiological arousal as an experienced emotion [15]. The two-factor theory suggests that physiological reactions contributed to the emotional experience by facilitating a focused cognitive judgment of a given physiologically arousing event and that this appraisal was what defined the subjective emotional experience. Emotions were thus a result of two-stage process: general physiological arousal and experience of emotion [16].

In more recent years, a growing number of neuroscientists have attempted to investigate the biological bases of emotions [17–20]. For example, Joseph E. LeDoux has proposed a model which attempted to explain how harmful stimuli are processed in the brain to produce defense reactions [17]. In his research, LeDoux uses a fear conditioning, i.e., an experimental paradigm in which a neutral stimulus is paired with a harmful event. As a result of fear conditioning procedure, a previously neutral stimulus acquires the ability to trigger inherent behavioral, autonomic, and endocrine responses that are expressed automatically in the presence of danger. LeDoux and other authors have shown that the key structure for threat conditioning is the amygdala. The activation of the amygdala neurons by threat signaling stimuli excites the pathways controlling threat responses. If the flow of information through the amygdala is disrupted, threat signaling stimuli do not trigger defense responses anymore. Sensory information about fear is transmitted to the amygdala through two independent pathways: a thalamic pathway, which provides the amygdala with a rapid but imprecise representation of the sensory input, and a cortical path, which conveys a more complex representation based on cortical computations. Since conscious processes are associated with cortical areas, this model explains how environmental stimuli trigger automatic threat responses before we are aware of the actual danger [17, 21].

More recently, Stefan Koelsch [22] presented a neurobiological theory of emotions that includes emotions which are uniquely human (such as complex moral emotions). This model integrates psychological, neurobiological, sociological, anthropological, and psycholinguistic perspectives on emotions in an interdisciplinary manner, aiming to advance the understanding of human emotions and their neural correlates. Koelsch proposes four classes of emotions, originated from as many neuroanatomically distinct cerebral systems. These emotional core systems constitute a "quartet" of *affect systems*: the *brainstem-*, *diencephalon-*, *hippocampus-*, and *orbitofrontal*-centered affect systems (Fig. 1). The affect systems were increasingly

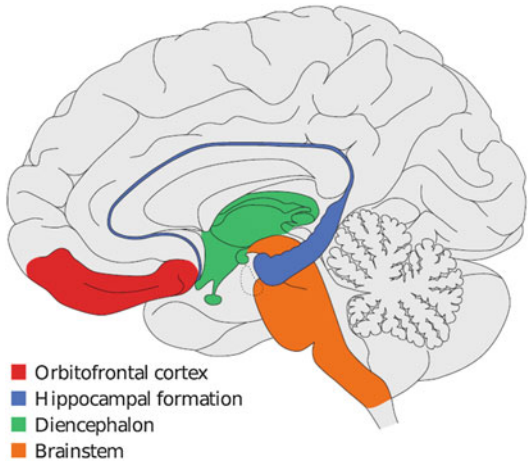

Fig. 1 The "quartet" of affect systems. (With courtesy of Prof. Stefan Koelsch)

differentiated during evolution, and each of these systems generates a specific class of affects, such as activation and deactivation, pain and pleasure, attachment-related emotions, and moral emotions. The activity of affect systems is coordinated by limbic/paralimbic structures, such as amygdala, basal ganglia, striatum, insula, and cingulate cortex [23]. The affect systems interact with each other, and activity of the affect systems has effects on – and interacts with – biological systems denoted as emotional *effector systems*. These effector systems include peripheral physiological arousal, motor systems (which produce actions, action tendencies, and motoric expression of emotion), as well as memory and attentional systems. Activity of affect systems and effector systems is synthesized into an emotion percept (preverbal subjective feeling), which can be transformed into language. Moreover, conscious cognitive evaluation (involving rational thought, logic, and language) can regulate, modulate, and partly initiate the activity of affect and effector systems [22].

Music-Evoked Emotions: Classification and Mechanisms

When talking about music and emotions, it is important to distinguish between *perceived* and *felt* emotions. *Perceived* emotions are related to emotion recognition or perception, while *felt* emotions are connected to the induction or evocation of emotions by music. Perceived and felt emotion do not necessarily move in the same direction (e.g., one might feel sad or joyful in response to sad-sounding music) [24], and even opposite, but simultaneous, emotional valences (happy vs. sad) can be experienced as pleasurable [25].

We will focus in this section on felt emotions, which we will call "music-evoked emotions." As mentioned above, music-evoked emotions can be widely varied. They may include joy, sadness, fear, and peacefulness or tranquility. Music can produce feelings of intense pleasure or euphoria in the listener, sometimes experienced as "thrills" or "chills down the spine." Musical pleasure is closely related to the intensity of emotional arousal, and listeners often report that the most moving music evokes two or more emotions at once [26].

According to Juslin [6], music-evoked emotions can be classified into the following groups:

1. *Everyday emotions*: emotions similar to others experienced in daily life, including discrete emotions such as happiness, sadness, interest, and surprise
2. *Aesthetic emotions*: emotion thought aroused when perceiver is engaged with an artwork
3. *Mixed emotions*, in which positive and negative affects are experienced simultaneously (e.g., pleasurable sadness)

The main difference between aesthetic and everyday emotions consists in the fact that the first category lacks an intentional object it is directed to [24]. Finally, *chills* could be considered other examples of emotional response to music, being a combination of subjective feeling (e.g., sadness, happiness, grief, joy, or calmness) and physiological arousal (e.g., tingling sensations, feelings of warmth or coldness, shivering down the spine, and lump-in-the-throat sensation) [24, 27].

But which are the psychological mechanisms responsible for music-evoked emotions? In 2008,

Juslin and Västfjäll [28] introduced the following mechanisms:

1. *Brain stem reflexes*: loud or dissonant music signals to the brain stem a potentially urgent event that needs attention, leading to automatic and quick emotional reactions such as changes in arousal or feeling of surprise [29]
2. *Evaluative conditioning*: a regular pairing of a piece of music and other positive or negative stimuli leading to a conditioned association, similar to how a funeral march can evoke sadness even not in the context of a funeral [30]
3. *Emotional contagion*: an internal "mimicry" of the perceived voice-like emotional expression of the music [31]
4. *Visual imagery*: music evokes images with emotional qualities, which in turn trigger an emotional response in the listener [32]
5. *Episodic memory*: an emotional response occurs because the music evokes a memory of a particular event in the listener's life [33]
6. *Musical expectancy*: a reaction to the gradual unfolding of the musical structure and its expected or unexpected continuation [34]

Further mechanisms were added later on [6] and include *rhythmic entrainment* (i.e., an internal body rhythm, such as such as heart and/or respiration rate, synchronizes with the rhythm of the music [35]), and *aesthetic judgment* (i.e., a subjective evaluation of the aesthetic value of the music based on an individual set of weighted criteria [6]) [24, 36].

As reported by Stefan Koelsch in 2014 [37], other sources within the music itself could trigger emotional reactions, conveying tension and expectancy via the musical piece: (1) *acoustic factors* (e.g., consonance/dissonance, loudness); (2) *structural stability* (e.g., moving to and from the tonal center); (3) the *extent of structural content* in the music; and (4) *structural breaches*. The first factor relates strongly to our responses to sound in general, while the other three are associated with the way that composers play with the structure within music as it progresses, creating an alternation of tension and relaxation, that in the right quantities provide the recipes for different emotional reactions. Koelsch also mentions *contagion* among the possible sources of emotional induction: the idea that when an emotion is triggered, we experience the physiological manifestations of that state (e.g., we might smile). That smile then goes back into the system, reinforcing the happy emotion that we feel [37].

Advances in neuroscience have attempted to examine the neural, endocrinological, and psychophysiological correlates of emotions induced by music, which will be presented in the next sections.

Neural Correlates of Music-Evoked Emotions

The potential of music to evoke emotions makes music a valuable tool for the investigation of emotions and their neural correlates. An advantage of music is that it enables researchers to study a wide range of emotional states, some of which are otherwise difficult to evoke in experimental settings.

The first functional neuroimaging study on music and emotion was a study by Anne Blood and colleagues [38]. Using positron emission tomography (PET), they investigated the emotional dimension of pleasantness/unpleasantness in ten volunteers listening to sequences of harmonized melodies. The stimuli varied systematically in the degree of dissonance and were perceived as less or more unpleasant (stimuli with the highest degree of continuous dissonance were rated as the most unpleasant). Variations in pleasantness/unpleasantness were shown to modulate activity in the (posterior) subcallosal cingulate cortex, as well as in several paralimbic structures.

A meta-analysis of functional neuroimaging studies on music and emotion published in 2014 [37], confirmed by more recent findings, reported activity changes in several brain regions involved in emotion, such as hippocampus, amygdala, auditory cortex, nucleus accumbens/ventral striatum, dorsal striatum, medial and lateral orbitofrontal cortex, and anterior cingulate cortex, as well as in the anterior insula, anterior portion of the supplementary motor area (pre-SMA), rostral

cingulate zone, and mediodorsal thalamus. In addition, brain stem structures of the auditory pathway seem involved in music-evoked emotions: for example, the very first auditory processing stages in the brain stem, the cochlear and vestibular nuclei, project into the reticular formation, contributing to the arousing or calming effects of music [23].

Koelsch [37] mentions three main candidate components of the core emotion brain network: the amygdala, the nucleus accumbens (NA), and the hippocampus.

The *amygdala* is a deep, central brain structure that receives some of the first projections from the lower brain centers. Music stimulates the amygdala in a similar way to faces [39], smells, and other sounds [40], most likely because all these stimuli are perceived as having social significance due to their communicative properties [41–43]. According to the author, the amygdala is part of a larger network that regulates approach-withdrawal behavior in response to socio-affective cues, including those given by music [44]. Finally, the amygdala likely has a role in how we evaluate and learn about positive or negative stimuli and therefore is involved in how our behavior eventually becomes reinforced toward or away from certain musical sounds [45, 46].

The *nucleus accumbens* (NA) is well-known to be activated by peak emotional experiences, known as "chills" or "frisson," but it is also activated as soon as music is experienced as pleasurable [26, 47]. In general, the NA is sensitive to primary rewards (food, sex) and secondary rewards (money, power), so it has a hedonic value for us and helps to initiate behaviors aimed at obtaining more of these rewards for consumption [48]. This finding suggests that music can be a rewarding emotional stimulus, as music lovers can confirm. The NA activation signals the anticipation of the rewarding experience of hearing pleasurable music, as well as the actual experience of enjoying the music [49].

Finally, the *hippocampus* is connected to our emotional reactions via its involvement in the regulation of our brain's chemical stress response, which comprises the hypothalamus-pituitary-adrenal axis (HPA axis) [50]. The hippocampus is implicated in music-evoked positive emotions which can reduce the release of stress hormones like cortisol. Apparently, the hippocampus is quite sensitive to chronic levels of stress hormones in general, and long-term exposure, such as in some cases of post-traumatic stress disorder (PTSD) and depression, can damage the neurons in this brain structure, thus impairing the ability to perceive or react to emotion in music [51]. Another emotional function of the hippocampus in humans is the formation and maintenance of social attachments. This is in accordance with the observation that the hippocampus hosts oxytocin receptors and that it is involved in the regulation of oxytocin release into the bloodstream by the pituitary gland [52]. The fact that the hippocampus reacts to emotional music (including fear and joy) suggests that it is responsive to the potential of music to stimulate the release of brain chemicals which affect its function.

More details regarding the interplay between brain regions responsible for music-evoked emotions and other systems (e.g., HPA axis, hormonal levels, etc.) will be further explored in the next paragraphs.

Neurochemistry and Psychophysiology of Music

Music-evoked emotions are connected not only with subjective emotional feelings but also with changes in the major somatic components of emotion, including physiological arousal, especially on the autonomic and endocrine systems, with the latter affecting the immune system in turn. These findings have raised attention toward musical experience itself as a factor that can produce changes in autonomic, hormonal, and immune activity [53].

The investigation of how music influences neurochemical changes in the brain and periphery has led to the identification of several biochemical mediators which may be involved in the processing of music. This growing field of research has often led to contrasting, disorganized observations that are difficult to interpret. Only a small

minority of these studies have discussed their results in the framework of precise physiological pathways, and even fewer have attempted to draft possible models to explain the mechanisms underlying the effects of music [54].

In the following paragraphs, neurochemically mediated music-health interactions will be organized into three domains: reward, motivation, and pleasure; stress and arousal; and social affiliation and bonding. This classification is meant to help in the approach to the wide variety of observations reported in the literature, but it does not necessarily reflect a concrete distinction between these systems, which are frequently overlapping and interconnected in their functions, mediators, and manifestations.

Reward, Motivation, and Pleasure

The ability to engage in motivated behaviors toward activities that are crucial for survival or well-being, such as acquisition and ingestion of food, is an essential feature that allows individuals to thrive [25]. The seeking of resources that benefit one's organism is rewarded with a feeling of pleasure when the target resource is successfully obtained, which motivates the individual to maintain that behavior.

The balance between behaviors that are directed toward different resources and rewards is achieved thanks to a cyclical pattern of phases that guide survival-related decision-making [55]. First, the *wanting* phase is characterized by motivation for reward, which generates goal-directed behaviors. When the reward is accomplished, the *liking* phase takes place, which constitutes the actual hedonic component of reward. Finally, the *learning* phase allows for associations to be formed from the experience, which will enable the individual to make more accurate predictions about future rewards. Although all three phases of the cycle tend to have a conscious component, they are rooted in unconscious mechanisms mediated by neurochemicals across specific brain regions.

The one molecule that has received the most attentions in relation to the reward system is dopamine. With its widespread network – which connects the substantia nigra pars compacta (SNc) and ventral tegmental area (VTA) with the striatum, nucleus accumbens (NAc), and prefrontal cortex [56] – the dopaminergic system altogether allows for the integration of cognitive and affective signals to promote action toward motivationally relevant goals [57].

Dopamine has at first been considered as a key mediator for all three phases of the pleasure cycle [55]. However, while this has been demonstrated to hold for the *wanting* [47] and *learning* [58] phases, the *liking* phase appears to be mediated by endogenous opioids and endorphins [59]. Endogenous opioids are released in "hedonic hotspots" in the NAc and have been shown to modulate dopamine cell firing in the VTA [60]. Nevertheless, dopamine maintains a fundamental role. Dopamine release generates selective reinforcement of associations between rewards and reward-producing behaviors based on past experiences, transforming otherwise neutral stimuli into incentive motivational stimuli [56].

Reward mechanisms are not limited to those behaviors that are linked to survival, such as the seeking of food and sex, and to those that display addictive properties, such as drugs of abuse. Perhaps surprisingly, the same system appears to be activated for more "abstract" rewards, such as with the case of music [60]. Music listening, in fact, has been shown to activate not only the perceptual pathway involving the auditory cortex but also the network of reward [55]. A pioneer study in this field has been conducted by Blood and Zatorre [26], who investigated the neural correlates of the pleasurable experience of musical chills and identified a correlation with activity in the reward circuitry at positron emission tomography (PET). Various researchers have since been using PET or functional magnetic resonance imaging (fMRI) to study brain responses to pleasant (or unpleasant) music (for a detailed account, see [55]). This field of research led to consistent findings in areas linked to the processing of reward, including striatum, NAc, VTA, and prefrontal cortex, but also in substantia nigra and hypothalamus, providing indirect evidence of the involvement of dopamine. Salimpoor and colleagues [47] were the first to directly demonstrate

the association between dopamine release and musical pleasure, combining fMRI with PET scanning and the dopamine-specific tracer [^{11}C] raclopride.

As reported by Mallik et al. [61], both positive and negative emotions to music were attenuated after administration of naltrexone (NTX), a μ-opioid antagonist, suggesting that also "endogenous opioids are critical to experiencing both positive and negative emotions in music, and that music uses the same reward pathways as food, drugs and sexual pleasure" [61].

Several theories have thus been developed to explain why music engages the human brain in reward mechanisms. According to some researchers [60], this occurs because music continuously generates and resolves expectations in listeners, which leads to desire and anticipation of predicted sound events as music unfolds in time. The creation of expectation as a strategy to engage listeners is actually well-known to the composers of all times: suspension, delay, evaded cadences, and applied dominants are only some of the devices that exploit the predictions that listeners implicitly develop – at least in Western, tonal music, in which these phenomena have mostly been studied.

Chord progression in particular has been the object of studies on musical pleasure. A recent study by Cheung and colleagues [57] has investigated the association between predictability of a specific chord in a succession and the pleasantness that listeners attributed to that chord. According to the authors, pleasure from music listening is generated in two different states: in the phase of anticipation, when the chord is expected with a degree of uncertainty that depends on the tonal harmonic context, and in the phase of surprise, in case the chord deviates from expectations. It would appear that violation of expectations is interpreted by the brain as especially pleasant: subjects reported higher pleasantness either when hearing a surprising chord when they had confidently expected a different one or when a familiar chord would resolve a harmonic context of high uncertainty. The two pleasant states identified in this study seem to reflect the dopamine-mediated phases of the pleasure cycle, where dopamine release is associated with both the desire to receive an expected stimulus and the assessment of an outcome that deviates from predictions [60].

These findings seem to indicate that the pleasure we find in music listening is generated by the subtle interplay between adherence and deviation from conventions in musical structures, oscillating between the extremes of excessive adherence – and the risk of boredom – and excessive deviation, which could escalate to nonsense. Personal taste in the appreciation of music may be explained by the subjectivity of such thresholds, which could be expected to derive from the integration of individualized cortical processes that are continuously updated on the base of previous experiences [60].

It is worth noting that both the tension generated by musical expectations and the surprise due to their violation should be expected to involve a rise in attention and arousal [55]. Such a state of vigilant preparation could be manifested through visceral responses mediated by the autonomic nervous system, such as increased heart rate and electrodermal activity [62]. This phenomenon should remind of a larger picture, where the systems of prediction and reward and those of attention, arousal, and stress response are inevitably interconnected. Therefore, the investigation of the relationship of music with either system cannot prescind from the consideration of the other.

Interestingly, the involvement of the mesolimbic dopaminergic system in musical reward has been confirmed also by the discovery of the so-called specific musical anhedonia [63], a condition characterized by the absence of feelings of pleasure in response to music, while pleasure and reward experiences to other stimuli (e.g., food, sex, or exercise) are normal. This phenomenon is associated with reduced activity changes in the NAc in response to music (and auditory-NAc functional connectivity). Moreover, Keller and colleagues (2013) reported that trait anhedonia is associated with reduced reactivity and connectivity of mesolimbic and paralimbic reward pathways in response to music [64]. However, evidence about brain lesions in people with musical anhedonia remain still inconsistent [23].

Stress and Arousal

The stress response is a complex system of physiological and behavioral responses that allow individuals to react rapidly to cognitive, emotional, neurosensory, and somatic stimuli to maintain homeostasis [65]. The main components of the stress system are the hypothalamic-pituitary-adrenal (HPA) axis, producing corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and cortisol, respectively; the locus coeruleus-norepinephrine system in the brainstem; and the autonomic nervous system, comprising the sympathetic and parasympathetic systems, which involve mediators such as epinephrine, norepinephrine (NE), acetylcholine, nitric oxide (NO), and lipid mediators of inflammation.

Many studies have been carried out in search for associations between music listening or performance and changes in the levels of these molecules, possibly reflecting an opportunity for the use of music therapy in clinical conditions that are worsened by stress. There is general consensus that listening to relaxing music can indeed decrease cortisol levels or buffer their increase in stressful situations [66–70], while milder evidence has been found for other markers such as ACTH [71], epinephrine and NE [72], and beta-endorphin [73]. Moreover, some researchers have also investigated the effects of stimulating music, which has been reported to be associated with an increase in cortisol, ACTH, epinephrine, and growth hormone [74]. There is also some evidence that music could lead to the release of NO, possibly bringing about reduction in blood pressure through its action on vasomotor tone [75].

A parallel strategy of research has evaluated changes in parameters that reflect the peripheral activity of the autonomic nervous system, such as heart rate (HR), heart rate variability (HRV), blood pressure (BP), respiratory rate (RR), and electrodermal skin response (ESR). The autonomic nervous system, which is linked bidirectionally with the central nervous system, endocrine system, and immune system, is indeed a promising target of research as a sensitive and dynamic mechanism potentially mediating beneficial effects of music on health [76].

According to systematic reviews [54], HR, BP, and RR, which are the most frequently assessed variables, are consistently found to decrease when listening to relaxing music. However, some researchers [76] have advocated deploying greater attention to HRV, instead of HR, as a parameter that could better reflect the complex interplay between the sympathetic and parasympathetic branches of the autonomic nervous system. High HRV would account for high flexibility of autonomic functions, making the individual more adaptable to changes in the environment [77], a feature that HR, being an average value, would fail to represent. However, literature reporting HRV as a dependent measure in musical interventions is still limited, and further investigation is needed for assessing its validity in laboratory and clinical settings. Skin conductance response (SCR), an easily measurable index of ESR, has also been used to evaluate the effects of music on emotions. As SCR varies with fluctuations in sweat glands activity, it allows to identify patterns in the sympathetic component alone, which is not possible with the measurement of HR and HRV [78].

In most studies, physiological parameters have been considered secondary outcome measures, while the primary target of research was usually a reduction in anxiety [76], especially in the clinical setting. For a complete account, a series of Cochrane Collection reviews has collected encouraging results for the role of music in reducing anxiety in various clinical populations, such as in patients with cancer [79] and coronary artery disease [80] and those undergoing surgery [81] and mechanical ventilation [82].

While there is a significant amount of evidence that music does have an impact on the stress response, it is also evident that results vary widely. Such variability is probably due to the lack of homogeneity in the design of experimental studies in this field, and several authors have advocated for greater rigor. Among others, Fancourt and colleagues [54] have proposed a model that could offer some guidance. First, the authors highlight how stressors should be distinguished as physiological or psychological in nature, and as acute or chronic in time course, since acute and

chronic stress have significantly different effects on individuals. Moreover, they suggest that musical stimuli should be characterized as for their purely auditory component, including factors such as tempo, tonality, and instrumentation; the type and degree of physical involvement of participants; social engagement, if present, such as when music listening or performance is carried out as a group; and personal responses to music, including familiarity, appreciation or dislike, and emotional responses.

Another possible confounder is whether music is selected by the experimenter or by the participants, a factor that is known as *locus of control*. Current evidence is controversial on this point, with some studies considering that giving the choice to patients could increase their sense of control, thus increasing the efficacy of the intervention [25], while others arguing that music selected according to research criteria leads to more consistent results [83]. However, there are no objective criteria to classify a musical piece as relaxing, although some attempts have been made to identify which specific features of music might account for any anxiolytic effects [84].

Social Affiliation and Bonding

Music fulfills social needs that are of vital importance for the individual. Therefore, the notion that music evokes only aesthetic experiences without goal relevance is doubtful [53]. Being an activity that promotes synchronization and connection, group music performance is one of those human behaviors that have long been known to foster interpersonal trust, bonding, and cooperation [25, 85–87]. In fact, music automatically engages social cognition [42] and co-pathy, promoting emotion regulation and favoring interindividual understanding and decreasing conflicts [88]. Finally, music making implicates the coordination of movements, typically associated with pleasure. Given the social valence of music, some of the researchers interested in the biological correlates of music and social bonding turned to the investigation of oxytocin.

A neuropeptide produced in the paraventricular nucleus of the hypothalamus and released from the posterior lobe of the pituitary, oxytocin appears to play a fundamental role in the organization of social behavior by modulating anxiety, affiliative motivation, and the processing of social clues [89–92]. The finding that the exchange of vocal cues – and not only physical contact, as previously understood – among mother and child can lead to a significant rise in oxytocin levels [93] hints at vocalizations as a deeply rooted mechanism of social bonding in humans. Some studies have been carried out that identify an increase in oxytocin levels during music listening [67] and especially during group singing [71, 94, 95]; however, it is currently not known whether peripheral levels of oxytocin can be considered representative of oxytocin levels in the brain [25, 92].

Oxytocin cannot be taken into account without vasopressin, a genetically and structurally related neuropeptide, as the two appear to produce reciprocal modulation in influencing social behavior [96, 97]. However, the role of vasopressin and its interaction with oxytocin in the mediation of music processing is yet to be explored [25].

Interestingly, it has been shown that passively listening to music increases interpersonal synchronization of cardiovascular and respiratory rhythms, which could further explain the role of music in favoring social bonds [98]. These preliminary results should encourage further research, which could potentially lead to evidence supporting the implementation of group music making as a therapeutic intervention in appropriate clinical populations, in concert with the practice already carried out by music therapists [71].

Music Therapy for the Brain and the Heart

Music therapy (MT) is defined by the World Federation of Music Therapy as "the professional use of music and its elements as an intervention in medical, educational, and everyday environments with individuals, groups, families, or communities who seek to optimize their quality of life and improve their physical, social, communicative, emotional, intellectual, and spiritual health and wellbeing." According to its definition, "research,

practice, education, and clinical training in music therapy are based on professional standards according to cultural, social, and political contexts" [99]. MT can be roughly classified in active and receptive MT. Active MT employs an interpersonal approach where participants sing or play musical instruments under the supervision of a music therapist or a trained healthcare provider. Receptive MT uses a relatively simple and less interactive approach, where participants stay and listen to music in a quiet place. It can be self-administrated with minimal professional support [99].

The ability of music to regulate emotions and to provoke psychophysiological and endocrinological modifications, as well as functional and plastic changes in this brain structures, has given rise to the investigation of the effects of music in people with different conditions, such as neuropsychiatric disorders or cardiovascular diseases. In the following paragraphs, we will focus on the therapeutic effects of MT and, more generally, of music-based interventions, which can be defined as any protocols using music [100].

Music Therapy for Neuropsychiatric Disorders

Depression

Major depressive disorder affects at least 4.4% of the global population, representing one of the leading causes of disability [101]. Depression is characterized by sadness, hopelessness, loss of energy, feels of worthlessness and excessive or inappropriate guilt, insomnia or hypersomnia, significant weight loss, diminished ability to concentrate, and recurrent thoughts of death [102]. There is some indication that depression affects the perception of emotions in music, similarly to other nonverbal communication channels [103]; therefore, music-evoked emotions in depressed subject might be different from healthy controls [104–106].

A moderate amount of evidence has suggested that MT can improve the mental health of people with depression. Several mechanisms have been proposed about the possible effectiveness of MT for depressive symptoms. First, music is used to modulate emotions and moods [107], also in everyday life [108]. Since depression is often accompanied by emotional dysregulation, music could thus represent a good way to alleviate this symptom [109]. Also, the act of playing musical instruments requires purposeful physical movement. The role of physical activity in averting depression and alleviating its effects is well recognized. This is not simply a matter of getting people moving, but also of enabling people to experience themselves as physical beings [109]. Finally, music making is a social, pleasurable, and meaningful activity; in fact, trials of music therapy have shown high levels of engagement with patient groups who are traditionally difficult to engage [109]. Literature showed that MT and, more broadly, music interventions may have beneficial effects on depression and anxiety symptoms in patients suffering from major depression disorder [110, 111]. The level of functioning in depressed individuals – an important aspect to take into account – also seemed to ameliorate, but up to date, it has been evaluated only by one study [112].

Anxiety, Obsessive-Compulsive Disorder (OCD), and Post-Traumatic Stress Disorder (PTSD)

Anxiety disorders are among the most prevalent mental illnesses worldwide [113, 114]. Anxiety has many negative impacts on health, daily life, and well-being and impair several cognitive [115] and emotional processes [116]. Currently, literature regarding the efficacy of music and MT on people with diagnosed anxiety and anxiety-related disorders have been barely explored. In a pilot study, Gutiérrez et al. [117] showed that MT was effective in reducing anxiety and depression levels in patients affected by generalized anxiety disorder (GAD). Also, in a small sample of children with chronic anxiety, music lessons improved self-confidence, social independence, creativity and emotional expression, and control over intrusive thoughts and feelings [118]. Recently, a meta-analysis by Panteleeva and colleagues [119] suggested that

music may reduce self-reported anxiety in non-clinical samples, despite such improvement is not always related to changes in physiological parameters typically associated with anxiety (e.g., blood pressure, cortisol, heart rate, etc.). Several meta-analyses have reported promising findings for the role of music in reducing anxiety in various clinical populations, such as in patients with cancer [79] and coronary artery disease [80] and those undergoing surgery [81] and mechanical ventilation [82].

Obsessive-compulsive disorder (OCD) is characterized by unwanted and disturbing thoughts, images, or urges (obsessions) that intrude into a person's mind and cause a great deal of anxiety or discomfort, which the patient then tries to reduce by engaging in repetitive behaviors or mental acts (compulsions) [102]. MT, as an adjunct to standard care, seems to be effective in reducing severity of obsessions and compulsions [120], as well as comorbid anxiety and depressive symptoms [121] in patients with OCD.

Post-traumatic stress disorder (PTSD) is characterized by an inability to recover from a reaction of stress following exposure to a traumatic event [102]. Symptoms can include reexperiencing the event, intrusive memories of the event, prolonged emotional distress and physiological reactivity after exposure to trauma-related stimuli, avoidance of trauma-related thoughts and external reminders, negative alterations in mood and cognition, and alterations in arousal and reactivity [102]. MT may offer an accessible and not-stigmatizing therapeutic option for treating PTSD [122], since it seems to improve post-traumatic symptoms, such as avoidance, hyperarousal, and reexperiencing [123, 124], as well as depressive symptoms [125] among individuals with trauma exposure and PTSD. Guided imagery music (GIM) is a specific method based on the assumption that it is indeed possible to select the most appropriate music for the client, depending on the therapist's understanding of the client's needs [126]. GIM has shown some effectiveness on different groups of individuals suffering from PTSD, such as refugees [127], military veterans [128] or abused women [129].

Schizophrenia and Other Psychotic Disorders

Schizophrenia and the other psychotic disorders are characterized by abnormalities in one or more of the following five domains: delusions, hallucinations, disorganized thinking or speech, grossly disorganized or abnormal motor behavior, and negative symptoms [102]. Functional abnormalities in the limbic system have been widely reported in people with schizophrenia [130], which in turn have been associated with cognitive impairments, such as diminished affect discrimination and verbal memory deficit [131, 132]. Consistent with altered limbic activity, some authors have reported that people with schizophrenia have impaired musical abilities [133, 134]. A recent study [135] suggests that music-evoked emotions in patients with schizophrenia might be different from the healthy population and also associated with symptoms severity. Thus, the authors proposed music-evoked emotions as a quick, noninvasive method to detect the presence or severity of cognitive changes in schizophrenia, and also for early diagnosis of the disease, and as a biomarker for treatment response [135].

As for other mental disorders, music-based interventions may represent potential therapeutic tools for schizophrenic patients. A recent meta-analysis [136] suggested that MT in addition to standard care may improve the global state, mental state (including negative and general symptoms), social functioning, and quality of life of people with schizophrenia or schizophrenia-like disorders. However, effects depended on the number of MT sessions as well as the quality of the interventions provided. Other recent studies showed that MT improved general psychiatric symptoms in patients with acute psychoses [137, 138].

Dementia

Dementia, also known as "major neurocognitive disorder," represents a serious neuropsychiatric condition currently affecting millions of older adults worldwide [139]. The disorder is mainly characterized by the progressive deterioration of cognitive functions, which causes progressive

impairments in autonomy and functioning [102]. Deficiencies in music perception are reported for patients with cerebral degeneration. Recognition of music expressing joy, sadness, anger, or fear is impaired in patients with frontotemporal lobar degeneration or damage of the amygdala [37].

Given the limited efficacy [140] and the side effects often caused by medications [141], more attention have been paid to the use of alternative and complementary therapies for people with dementia [142, 143]. Of note, brain areas underlying musical memory seem to be among the last to show atrophy [144]. Indeed, it has been shown that MT may enhance communication and emotional well-being: through the nonverbal language of music, it is possible to establish a contact also when verbal language deteriorates [145].

According to a recent Cochrane review, music-based therapeutic interventions for people with dementia seemed to improve depressive symptoms and emotional well-being including quality of life [146]. Results regarding the efficacy of MT behavioral and psychological symptoms of dementia (BPSD), such as agitation, disruptive behavior, and anxiety in older people with dementia, are still inconsistent [147–149]. Cognitive symptoms, which represent the core impairments of dementia, have been barely investigated. However, some authors suggested promising effects of active MT [149, 150], in which the combination of music and movement might promote beneficial effects on general cognition.

Autism Spectrum Disorder (ASD)

Autism spectrum disorder (ASD) is a group of lifelong neurodevelopmental conditions, characterized by deficits in socio-communication and by the presence of restricted interests of repetitive behaviors [102]. The prevalence of ASD has been constantly increasing, and it is currently estimated that around 1.5% of the general population might belong to the autism spectrum [151]. Since the first description of the condition, the strong connection between music and ASD has been described in terms of extraordinary skills in numerous peculiar areas of interest, including an exceptional musical interest [152, 153]. Interestingly, musical giftedness may be positively exploited within rehabilitation programs in autism to promote social interactions, communicative behavior, and emotional responsiveness [154]. Functional neuroimaging studies show that individuals with ASD exhibit relatively intact perception and processing of music-evoked emotions [155], despite their deficit in the ability to understand emotions in non-musical social communication [102]. In fact, music may sometimes represent an alternative attempt of communication and emotional expression by nonverbal subjects with ASD [156–159]. For this reason, it has been hypothesized that MT can be used to develop communication skills since music involves communication capabilities of autistic individuals [37]. Additionally, given the lack of effective psychopharmacological treatment for ASD core symptoms [160], the use of complementary and alternative therapies, such as music and music-related therapy, among autistic subjects has been constantly growing [161].

As reported by a recent systematic review, the short- and medium-term effect of music therapy interventions for children with ASD appears superior to placebo or standard care in several domains of communication and social interaction, as well as in secondary outcome areas, including social adaptation and quality of parent-child relationships [162]. Conversely, a large multicenter study did not confirm the result, showing that improvisational MT, compared with standard care alone, resulted in no significant difference in severity of ASD core symptoms [163, 164], even if changes in socio-communication seemed related to the quality of therapeutic relationship [165]. Another recent study [166] provided evidence that individual music intervention can indeed improve not only social communication but also functional brain connectivity, supporting further investigations of neurobiologically oriented models of music interventions in ASD.

Interestingly, a tool for the diagnosis of ASD in adults with intellectual disability (ID) specifically based on music – the Music-based Autism Diagnostics (MUSAD) – has been recently validated [167, 168]. This instrument was developed along the ICD-10 research criteria for autism, taking into account the latest changes made in

the DSM-5. It consist of ten predefined active musical interactional situations used to create a playful, naturalistic, and age-appropriate framework, also engaging non-speakers in a diagnostic assessment [167].

Substance Use Disorders

Substance use disorder (SUD) is a medical condition in which the use of one or more substances leads to a clinically significant impairment or distress. It is characterized by an array of mental, physical, and behavioral symptoms that may cause problems related to loss of control, strain to one's interpersonal life, dangerous use, tolerance, and withdrawal [102].

Literature showed that music-based interventions may provide some beneficial effects for individuals with SUD [169], such as self-expression, cooperative group activity, imagination, and synchronized sensorimotor experience, compared to commonly used verbal psychological therapies. In addition, there is evidence of beneficial impact of MT on other impaired aspects of SUD, such as mood, stress, self-esteem, motivation, emotional expression, social cohesion, global functioning, and anxiety [169].

Sleep Disorders

Sleep disorders are distressing and disabling conditions affecting a significant proportion of the general population, with a prevalence estimated around 10–48%. Insomnia is the most common sleep disorder, with a prevalence in the past year which has been estimated around 30% of the adult population and chronic insomnia complained by 10% of adults [170]. Chronic insomnia is defined by difficulties in falling asleep, maintaining sleep, and early morning awakening and is coupled with daytime consequences such as fatigue, attention deficits, and mood instability [171]. Some authors hypothesized that increased arousal levels in the cognitive, emotional, and physiological domains may represent both predisposing and perpetuating factors for insomnia [171]. For this reason, it could be hypothesized that music which, as previously reported, has been shown to regulate arousal and stress may act as a complementary tool for the treatment of insomnia and, more broadly, of sleep disorders. Such hypothesis has been confirmed by some recent systematic reviews and experimental studies, which have reported that music interventions seem to offer clear advantages for adults with insomnia or sleep disorders, with large effects on overall sleep quality, sleep-onset latency, and sleep efficiency [172–175].

Music Therapy for Cardiovascular Diseases

Hypertension

Hypertension represents a major risk factor for cardiovascular morbidity and mortality. Its prevalence in developed countries is currently estimated at 37 % [176]. The first-line treatment for the management of hypertension consists in lifestyle adjustment; however, if this approach fails, pharmacological therapy is needed as the main treatment modality in hypertension is pharmacological treatment, with high costs and various adverse effects [177]. This has led to a growing interest in non-pharmacological complementary therapies, such as music interventions, in the treatment of hypertension.

Nevertheless, findings regarding the effectiveness of MT on hypertension are still contrasting. Kühlmann and colleagues [178] recently published a meta-analysis in which they evaluated the effect of music interventions on blood pressure in adults with hypertension, showing a trend toward a decrease in mean systolic blood pressure (SBP) and diastolic blood pressure (DBP). Another systematic review, involving a smaller number of studies [179], showed a significant reduction in SBP in hypertensive patients receiving MT when compared with control subjects, while no significant difference was found for the DBP.

Zanini and colleagues evaluated the effect of music therapy on blood pressure and quality of life in patients with hypertension [180]. The results of this study indicated that music therapy had a beneficial effect on the quality of life and the

control of blood pressure in individuals with hypertension at first stage. The authors concluded that music therapy approach may be suggested as an adjuvant nonmedical treatment for hypertensive people.

Coronary Heart Disease

Coronary heart disease (CHD), or ischemic heart disease, is a condition in which a narrowing or blockage of the coronary arteries may cause a reduction of the blood flow to the myocardium. Although the mortality for this condition has gradually declined over the last decades in Western countries, CHD remains still a major cause of death and disability in developed countries [181]. A Cochrane systematic review [80] evaluated the effect of music interventions on patients with CHD. The review identified 26 trials, with a total of 1369 participants. Results indicated that music interventions have a small beneficial effect on psychological distress in people with CHD. Listening to music had a moderate effect on anxiety in people with CHD, particularly in people with myocardial infarction and in those studies in which a patient-selected music was used. Of note, listening to music reduced heart rate, respiratory rate, and systolic blood pressure, which represent somatic effects of anxiety. Results also suggested a reduction in pain, particularly in those studies that included two or more music sessions, and an improvement in patients' quality of sleep following a cardiac procedure or surgery. Bradt and colleagues [80] found no strong evidence for heart rate variability and depression. Only one study considered hormone levels and quality of life as an outcome variable. A small number of studies pointed to a possible beneficial effect of music on opioid intake after cardiac procedures or surgery.

Heart Surgery

Music has been used to reduce anxiety and pain after open-heart procedures [182–184] and after percutaneous coronary interventions in patients undergoing a C-clamp procedure [185]. Other authors have suggested a significant improvement in oxygen saturation [186], as well as in other physiological parameters, such as heart rate, systolic blood pressure, and mean arterial pressure [187].

Conclusions

Music is a universal means of communication, widespread since thousands of years, which, contrary to food or sex, does not show a clear survival benefit, nor does it display the addictive properties associated with drugs of abuse. Nonetheless, the average person spends a considerable amount of time listening to music, considering it as one of the most enjoyable activities in a person's life. Many people cite emotional impact and regulation among the main reasons why they listen to music; others believe that music has special and mystical properties [25]. As Oliver Sacks wrote, "the power of music is a question that goes to the heart of being human" [188].

Our chapter showed that emotions evoked by music can be considered as "real" emotions, with several underlying neural mechanisms, which neuroscientists are attempting to elucidate. Moreover, music regulates many of the systems of human body, from HPA axis to ANS; the influence of music on these systems lays the ground for using music as therapeutic tool in several disorders of the brain and heart. Given the promising, but still scarce, evidence reported in literature, researchers should further evaluate the direct interplay between mind, heart, and the whole body, in the context of music-evoked emotions. Additionally, there is the urgent need for the implementation of experimental studies aimed at evaluating the efficacy of music-based interventions in people with mental or cardiovascular disorders.

Cross-References

- ▶ Biofeedback
- ▶ Emotional Processing and Heart Activity
- ▶ Immune System and Mind-Body Medicine: An Overview

References

1. Morley IR. A multi-disciplinary approach to the origins of music: perspectives from anthropology, archaeology, cognition and behaviour. J Anthropol Sci. 2014;92:147.
2. Conard NJ, Malina M, Münzel SC. New flutes document the earliest musical tradition in southwestern Germany. Nature. 2009;460(7256):737–40.
3. Cervellin G, Lippi G. From music-beat to heart-beat: a journey in the complex interactions between music, brain and heart. Eur J Intern Med. 2011;22(4):371–4.
4. Lawendowski R, Bieleninik Ł. Identity and self-esteem in the context of music and music therapy: a review. Health Psychol Rep. 2017;5(2):85–99.
5. Schaefer H-E. Music and man–current studies of music-evoked emotions. Front Neurosci. 2017; 11:600.
6. Juslin PN. From everyday emotions to aesthetic emotions: towards a unified theory of musical emotions. Phys Life Rev. 2013;10(3):235–66.
7. Darwin C, Prodger P. The expression of the emotions in man and animals. Oxford: Oxford University Press; 1998.
8. Dębiec J. The matter of emotions: toward the brain-based theory of emotions. In: The emotional brain revisited. Kraków: Copernicus Center Press; 2014. p. 145–61.
9. Ekman P. An argument for basic emotions. Cognit Emot. 1992;6(3-4):169–200.
10. Wundt W. Fundamentals of physiological psychology. Leipzig: Engelmann; 1905.
11. Russell JA. A circumplex model of affect. J Pers Soc Psychol. 1980;39(6):1161.
12. James W. What is an emotion? Mind. 1884;9(34): 188–205.
13. Cannon WB. Again the James-Lange and the thalamic theories of emotion. Psychol Rev. 1931;38(4):281.
14. Bard P. On emotional expression after decortication with some remarks on certain theoretical views: part I. Psychol Rev. 1934;41(4):309.
15. Marañon G. Contribution a l'etude de l'action emotive de l'adrenaline. Rev Fr d'Endocrinol. 1924;2: 301–25.
16. Schachter S, Singer J. Cognitive, social, and physiological determinants of emotional state. Psychol Rev. 1962;69(5):379.
17. LeDoux J. The emotional brain: the mysterious underpinnings of emotional life. World I. 1997;12:281–5.
18. Panksepp J, Knutson B, Pruitt DL. Toward a neuroscience of emotion. In: What develops in emotional development?. Springer; 1998. p. 53–84.
19. Cacioppo JT, Berntson GG, Larsen JT, Poehlmann KM, Ito TA. The psychophysiology of emotion. In: Handbook of emotions. 2nd ed. New York: Guilford; 2000. p. 173–91.
20. Damasio A. Neural basis of emotions. Scholarpedia. 2011;6(3):1804.
21. LeDoux JE. Brain mechanisms of emotion and emotional learning. Curr Opin Neurobiol. 1992;2(2):191–7.
22. Koelsch S, Jacobs AM, Menninghaus W, Liebal K, Klann-Delius G, von Scheve C, et al. The quartet theory of human emotions: an integrative and neurofunctional model. Phys Life Rev. 2015;13:1–27.
23. Koelsch S. Investigating the neural encoding of emotion with music. Neuron. 2018;98(6):1075–9.
24. Taruffi L. The neuropsychology of music and emotions. Emotionen: Springer; 2019. p. 427–32.
25. Chanda ML, Levitin DJ. The neurochemistry of music. Trends Cogn Sci. 2013;17(4):179–93.
26. Blood AJ, Zatorre RJ. Intensely pleasurable responses to music correlate with activity in brain regions implicated in reward and emotion. Proc Natl Acad Sci. 2001;98(20):11818–23.
27. Bannister SC, Eerola T. Suppressing the chills: effects of musical manipulation on the chills response. Front Psychol. 2018;9:2046.
28. Juslin PN, Vastfjall D. Emotional responses to music: the need to consider underlying mechanisms. Behav Brain Sci. 2008;31(5):559–75; discussion 75–621.
29. Simons RC. Boo!: culture, experience, and the startle reflex. New York: Oxford University Press; 1996.
30. Blair ME, Shimp TA. Consequences of an unpleasant experience with music: a second-order negative conditioning perspective. J Advert. 1992;21(1):35–43.
31. Juslin PN. Communicating emotion in music performance: a review and a theoretical framework. In: Music and emotion: theory and research. New York: Oxford University Press; 2001.
32. Osborne JW. The mapping of thoughts, emotions, sensations, and images as responses to music. J Ment Imag. 1981;5:133.
33. Baumgartner H. Remembrance of things past: music, autobiographical memory, and emotion. ACR North Am Adv. 1992;19:613.
34. Meyer LB. Emotion and meaning in music. Chicago: University of Chicago Press; 2008.
35. Harrer G, Harrer H. Music, emotion and autonomic function. In: Music and the brain. Elsevier; 1977. p. 202–16.

    Harrer G, Harrer H. Music, emotion and autonomic function. In: Music and the brain. Oxford: Butterworth–Heinemann; 1977. p. 202–16.
36. Juslin PN, Harmat L, Eerola T. What makes music emotionally significant? Exploring the underlying mechanisms. Psychol Music. 2014;42(4):599–623.
37. Koelsch S. Brain correlates of music-evoked emotions. Nat Rev Neurosci. 2014;15(3):170.
38. Blood AJ, Zatorre RJ, Bermudez P, Evans AC. Emotional responses to pleasant and unpleasant music correlate with activity in paralimbic brain regions. Nat Neurosci. 1999;2(4):382.

39. Bzdok D, Langner R, Caspers S, Kurth F, Habel U, Zilles K, et al. ALE meta-analysis on facial judgments of trustworthiness and attractiveness. Brain Struct Funct. 2011;215(3–4):209–23.
40. Kumar S, von Kriegstein K, Friston K, Griffiths TD. Features versus feelings: dissociable representations of the acoustic features and valence of aversive sounds. J Neurosci. 2012;32(41):14184–92.
41. Cross I, Morley I. Communicative musicality: exploring the basis of human companionship. Oxford: Oxford University Press; 2009.
42. Steinbeis N, Koelsch S. Understanding the intentions behind man-made products elicits neural activity in areas dedicated to mental state attribution. Cereb Cortex. 2008;19(3):619–23.
43. Koelsch S. Brain and music. Chichester: Wiley; 2012.
44. Koelsch S, Skouras S, Fritz T, Herrera P, Bonhage C, Küssner MB, et al. The roles of superficial amygdala and auditory cortex in music-evoked fear and joy. NeuroImage. 2013;81:49–60.
45. LeDoux JE. Emotion circuits in the brain. Annu Rev Neurosci. 2000;23(1):155–84.
46. Roozendaal B, McEwen BS, Chattarji S. Stress, memory and the amygdala. Nat Rev Neurosci. 2009;10(6):423.
47. Salimpoor VN, Benovoy M, Larcher K, Dagher A, Zatorre RJ. Anatomically distinct dopamine release during anticipation and experience of peak emotion to music. Nat Neurosci. 2011;14(2):257.
48. Sescousse G, Caldú X, Segura B, Dreher J-C. Processing of primary and secondary rewards: a quantitative meta-analysis and review of human functional neuroimaging studies. Neurosci Biobehav Rev. 2013;37(4):681–96.
49. Salimpoor VN, van den Bosch I, Kovacevic N, McIntosh AR, Dagher A, Zatorre RJ. Interactions between the nucleus accumbens and auditory cortices predict music reward value. Science. 2013;340(6129):216–9.
50. Jacobson L, Sapolsky R. The role of the hippocampus in feedback regulation of the hypothalamic-pituitary-adrenocortical axis. Endocr Rev. 1991;12(2):118–34.
51. Bremner JD. Does stress damage the brain? Biol Psychiatry. 1999;45(7):797–805.
52. Neumann ID, Landgraf R. Balance of brain oxytocin and vasopressin: implications for anxiety, depression, and social behaviors. Trends Neurosci. 2012;35(11):649–59.
53. Koelsch S. Towards a neural basis of music-evoked emotions. Trends Cogn Sci. 2010;14(3):131–7.
54. Fancourt D, Ockelford A, Belai A. The psychoneuroimmunological effects of music: a systematic review and a new model. Brain Behav Immun. 2014;36:15–26.
55. Gebauer L, Kringelbach ML, Vuust P. Ever-changing cycles of musical pleasure: the role of dopamine and anticipation. PsychoMcol. 2012;22(2):152.
56. Arias-Carrión O, Stamelou M, Murillo-Rodríguez E, Menéndez-González M, Pöppel E. Dopaminergic reward system: a short integrative review. Int Arch Med. 2010;3(1):24.
57. Cheung VK, Harrison PM, Meyer L, Pearce MT, Haynes J-D, Koelsch S. Uncertainty and surprise jointly predict musical pleasure and amygdala, hippocampus, and auditory cortex activity. Curr Biol. 2019;29(23):4084.e4–92.e4.
58. Berridge KC, Kringelbach ML. Affective neuroscience of pleasure: reward in humans and animals. Psychopharmacology. 2008;199(3):457–80.
59. Stefano GB, Zhu W, Cadet P, Salamon E, Mantione KJ. Music alters constitutively expressed opiate and cytokine processes in listeners. Med Sci Monit. 2004;10(6):MS18–27.
60. Salimpoor VN, Zald DH, Zatorre RJ, Dagher A, McIntosh AR. Predictions and the brain: how musical sounds become rewarding. Trends Cogn Sci. 2015;19(2):86–91.
61. Mallik A, Chanda ML, Levitin DJ. Anhedonia to music and mu-opioids: evidence from the administration of naltrexone. Sci Rep. 2017;7:41952.
62. Friston KJ, Friston DA. A free energy formulation of music generation and perception: Helmholtz revisited. In: Sound-perception-performance. Berlin: Springer; 2013. p. 43–69.
63. Martínez-Molina N, Mas-Herrero E, Rodríguez-Fornells A, Zatorre RJ, Marco-Pallarés J. Neural correlates of specific musical anhedonia. Proc Natl Acad Sci. 2016;113(46):E7337–E45.
64. Keller J, Young CB, Kelley E, Prater K, Levitin DJ, Menon V. Trait anhedonia is associated with reduced reactivity and connectivity of mesolimbic and paralimbic reward pathways. J Psychiatr Res. 2013;47(10):1319–28.
65. Charmandari E, Tsigos C, Chrousos G. Endocrinology of the stress response. Annu Rev Physiol. 2005;67:259–84.
66. Leardi S, Pietroletti R, Angeloni G, Necozione S, Ranalletta G, Del Gusto B. Randomized clinical trial examining the effect of music therapy in stress response to day surgery. Br J Surg. 2007;94(8):943–7.
67. Nilsson U. The effect of music intervention in stress response to cardiac surgery in a randomized clinical trial. Heart Lung. 2009;38(3):201–7.
68. Lai HL, Li YM. The effect of music on biochemical markers and self-perceived stress among first-line nurses: a randomized controlled crossover trial. J Adv Nurs. 2011;67(11):2414–24.
69. Kar SK, Sen C, Goswami A, editors. Effect of Indian classical music (raga therapy) on fentanyl, vecuronium, propofol requirement and cortisol levels in cardiopulmonary bypass. Oxford, UK: Oxford University Press; 2012. British Journal of Anaesthesia.
70. Ventura T, Gomes M, Carreira T. Cortisol and anxiety response to a relaxing intervention on pregnant

women awaiting amniocentesis. Psychoneuroendocrinology. 2012;37(1):148–56.
71. Keeler JR, Roth EA, Neuser BL, Spitsbergen JM, Waters DJM, Vianney J-M. The neurochemistry and social flow of singing: bonding and oxytocin. Front Hum Neurosci. 2015;9:518.
72. Okada K, Kurita A, Takase B, Otsuka T, Kodani E, Kusama Y, et al. Effects of music therapy on autonomic nervous system activity, incidence of heart failure events, and plasma cytokine and catecholamine levels in elderly patients with cerebrovascular disease and dementia. Int Heart J. 2009;50(1):95–110.
73. McKinney CH, Tims FC, Kumar AM, Kumar M. The effect of selected classical music and spontaneous imagery on plasma β-endorphin. J Behav Med. 1997;20(1):85–99.
74. Gerra G, Zaimovic A, Franchini D, Palladino M, Giucastro G, Reali N, et al. Neuroendocrine responses of healthy volunteers totechno-music': relationships with personality traits and emotional state. Int J Psychophysiol. 1998;28(1):99–111.
75. Boso M, Politi P, Barale F, Emanuele E. Neurophysiology and neurobiology of the musical experience. Funct Neurol. 2006;21(4):187.
76. Ellis RJ, Koenig J, Thayer JF. Getting to the heart: autonomic nervous system function in the context of evidence-based music therapy. Music Med. 2012;4(2):90–9.
77. Lynar E, Cvejic E, Schubert E, Vollmer-Conna U. The joy of heartfelt music: an examination of emotional and physiological responses. Int J Psychophysiol. 2017;120:118–25.
78. Khalfa S, Isabelle P, Jean-Pierre B, Manon R. Event-related skin conductance responses to musical emotions in humans. Neurosci Lett. 2002;328(2):145–9.
79. Bradt J, Dileo C, Magill L, Teague A. Music interventions for improving psychological and physical outcomes in cancer patients. Cochrane Database Syst Rev. 2016;2016(8):CD006911.
80. Bradt J, Dileo C, Potvin N. Music for stress and anxiety reduction in coronary heart disease patients. Cochrane Database Syst Rev. 2013;2013(12):CD006577.
81. Bradt J, Dileo C, Shim M. Music interventions for preoperative anxiety. Cochrane Database Syst Rev. 2013;2013(6):CD006908.
82. Bradt J, Dileo C. Music interventions for mechanically ventilated patients. Cochrane Database Syst Rev. 2014;2014(12):CD006902.
83. Pelletier CL. The effect of music on decreasing arousal due to stress: a meta-analysis. J Music Ther. 2004;41(3):192–214.
84. Elliott D, Polman R, McGregor R. Relaxing music for anxiety control. J Music Ther. 2011;48(3):264–88.
85. Rilling JK, Gutman DA, Zeh TR, Pagnoni G, Berns GS, Kilts CD. A neural basis for social cooperation. Neuron. 2002;35(2):395–405.
86. Tomasello M, Carpenter M, Call J, Behne T, Moll H. Understanding and sharing intentions: the origins of cultural cognition. Behav Brain Sci. 2005;28(5):675–91.
87. Fitch WT. The biology and evolution of music: a comparative perspective. Cognition. 2006;100(1):173–215.
88. Alcorta CS, Sosis R, Finkel D. Ritual harmony: toward an evolutionary theory of music. Behav Brain Sci. 2008;31(5):576–7.
89. Bartz JA, Zaki J, Bolger N, Ochsner KN. Social effects of oxytocin in humans: context and person matter. Trends Cogn Sci. 2011;15(7):301–9.
90. Rocchetti M, Radua J, Paloyelis Y, Xenaki LA, Frascarelli M, Caverzasi E, et al. Neurofunctional maps of the 'maternal brain'and the effects of oxytocin: a multimodal voxel-based meta-analysis. Psychiatry Clin Neurosci. 2014;68(10):733–51.
91. Brondino N, Fusar-Poli L, Politi P. Something to talk about: gossip increases oxytocin levels in a near real-life situation. Psychoneuroendocrinology. 2017;77:218–24.
92. De Cagna F, Fusar-Poli L, Damiani S, Rocchetti M, Giovanna G, Mori A, et al. The role of intranasal oxytocin in anxiety and depressive disorders: a systematic review of randomized controlled trials. Clin Psychopharmacol Neurosci. 2019;17(1):1.
93. Seltzer LJ, Ziegler TE, Pollak SD. Social vocalizations can release oxytocin in humans. Proc R Soc B Biol Sci. 2010;277(1694):2661–6.
94. Grape C, Sandgren M, Hansson L-O, Ericson M, Theorell T. Does singing promote well-being?: an empirical study of professional and amateur singers during a singing lesson. Integr Physiol Behav Sci. 2002;38(1):65–74.
95. Kreutz G. Does singing facilitate social bonding. Music Med. 2014;6(2):51–60.
96. Carter CS. Oxytocin pathways and the evolution of human behavior. Annu Rev Psychol. 2014;65:17–39.
97. Rutigliano G, Rocchetti M, Paloyelis Y, Gilleen J, Sardella A, Cappucciati M, et al. Peripheral oxytocin and vasopressin: biomarkers of psychiatric disorders? A comprehensive systematic review and preliminary meta-analysis. Psychiatry Res. 2016;241:207–20.
98. Bernardi NF, Codrons E, Di Leo R, Vandoni M, Cavallaro F, Vita G, et al. Increase in synchronization of autonomic rhythms between individuals when listening to music. Front Physiol. 2017;8:785.
99. Vink A, Hanser S. Music-based therapeutic interventions for people with dementia: a mini-review. Medicines. 2018;5(4):109.
100. Sihvonen AJ, Sarkamo T, Leo V, Tervaniemi M, Altenmuller E, Soinila S. Music-based interventions in neurological rehabilitation. Lancet Neurol. 2017;16(8):648–60.
101. World Health Organization. Depression and other common mental disorders: global health estimates. Geneva: World Health Organization; 2017.
102. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-5®). Arlington: American Psychiatric Publication; 2013.

103. Naranjo C, Kornreich C, Campanella S, Noël X, Vandriette Y, Gillain B, et al. Major depression is associated with impaired processing of emotion in music as well as in facial and vocal stimuli. J Affect Disord. 2011;128(3):243–51.
104. Bodner E, Iancu I, Gilboa A, Sarel A, Mazor A, Amir D. Finding words for emotions: the reactions of patients with major depressive disorder towards various musical excerpts. Arts Psychother. 2007; 34(2):142–50.
105. Al'tman YA, Alyanchikova YO, Guzikov B, Zakharova L. Estimation of short musical fragments in normal subjects and patients with chronic depression. Hum Physiol. 2000;26(5):553–7.
106. Sakka LS, Juslin PN. Emotional reactions to music in depressed individuals. Psychol Music. 2018;46(6):862–80.
107. Koelsch S. Music-evoked emotions: principles, brain correlates, and implications for therapy. Ann N Y Acad Sci. 2015;1337(1):193–201.
108. Saarikallio S, Nieminen S, Brattico E. Affective reactions to musical stimuli reflect emotional use of music in everyday life. Music Sci. 2013;17(1):27–39.
109. Maratos A, Crawford MJ, Procter S. Music therapy for depression: it seems to work, but how? Br J Psychiatry. 2011;199:92.
110. Aalbers S, Fusar-Poli L, Freeman RE, Spreen M, Ket JC, Vink AC, et al. Music therapy for depression. Cochrane Database Syst Rev. 2017;2017(11):CD004517.
111. Leubner D, Hinterberger T. Reviewing the effectiveness of music interventions in treating depression. Front Psychol. 2017;8:1109.
112. Erkkilä J, Punkanen M, Fachner J, Ala-Ruona E, Pöntiö I, Tervaniemi M, et al. Individual music therapy for depression: randomised controlled trial. Br J Psychiatry. 2011;199(2):132–9.
113. Remes O, Brayne C, Van Der Linde R, Lafortune L. A systematic review of reviews on the prevalence of anxiety disorders in adult populations. Brain and Behav. 2016;6(7):e00497.
114. Booth RW, Sharma D, Leader T. The age of anxiety? It depends where you look: changes in STAI trait anxiety, 1970–2010. Soc Psychiatry Psychiatr Epidemiol. 2016;51(2):193–202.
115. Robinson OJ, Vytal K, Cornwell BR, Grillon C. The impact of anxiety upon cognition: perspectives from human threat of shock studies. Front Hum Neurosci. 2013;7:203.
116. D'Avanzato C, Joormann J, Siemer M, Gotlib IH. Emotion regulation in depression and anxiety: examining diagnostic specificity and stability of strategy use. Cogn Ther Res. 2013;37(5):968–80.
117. Gutiérrez EOF, Camarena VAT. Music therapy in generalized anxiety disorder. Arts Psychother. 2015;44:19–24.
118. Walker J, Boyce-Tillman J. Music lessons on prescription? The impact of music lessons for children with chronic anxiety problems. Health Educ. 2002;102(4):172–9.
119. Panteleeva Y, Ceschi G, Glowinski D, Courvoisier DS, Grandjean D. Music for anxiety? Meta-analysis of anxiety reduction in non-clinical samples. Psychol Music. 2017;46(4):473–87.
120. Abdulah DM, Miho Alhakem SS, Piro RS. Effects of music as an adjunctive therapy on severity of symptoms in patients with obsessive-compulsive disorder: randomized controlled trial. Nord J Music Ther. 2019;28(1):27–40.
121. Shirani Bidabadi S, Mehryar A. Music therapy as an adjunct to standard treatment for obsessive compulsive disorder and co-morbid anxiety and depression: a randomized clinical trial. J Affect Disord. 2015;184:13–7.
122. Landis-Shack N, Heinz AJ, Bonn-Miller MO. Music therapy for posttraumatic stress in adults: a theoretical review. PsychoMcol. 2017;27(4):334.
123. Bensimon M. Drumming through trauma: music therapy with post-traumatic soldiers. Arts Psychother. 2008;35:34.
124. Carr C, d'Ardenne P, Sloboda A, Scott C, Wang D, Priebe S. Group music therapy for patients with persistent post-traumatic stress disorder–an exploratory randomized controlled trial with mixed methods evaluation. Psychol Psychother Theory Res Pract. 2012;85(2):179–202.
125. Pezzin LE, Larson ER, Lorber W, McGinley EL, Dillingham TR. Music-instruction intervention for treatment of post-traumatic stress disorder: a randomized pilot study. BMC Psychol. 2018;6(1):60.
126. Bonny HL. Music and healing. Music Ther. 1986;6(1):3–12.
127. Beck BD, Messel C, Meyer SL, Cordtz TO, Søgaard U, Simonsen E, et al. Feasibility of trauma-focused guided imagery and music with adult refugees diagnosed with PTSD: a pilot study. Nord J Music Ther. 2018;27(1):67–86.
128. Story KM, Beck BD. Guided Imagery and Music with female military veterans: an intervention development study. Arts Psychother. 2017;55:93–102.
129. Rudstam G, Elofsson U, Søndergaard HP, Bonde LO, Beck BD. Trauma-focused group music and imagery with women suffering from PTSD/complex PTSD: a feasibility study. Approach. 2017;9:202–16.
130. White T, Cullen K, Rohrer LM, Karatekin C, Luciana M, Schmidt M, et al. Limbic structures and networks in children and adolescents with schizophrenia. Schizophr Bull. 2007;34(1):18–29.
131. Hempel A, Hempel E, Schönknecht P, Stippich C, Schröder J. Impairment in basal limbic function in schizophrenia during affect recognition. Psychiatry Res Neuroimaging. 2003;122(2):115–24.
132. Suazo V, Díez Á, Tamayo P, Montes C, Molina V. Limbic hyperactivity associated to verbal memory deficit in schizophrenia. J Psychiatr Res. 2013;47(6):843–50.
133. Hatada S, Sawada K, Akamatsu M, Doi E, Minese M, Yamashita M, et al. Impaired musical ability in people with schizophrenia. J Psychiatry Neurosci. 2014; 39(2):118.

134. Wen Y, Nie X, Wu D, Liu H, Zhang P, Lu X. Amusia and cognitive deficits in schizophrenia: is there a relationship? Schizophr Res. 2014;157(1-3):60–2.
135. Abe D, Arai M, Itokawa M. Music-evoked emotions in schizophrenia. Schizophr Res. 2017;185:144–7.
136. Geretsegger M, Mössler KA, Bieleninik Ł, Chen XJ, Heldal TO, Gold C. Music therapy for people with schizophrenia and schizophrenia-like disorders. Cochrane Libr. 2017. Cochrane Database Syst Rev. 2017;2017(5):CD004025.
137. Metzner S, Jaeger U, Masuhr O, Olschewski U, Gräfe E, Böske AC, et al. Forms of attunement during the initial stages of music therapy for patients with acute psychosis – a multicentre clinical study. Nord J Music Ther. 2018;27(5):360–80.
138. Volpe U, Gianoglio C, Autiero L, Marino ML, Facchini D, Mucci A, et al. Acute effects of music therapy in subjects with psychosis during inpatient treatment. Psychiatry. 2018;81(3):218–27.
139. Wortmann M. Dementia: a global health priority-highlights from an ADI and World Health Organization report. Alzheimers Res Ther. 2012;4(5):40.
140. Van De Glind EM, Van Enst WA, Van Munster BC, Rikkert MGO, Scheltens P, Scholten RJ, et al. Pharmacological treatment of dementia: a scoping review of systematic reviews. Dement Geriatr Cogn Disord. 2013;36(3–4):211–28.
141. Kamiya K, Kamiya Y, Niwa H. Anticholinergic side effects. Gen Med. 2015;16(2):117–8.
142. Oliveira AMD , Radanovic M, Mello PCHD, Buchain PC, Vizzotto ADB, Celestino DL, et al. Nonpharmacological interventions to reduce behavioral and psychological symptoms of dementia: a systematic review. Biomed Res Int. 2015;2015:1.
143. Brondino N, Fusar-Poli L, Panisi C, Politi P. Potential neuroprotective effects of curcumin against dementia. In: Neuroprotective effects of phytochemicals in neurological disorders. Hoboken: Wiley; 2017. p. 435.
144. Jacobsen J-H, Stelzer J, Fritz TH, Chételat G, La Joie R, Turner R. Why musical memory can be preserved in advanced Alzheimer's disease. Brain. 2015;138 (8):2438–50.
145. Brotons M, Koger SM. The impact of music therapy on language functioning in dementia. J Music Ther. 2000;37(3):183–95.
146. van der Steen JT, Smaling HJ, van der Wouden JC, Bruinsma MS, Scholten RJ, Vink AC. Music-based therapeutic interventions for people with dementia. Cochrane Database Syst Rev. 2018;2018(7): CD003477.
147. Ueda T, Suzukamo Y, Sato M, Izumi S-I. Effects of music therapy on behavioral and psychological symptoms of dementia: a systematic review and meta-analysis. Ageing Res Rev. 2013;12(2):628–41.
148. Zhang Y, Cai J, An L, Hui F, Ren T, Ma H, et al. Does music therapy enhance behavioral and cognitive function in elderly dementia patients? A systematic review and meta-analysis. Ageing Res Rev. 2017;35:1–11.
149. Tsoi KKF, Chan JYC, Ng Y-M, Lee MMY, Kwok TCY, Wong SYS. Receptive music therapy is more effective than interactive music therapy to relieve behavioral and psychological symptoms of dementia: a systematic review and meta-analysis. J Am Med Dir Assoc. 2018;19(7):568.e3–76.e3.
150. Fusar-Poli L, Bieleninik Ł, Brondino N, Chen X-J, Gold C. The effect of music therapy on cognitive functions in patients with dementia: a systematic review and meta-analysis. Aging Ment Health. 2018;22(9):1097–1106.
151. Baxter AJ, Brugha T, Erskine H, Scheurer R, Vos T, Scott J. The epidemiology and global burden of autism spectrum disorders. Psychol Med. 2015; 45(3):601–13.
152. Boso M, D'Angelo E, Barale F. Neurophysiological correlates of musical giftedness in autism spectrum disorders. Music Med. 2013;5(4):223–7.
153. Kanner L. Autistic disturbances of affective contact. Nerv Child. 1943;2(3):217–50.
154. Boso M, Barale F, D'Angelo E. Autism and genius: is there a link? The involvement of central brain loops and hypotheses for functional testing. Funct Neurol. 2010;25(1):27–32.
155. Caria A, Venuti P, de Falco S. Functional and dysfunctional brain circuits underlying emotional processing of music in autism spectrum disorders. Cereb Cortex. 2011;21(12):2838–49.
156. Fusar-Poli L, Rocchetti M, Garda M, Politi P. 'Aut'-sider: the invisible talent of Simona Concaro. Epidemiol Psychiatr Sci. 2017;26(2):119–21.
157. Fusar-Poli L, Brondino N, Damiani S, Mandrini A, Migliardi M, Vercesi M, et al. Abilitar suonando. Dieci anni di orchestra invisibile. Ricerche Di Psicologia. 2016;39:239.
158. Bonoldi I, Emanuele E, Politi P. A piano composer with low-functioning severe autism. Acta Neuropsychiatr. 2009;21(1):2–3.
159. Boso M, Forth J, Bordin A, Faggioli R, D'Angelo E, Politi P, et al. Transposition ability in a young musician with autism and blindness: testing cognitive models of autism. PsychoMcol. 2013;23(2):109.
160. Howes OD, Rogdaki M, Findon JL, Wichers RH, Charman T, King BH, et al. Autism spectrum disorder: consensus guidelines on assessment, treatment and research from the British Association for Psychopharmacology. J Psychopharmacol. 2018;32(1):3–29.
161. Brondino N, Fusar-Poli L, Rocchetti M, Provenzani U, Barale F, Politi P. Complementary and alternative therapies for autism spectrum disorder. Evid Based Complement Alternat Med. 2015;2015:1–31.
162. Geretsegger M, Elefant C, Mössler KA, Gold C. Music therapy for people with autism spectrum disorder. Cochrane Libr. 2014;2014(6):CD004381.
163. Bieleninik Ł, Geretsegger M, Mössler K, Assmus J, Thompson G, Gattino G, et al. Effects of improvisational music therapy vs enhanced standard care on symptom severity among children with autism

spectrum disorder: the TIME-A randomized clinical trial. JAMA. 2017;318(6):525–35.
164. Crawford MJ, Gold C, Odell-Miller H, Thana L, Faber S, Assmus J, et al. International multicentre randomised controlled trial of improvisational music therapy for children with autism spectrum disorder: TIME-A study. Health Technol Assess. 2017;21(59):1–40.
165. Mössler K, Gold C, Aßmus J, et al. The therapeutic relationship as predictor of change in music therapy with young children with autism spectrum disorder. J Autism Dev Disord. 2019;49(7):2795–2809.
166. Sharda M, Tuerk C, Chowdhury R, Jamey K, Foster N, Custo-Blanch M, et al. Music improves social communication and auditory–motor connectivity in children with autism. Transl Psychiatry. 2018;8(1):231.
167. Bergmann T, Sappok T, Diefenbacher A, Dames S, Heinrich M, Ziegler M, et al. Music-based Autism Diagnostics (MUSAD) – a newly developed diagnostic measure for adults with intellectual developmental disabilities suspected of autism. Res Dev Disabil. 2015;43:123–35.
168. Bergmann T, Sappok T, Diefenbacher A, Dziobek I. Music in diagnostics: using musical interactional settings for diagnosing autism in adults with intellectual developmental disabilities. Nord J Music Ther. 2016;25(4):319–51.
169. Hohmann L, Bradt J, Stegemann T, Koelsch S. Effects of music therapy and music-based interventions in the treatment of substance use disorders: a systematic review. PLoS One. 2017;12(11):e0187363.
170. Ferrie JE, Kumari M, Salo P, Singh-Manoux A, Kivimäki M. Sleep epidemiology – a rapidly growing field. Int J Epidemiol. 2011;40(6):1431–7.
171. Riemann D, Nissen C, Palagini L, Otte A, Perlis ML, Spiegelhalder K. The neurobiology, investigation, and treatment of chronic insomnia. Lancet Neurol. 2015;14(5):547–58.
172. De Niet G, Tiemens B, Lendemeijer B, Hutschemaekers G. Music-assisted relaxation to improve sleep quality: meta-analysis. J Adv Nurs. 2009;65(7):1356–64.
173. Feng F, Zhang Y, Hou J, Cai J, Jiang Q, Li X, et al. Can music improve sleep quality in adults with primary insomnia? A systematic review and network meta-analysis. Int J Nurs Stud. 2018;77:189–96.
174. Jespersen KV, Koenig J, Jennum P, Vuust P. Music for insomnia in adults. Cochrane Database Syst Rev. 2015;2015(8):CD010459.
175. Jespersen KV, Otto M, Kringelbach M, Van Someren E, Vuust P. A randomized controlled trial of bedtime music for insomnia disorder. J Sleep Res. 2019;28:e12817.
176. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. Lancet. 2005;365(9455):217–23.
177. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension. Eur Heart J. 2018;39(33):3021–104.
178. Kühlmann AY, Etnel JR, Roos-Hesselink JW, Jeekel J, Bogers AJ, Takkenberg JJ. Systematic review and meta-analysis of music interventions in hypertension treatment: a quest for answers. BMC Cardiovasc Disord. 2016;16(1):69.
179. do Amaral MAS, Neto MG, de Queiroz JG, Martins-Filho PRS, Saquetto MB, Carvalho VO. Effect of music therapy on blood pressure of individuals with hypertension: a systematic review and Meta-analysis. Int J Cardiol. 2016;214:461–4.
180. Zanini CRDO, Jardim PCBV, Salgado CM, Nunes MC, Urzêda FLD, Carvalho MVC, et al. Music therapy effects on the quality of life and the blood pressure of hypertensive patients. Arq Bras Cardiol. 2009;93(5):534–40.
181. Nichols M, Townsend N, Scarborough P, Rayner M. Cardiovascular disease in Europe 2014: epidemiological update. Eur Heart J. 2014;35(42):2950–9.
182. Sendelbach SE, Halm MA, Doran KA, Miller EH, Gaillard P. Effects of music therapy on physiological and psychological outcomes for patients undergoing cardiac surgery. J Cardiovasc Nurs. 2006;21(3):194–200.
183. Voss JA, Good M, Yates B, Baun MM, Thompson A, Hertzog M. Sedative music reduces anxiety and pain during chair rest after open-heart surgery. Pain. 2004;112(1-2):197–203.
184. Twiss E, Seaver J, McCaffrey R. The effect of music listening on older adults undergoing cardiovascular surgery. Nurs Crit Care. 2006;11(5):224–31.
185. Chan MF. Effects of music on patients undergoing a C-clamp procedure after percutaneous coronary interventions: a randomized controlled trial. Heart Lung. 2007;36(6):431–9.
186. Ozer N, Karaman Ozlu Z, Arslan S, Gunes N. Effect of music on postoperative pain and physiologic parameters of patients after open heart surgery. Pain Manag Nurs. 2013;14(1):20–8.
187. Emami Zeydi A, Jafari H, Khani S, Esmaeili R, Gholipour BA. The effect of music on the vital signs and SpO_2 of patients after open heart surgery: a randomized clinical trial. J Mazandaran Univ Med Sci. 2011;21(82):73–82.
188. Sacks O. The power of music. Brain. 2006;129(10):2528–32.

Psychological and Cardiovascular Effects of Meditation and Yoga

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Marcelo Bigliassi

Contents

Abstract

Through the continuous scientific exploration into the deep realms of consciousness, researchers have discovered precious *gems* of knowledge, commonly referred to as meditation and yoga. Such "techniques" have been used for millennia as a means by which to optimize awareness, enhance compassion and empathy, and bring joy to one's life. In the present chapter, the author briefly reviews some of the most recent and compelling studies addressing the psychological and cardiovascular effects of meditation and yoga. Special emphasis is given to mindfulness-based interventions and the traditional Indian spiritual practice of yoga. Overall, the results indicate that meditation and yoga are efficient strategies to downregulate psychophysiological arousal, facilitate handling of undesired thoughts, optimize one's ability to deal with negative emotions, and reduce cardiovascular risk. Nevertheless, it is worth noting that the brain mechanisms that underlie the effects of meditation and yoga on psychological and cardiovascular responses are hitherto underresearched. Future studies are still necessary to further understanding of the long-term effects of meditation and yoga on emotion regulation, psychosocial skills, and cardiovascular health (e.g., blood pressure reduction and prevention of cardiovascular disease).

Keywords

Cardiovascular system · Mindfulness · Mental health · Relaxation techniques

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*,
https://doi.org/10.1007/978-3-030-28008-6_57

Introduction

Tenzin Gyatso, the spiritual leader of the Gelug school of Tibetan Buddhism and the fourteenth and current Dalai Lama, once said that "calm mind brings inner strength and self-confidence, so that's very important for good health." Indeed, a conspicuous relationship has been frequently reported among one's state of relaxation, psychological skills, and physical health [1–3]. Compelling evidence indicates that a state of tranquility can induce a series of psychological and physical benefits, such as stress reduction, pain relief, and even longevity [4, 5]. There is, however, a chain of psychophysiological events that underpin the benefits of calmness on physical reactions [6, 7]. In the present chapter, the author will explore the effects of meditation and yoga as valuable techniques to downregulate psychophysiological arousal, facilitate handling of undesired thoughts, optimize one's ability to deal with negative emotions, and reduce cardiovascular risk. The putative brain mechanisms that underlie the effects of meditation and yoga on psychological and cardiovascular responses will also be briefly discussed herein.

Although meditation and yoga might differ substantially in terms of applicability and methodology, the primary purpose of these techniques is to enhance awareness [8, 9]. In fact, meditation and yoga are utterly entangled. For example, breathing meditation techniques are commonly used during the practice of yoga as a means by which to enhance self-awareness and facilitate the control of certain movement patterns. One of the most impactful and immediate effects of meditation and yoga is the downregulation of psychophysiological arousal [10, 11]. The state of calmness induced during meditative practices naturally facilitates the reappraisal of negative thoughts and emotions, leading to a series of physiological adjustments that are beneficial to one's health [12, 13].

The psychological mechanisms and reactions associated with meditative practices are highly complex in nature. Recent evidence suggests that through the continuous reallocation of attention toward the present moment, one's ability to interpret negative thoughts and emotions is optimized [14, 15]. However, it is noteworthy that meditative practices do not involve solely the control of attention. For example, movements and mantras are commonly used as a means to facilitate the connection between brain and body, ameliorate the detrimental effects of anxiety, and improve one's quality of life [16]. These techniques serve primarily to partially inhibit processing of task-unrelated thoughts. In some cases, such disruptive thoughts are not exclusively blocked, but instead, they are processed with greater acceptance [17, 18]. This sequence of interpretative mechanisms is key to inducing a state of tranquility that may have residual effects and pervade during other activities of daily life [19, 20].

The effects of meditative practices, such as mindfulness-based interventions and yoga, have been extensively investigated by the scientific community [21, 22]. Although numerous randomized controlled trials have been conducted in this field, the overall quality of most studies has been deemed as "fair" (for details, see Goyal et al. [21]). Therefore, readers are advised to be extremely cautious while interpreting the findings that are readily available in the literature. The present author decided to report in this chapter only a limited number of recent and compelling studies in this field of scientific enquiry. These studies were selected on the basis of relevance, availability, and replicability. It is also important to emphasize that various forms of meditation and yoga differ considerably in terms of techniques and principles. In the present chapter, the author will not describe how exactly these methods differ from one another (for a detailed description, see e.g., [16, 23, 24]).

Effects of Meditative Practices on Psychological Health

A recent randomized controlled trial conducted by Galante and colleagues [25] investigated the effects of an 8-week mindfulness course adapted for university students on psychological distress during the examination period. The results of the

study mentioned above indicated that the meditation program was sufficiently potent to reduce distress scores, maintain well-being, and engender resilience to the accumulation of stress. It is also important to emphasize that this study was designed specifically to recreate a real-life scenario and assess the effectiveness of a mental health support service. Accordingly, the program of meditation assessed by Galante et al. [25] could be easily implemented during the most stressful periods of the academic year as a means to facilitate coping with extreme levels of stress and protect students, to a certain extent, against mental health complications that are recurrently reported.

May et al. [14] have also investigated the effects of meditation on affective responses, well-being, and the five facets of mindfulness (i.e., observing, describing, nonjudging, nonreacting, and acting with awareness) in first-year psychology students and community members. The authors designed a very elegant study using one of the most effective strategies to improve well-being and psychological functioning – holidays. An 8-week A-B-A-B experimental protocol was used to verify whether meditation would be equally efficient in alleviating stress and enhancing one's affective state when compared to holidays. The results of this study indicated that the practice of meditation was sufficient to improve well-being, induce positive affective responses, and made participants more mindful of their physical sensations, thoughts, and emotions. Interestingly, holidays appear to elicit similar effects on affective valence and the facets of mindfulness when compared to days of meditation. The findings reported by May and colleagues [14] are particularly exciting, given the practical implications associated with this study. Whenever the ideal scenario of holidays is not a possibility, a 15-min meditation routine should suffice.

Davis and Hayes have conducted a comprehensive review in 2011 [26], where the authors explored the effects of mindfulness-based interventions on a myriad of psychological constructs such as emotion regulation, response flexibility, reactivity, stress, and anxiety. Mindfulness meditation appears to be sufficiently potent to improve voluntary control of several mental processes and, consequently, elicit feelings of tranquility and clarity. This chain of psychological processes might ultimately reduce anxiety and optimize the handling of negative thoughts and emotions. Davis and Hayes [26] have also reported that mindfulness-based therapies have the propensity to reduce depressive symptoms and are inversely associated with ruminative thinking. One of the most important aspects to consider during the practice of meditation is the element of nonjudgment. As humans, we are naturally designed to provide quick judgments on every situation. Although this is an extremely relevant psychosocial skill, constant judgmental thoughts can lead to ruminative thoughts and may compromise one's ability to accept any given situation. As a result, individuals tend to overreact to certain events – a psychological reaction that can have a negative impact upon appreciation, gratitude, life satisfaction, and compassion. Accordingly, meditative practices that somehow involve elements of nonjudgment are worthwhile strategies to pursue.

The ancient practice of yoga has also been investigated widely by the scientific community [7, 10]. It is worth noting that meditation and yoga are entirely intertwined [9]. It can be considerably challenging to dissociate these terms as both techniques share a common objective [8]. For example, breathing meditation techniques are frequently used during yoga sessions as a means to enhance awareness and facilitate the control of complex movement patterns [27]. Some meditation techniques are also employed in order to ameliorate the detrimental effects of pain and improve resilience [28–31]. Yoga-related movements can also elicit some level of discomfort that is used to direct attention toward the present moment and create a scenario where external influences remain outside focal awareness [32]. This can be considered as a feedback strategy that allows individuals to focus on the movement that is being executed, partially block task-irrelevant thoughts, and improve voluntary control. On some occasions, individuals can also be advised to control their facial expressions given the fact that negative physical reactions might hamper their movements, facilitate the processing of task-unrelated thoughts, and initiate a cascade of

reactions that might ultimately increase one's perceived exertion and evoke negative emotional responses [32, 33].

Yoga has been proposed as a complementary form of therapy and treatment for patients with depression. One of the most exciting findings reported by Bridges and Sharma in 2017 [22] indicates that the practice of yoga is not only sufficient to reduce depression, but yoga can also be used to prevent an increase in depressive symptoms. Moreover, it has been demonstrated that the practice of yoga tends to lessen depressive symptoms and lower the levels of cortisol during early pregnancy and postpartum [34]. More recently, Maddux and colleagues [35] recruited 90 individuals reporting moderate-to-high stress in order to investigate the effects of yoga on psychological health. They have assigned participants to two different programs of yoga to explore the differences between 8- and 16-week interventions. The findings reported by Maddux et al. [35] indicated that a 16-week yoga intervention significantly reduced stress, anxiety, depression, and improved psychological health. Interestingly, an 8-week intervention was also beneficial in terms of lessening perceived stress when compared to both the control group and their baseline values. Additional 8 weeks of yoga intervention can certainly induce more pronounced effects on mental health, but the results of the aforementioned study indicate that even short-term interventions are highly positive in stressed individuals.

Effects of Meditative Practices on Cardiovascular Health

Meditation and yoga have also been proposed as efficient strategies to protect the organism against cardiovascular complications. Meditative practices are considerably effective to downregulate perceived activation, ameliorate anxiety, and reduce blood pressure in healthy individuals and clinical populations [36, 37]. The psychobiological mechanisms underlying the effects of meditation and yoga on cardiovascular health are largely unknown. However, compelling evidence indicates that meditative practices have the potential to facilitate handling negative thoughts and emotions, induce a state of calmness and presence, and increase the activity of the vagal nerve [38, 39]. In a recent laboratory experiment conducted by Koerten and colleagues [12, 40], the authors investigated the effects of mindfulness, with a focus on nonjudgment, on recovery from stress in perfectionists. In the aforementioned experiment, the authors made use of heart rate variability analysis to further understand the impact of brief mindfulness meditation on cardiovascular responses. The results indicated that a brief mindfulness meditation training session with a focus on nonjudgment of experiences was sufficiently potent to increase heart rate variability and facilitate heart rate recovery from failure in perfectionists. Accordingly, it appears that some forms of meditation are sufficient to make individuals interpret failure with greater acceptance and optimize psychophysiological recovery.

It is logical to assume that some of the effects of meditation and yoga on cardiovascular health occur primarily through indirect pathways [32, 41]. For example, a state of calmness induced by the practice of meditation has the propensity to alleviate stress and, subsequently, decrease heart rate [42]. It is also possible that the continuous practice of meditation and yoga would have residual effects that may naturally make individuals more efficient to handle stressful situations (i.e., individuals become less reactive and defensive) [20, 43]. In such circumstances, meditative practices may function as *shields* to protect our bodies against extreme patterns of emotional reactivity, rumination, and anxiety-related thoughts. As a consequence of such psychological and psychosocial mechanisms, meditation and yoga may influence cardiovascular health to a certain degree [4, 5]. It is of supreme importance to emphasize that short-term interventions are generally sufficient to influence emotional and behavioral outcomes [44]. Conversely, anatomical and physiological changes usually require individuals to engage in meditative practices for long periods of time [45].

Gainey et al. [46] explored the effects of a Buddhism-based walking meditation program on glycemic control, arterial stiffness, stress

hormone, and vascular function in patients with type 2 diabetes mellitus. In the walking meditation condition, participants were asked to repeat the words "Budd" and "Dha" in their minds with each step in an attempt to practice mindfulness and switch attention toward the present moment. The program consisted of a 30-min exercise session performed at 50–70% of maximum heart rate, with a frequency of 3 times/week for a period of 12 weeks. The authors hypothesized that this form of meditation would facilitate attention allocation, induce a state of calmness, and improve endothelium-dependent vasodilation. The findings of this study indicated that glycated hemoglobin was significantly reduced in the group of participants who engaged in the walking meditation program. Moreover, a significant reduction in plasma cortisol was only identified in the walking meditation group. The authors speculated that a significant reduction in plasma cortisol could have influenced inflammatory processes, tension in the vascular wall, and sympathetic activity. Taken holistically, the results of Gainey and colleagues [46] indicate that simple instructions implemented during walking-related tasks to guide attention toward the present moment can lead to multifarious benefits for physical and mental health in patients with diabetes.

It is also relevant to note that the findings in this particular topic vary considerably in terms of efficacy and effectiveness. For instance, a recent randomized controlled trial was conducted to investigate the effects of a yoga intervention plus usual care versus usual care alone following an acute coronary event [47]. The yoga intervention was designed and conducted by a certified yoga teacher and delivered twice a week for a period of 12 weeks alongside the usual care (i.e., physical activity, diet and weight management, and smoking cessation). A wide range of variables was measured, including exercise capacity, physical fitness, and vascular parameters. The authors reported that the addition of a structured 3-month yoga intervention to usual care was not sufficient to influence cardiovascular and neuroendocrine responses. However, it is important to emphasize that only 25 participants in the yoga + usual care group and 35 participants in the usual care group completed the study. Therefore, the initially planned statistical power was not achieved (i.e., 33 participants in each group).

Effects of Meditation During Physical Activity

Meditation-based interventions have also been used during physical activity as a means by which to enhance one's affective state and facilitate the control of working muscles [28, 48]. This combination of elements could potentially influence exercise behavior and alter interpretation of internal sensory cues during execution of movements. In a recent experiment conducted by Bigliassi and colleagues in 2020 [44], the authors investigated the effects of an audio-guided mindfulness single session on affective, perceptual, and psychophysiological responses during self-paced walking. Participants were asked to walk 200 m at a pace of their choosing, and a portable electroencephalography system was used to measure the brain's electrical activity during the walking task. A second experimental condition (i.e., mindlessness meditation) was used to facilitate identification of extremely different patterns of attention allocation during the exercise session. The results of this study indicated that the mindfulness meditation intervention was sufficient to down-modulate perceived activation (i.e., participants felt more relaxed), make participants more aware of their physical sensations, thoughts, and emotions, and enhance their affective states. The psychophysiological data also indicated that the mindfulness intervention was sufficient to enhance interhemispheric connectivity between right frontal and left temporo-parietal regions of the brain. The authors hypothesized that this pattern of communication could be indicative of enhanced awareness of affective and cognitive mental states.

Researchers have also theorized that some of the benefits of physical activity could be, to a certain extent, maximized with meditation [3]. Bigliassi and Bertuzzi [3] proposed that meditation-based interventions may have a facilitative effect on exercise behavior. The authors suggested the possibility of using meditation to promote

well-being, improve psychological functioning, and stimulate self-care and preservation. In such circumstances, meditation could potentially facilitate implementation of healthy behaviors (e.g., physical activity), increase exercise adherence, and counteract the detrimental effects of sedentariness. They also provided a series of specific recommendations for researchers and health professionals on how to use meditation prior to, during, and immediately after exercise sessions. For example, prior to commencing an exercise session, meditation can be used to regulate one's arousal state before the warm-up phase. This approach could be implemented as a means by which to reduce ruminative thinking and muscle tension. Accordingly, meditation-based interventions could be used in physical activity programs to maximize the exercise experience and optimize the handling of undesired thoughts that are naturally evoked during certain movement patterns. Sedentary individuals might also want to try meditation as a means to recreate an emotional backdrop against which healthy behaviors can be forged.

In a recent study conducted in my laboratory, I have also identified that meditation has the potential to ameliorate fatigue-related symptoms during exercise tasks performed at moderate intensity (study submitted for publication). The intervention was specially designed by a group of researchers to direct attention towards the present moment and change the way participants process internal sensory cues (example of instruction provided: "If you feel something, simply accept and embrace it. You don't have to control it but remember that it is your decision how this feeling will affect your performance"). Participants were asked to exercise for a total of 8 min at ventilatory threshold (i.e., an index of transition between aerobic and anaerobic metabolism). Throughout the exercise session, participants received instructions via earphones to focus on task-related factors. The experimental manipulation was sufficient to assuage overall exertion and limb discomfort to a greater degree than the other two conditions (i.e., control and counterproof conditions). The abovementioned study indicates that meditation-based interventions can be used to influence perception of afferent feedback and interpretation of negative bodily sensations. Consequently, exercise-related tasks might be perceived as more enjoyable than under normal conditions.

Conclusions

The results reported herein indicate that meditative practices have the potential to make individuals more conscious of their thoughts, emotions, and physical sensations, ameliorate anxiety, induce a state of calmness, facilitate handling of undesired thoughts, and optimize one's ability to deal with negative emotions. Although the effects of meditation and yoga on cardiovascular health are not well established, there is tentative evidence that such practices can be beneficial in terms of reducing blood pressure and increasing heart rate variability. The exact mechanisms underlying the effects of meditation and yoga on psychological and cardiovascular health are uncharted territories that require further scientific exploration. Researchers and health professionals are encouraged to explore the use of meditation and yoga as a means by which to downregulate psychophysiological arousal and promote self-control; especially, in clinical populations. For example, meditative practices can be used as valuable tools to alleviate stress, increase hope, and improve quality of life in mental health patients. In a world of electronic gadgets and social distance, meditation could bring us closer to ourselves and function as lens of positivity through which we see the world around us.

References

1. Ma X, Yue ZQ, Gong ZQ, Zhang H, Duan NY, Shi YT, Wei GX, Li YF. The effect of diaphragmatic breathing on attention, negative affect and stress in healthy adults. Front Psychol. 2017;8:e874.
2. Demarzo MMP, Montero-Marin J, Stein PK, Cebolla A, Provinciale JG, García-Campayo J. Mindfulness may both moderate and mediate the effect of physical fitness on cardiovascular responses to stress: a speculative hypothesis. Front Physiol. 2014;5:e105.

3. Bigliassi M, Bertuzzi R. Exploring the use of meditation as a valuable tool to counteract sedentariness. Front Psychol. 2020;11:e299.
4. Cramer H, Lauche R, Haller H, Steckhan N, Michalsen A, Dobos G. Effects of yoga on cardiovascular disease risk factors: a systematic review and meta-analysis. Int J Cardiol. 2014;173:170–83.
5. Levine G, Lange R, Bairey-Merz C, et al. Meditation and cardiovascular risk reduction: a scientific statement from the American Heart Association. J Am Heart Assoc. 2017;6:e002218.
6. Hölzel BK, Carmody J, Vangel M, Congleton C, Yerramsetti SM, Gard T, Lazar SW. Mindfulness practice leads to increases in regional brain gray matter density. Psychiatry Res Neuroimaging. 2011;191:36–43.
7. Luu K, Hall PA. Examining the acute effects of hatha yoga and mindfulness meditation on executive function and mood. Mindfulness. 2017;8:873–80.
8. de Bruin EI, Formsma AR, Frijstein G, Bögels SM. Mindful2work: effects of combined physical exercise, yoga, and mindfulness meditations for stress relieve in employees. A proof of concept study. Mindfulness. 2017;8:204–17.
9. Breedvelt JJF, Amanvermez Y, Harrer M, Karyotaki E, Gilbody S, Bockting CLH, Cuijpers P, Ebert DD. The effects of meditation, yoga, and mindfulness on depression, anxiety, and stress in tertiary education students: a meta-analysis. Front Psych. 2019;10:e193.
10. Groessl EJ, Liu L, Chang DG, Wetherell JL, Bormann JE, Atkinson JH, Baxi S, Schmalzl L. Yoga for military veterans with chronic low back pain: a randomized clinical trial. Am J Prev Med. 2017;53:599–608.
11. Zeidan F, Johnson SK, Diamond BJ, David Z, Goolkasian P. Mindfulness meditation improves cognition: evidence of brief mental training. Conscious Cogn. 2010;19:597–605.
12. Koerten HR, Watford TS, Dubow EF, O'Brien WH. Cardiovascular effects of brief mindfulness meditation among perfectionists experiencing failure. Psychophysiology. 2020;57:e13517.
13. van der Zwan JE, de Vente W, Huizink AC, Bögels SM, de Bruin EI. Physical activity, mindfulness meditation, or heart rate variability biofeedback for stress reduction: a randomized controlled trial. Appl Psychophysiol Biofeedback. 2015;40:257–68.
14. May CJ, Ostafin BD, Snippe E. The relative impact of 15-minutes of meditation compared to a day of vacation in daily life: an exploratory analysis. J Posit Psychol. 2020;15:278–84.
15. Troy AS, Brunner A, Shallcross AJ, Friedman R, Jones MC. Cognitive reappraisal and acceptance: effects on emotion, physiology, and perceived cognitive costs. Emotion. 2018;18:58–74.
16. Matko K, Sedlmeier P. What is meditation? Proposing an empirically derived classification system. Front Psychol. 2019;10:e2276.
17. Hildebrandt LK, McCall C, Singer T. Differential effects of attention-, compassion-, and socio-cognitively based mental practices on self-reports of mindfulness and compassion. Mindfulness. 2017;8:1488–512.
18. Wersebe H, Lieb R, Meyer AH, Hofer P, Gloster AT. The link between stress, well-being, and psychological flexibility during an Acceptance and Commitment Therapy self-help intervention. Int J Clin Health Psychol. 2018;18:60–8.
19. Daubenmier J, Moran PJ, Kristeller J, et al. Effects of a mindfulness-based weight loss intervention in adults with obesity: a randomized clinical trial. Obesity. 2016;24:794–804.
20. Ruffault A, Czernichow S, Hagger MS, Ferrand M, Erichot N, Carette C, Boujut E, Flahault C. The effects of mindfulness training on weight-loss and health-related behaviours in adults with overweight and obesity: a systematic review and meta-analysis. Obes Res Clin Pract. 2017;11:90–111.
21. Goyal M, Singh S, Sibinga EMS, et al. Meditation programs for psychological stress and well-being: a systematic review and meta-analysis. JAMA Intern Med. 2014;174:357–68.
22. Bridges L, Sharma M. The efficacy of yoga as a form of treatment for depression. J Evid Based Complement Altern Med. 2017;22:1017–28.
23. Lindahl JR, Fisher NE, Cooper DJ, Rosen RK, Britton WB. The varieties of contemplative experience: a mixed-methods study of meditation-related challenges in Western Buddhists. PLoS One. 2017; https://doi.org/10.1371/journal.pone.0176239.
24. Davidson RJ, Kaszniak AW. Conceptual and methodological issues in research on mindfulness and meditation. Am Psychol. 2015;70:581–92.
25. Galante J, Dufour G, Vainre M, Wagner AP, Stochl J, Benton A, Lathia N, Howarth E, Jones PB. A mindfulness-based intervention to increase resilience to stress in university students (The Mindful Student Study): a pragmatic randomised controlled trial. Lancet Public Health. 2018;3:72–81.
26. Davis DM, Hayes JA. What are the benefits of mindfulness? A practice review of psychotherapy-related research. Psychotherapy. 2011;48:198–208.
27. Tellhed U, Daukantaitė D, Maddux RE, Svensson T, Melander O. Yogic breathing and mindfulness as stress coping mediate positive health outcomes of yoga. Mindfulness. 2019;10:2703–15.
28. Jay K, Brandt M, Jakobsen MD, Sundstrup E, Berthelsen KG, Schraefel M, Sjøgaard G, Andersen LL. Ten weeks of physical-cognitive-mindfulness training reduces fear-avoidance beliefs about work-related activity. Medicine (Baltimore). 2016;95:e3945.
29. Hilton L, Hempel S, Ewing BA, et al. Mindfulness meditation for chronic pain: systematic review and meta-analysis. Ann Behav Med. 2017;51:199–213.
30. Ramasubramanian S. Mindfulness, stress coping and everyday resilience among emerging youth in a university setting: a mixed methods approach. Int J Adolesc Youth. 2017;22:308–21.
31. Bilderbeck AC, Farias M, Brazil IA, Jakobowitz S, Wikholm C. Participation in a 10-week course of

yoga improves behavioural control and decreases psychological distress in a prison population. J Psychiatr Res. 2013;47:1438–45.
32. Gard T, Noggle JJ, Park CL, Vago DR, Wilson A. Potential self-regulatory mechanisms of yoga for psychological health. Front Hum Neurosci. 2014;8:e770.
33. Reicherts P, Gerdes ABM, Pauli P, Wieser MJ. On the mutual effects of pain and emotion: facial pain expressions enhance pain perception and vice versa are perceived as more arousing when feeling pain. Pain. 2013;154:793–800.
34. Bershadsky S, Trumpfheller L, Kimble HB, Pipaloff D, Yim IS. The effect of prenatal hatha yoga on affect, cortisol and depressive symptoms. Complement Ther Clin Pract. 2014;20:106–13.
35. Maddux RE, Daukantaité D, Tellhed U. The effects of yoga on stress and psychological health among employees: an 8- and 16-week intervention study. Anxiety Stress Coping. 2018;31:121–34.
36. Loucks EB, Nardi WR, Gutman R, et al. Mindfulness-based blood pressure reduction (MB-BP): stage 1 single-arm clinical trial. PLoS One. 2019;14:e0223095.
37. Goldstein CM, Josephson R, Xie S, Hughes JW. Current perspectives on the use of meditation to reduce blood pressure. Int J Hypertens. 2012;2012:e578397.
38. Peng CK, Henry IC, Mietus JE, Hausdorff JM, Khalsa G, Benson H, Goldberger AL. Heart rate dynamics during three forms of meditation. Int J Cardiol. 2004;95:19–27.
39. Bornemann B, Kovacs P, Singer T. Voluntary upregulation of heart rate variability through biofeedback is improved by mental contemplative training. Sci Rep. 2019;9:e7860.
40. Watford TS, O'Brien WH, Koerten HR, Bogusch LM, Moeller MT, Sonia Singh R, Sims TE. The mindful attention and awareness scale is associated with lower levels of high-frequency heart rate variability in a laboratory context. Psychophysiology. 2020;57:e13506.
41. Malinowski P. Neural mechanisms of attentional control in mindfulness meditation. Front Neurosci. 2013;7:e8.
42. Steinhubl SR, Wineinger NE, Patel S, et al. Cardiovascular and nervous system changes during meditation. Front Hum Neurosci. 2015;9:e145.
43. Wielgosz J, Schuyler BS, Lutz A, Davidson RJ. Long-term mindfulness training is associated with reliable differences in resting respiration rate. Sci Rep. 2016;6:e27533.
44. Bigliassi M, Galano BM, Lima-Silva AE, Bertuzzi R. Effects of mindfulness on psychological and psychophysiological responses during self-paced walking. Psychophysiology. 2020;57:e13529.
45. Laneri D, Schuster V, Dietsche B, Jansen A, Ott U, Sommer J. Effects of long-term mindfulness meditation on Brain's white matter microstructure and its aging. Front Aging Neurosci. 2016;7:e254.
46. Gainey A, Himathongkam T, Tanaka H, Suksom D. Effects of Buddhist walking meditation on glycemic control and vascular function in patients with type 2 diabetes. Complement Ther Med. 2016;26:92–7.
47. Tillin T, Tuson C, Sowa B, et al. Yoga and Cardiovascular Health Trial (YACHT): a UK-based randomised mechanistic study of a yoga intervention plus usual care versus usual care alone following an acute coronary event. BMJ Open. 2019;9:e030119.
48. Edwards MK, Loprinzi PD. Affective responses to acute bouts of aerobic exercise, mindfulness meditation, and combinations of exercise and meditation: a randomized controlled intervention. Psychol Rep. 2018; https://doi.org/10.1177/0033294118755099.

Part XI

Gender and Age Differences Affecting Brain and Heart Connection

Pediatric Age and the Ontogeny of the Brain and Heart Connection

58

Lorenzo Mangone, Renzo Guerrini, and Michele Emdin

Contents

Abstract

During development individuals change enormously, and so does the main structure devoted to control their internal organ functioning, the autonomic nervous system (ANS). The connection between the brain and heart starts with few cells from the neural crest exchanging chemical signals with the dorsal aorta and progressively develops into a complex neural network. This network receives afferent inputs from structures such as the carotid sinus and body; it is under the control of higher-order regulatory neural structures and instantly responds, adjusting the heart chronotropism and inotropism and providing a progressively more refined control during its maturation. The acquired flexibility makes the organism capable to adapt to the different environmental conditions that an individual experiences from fetal life until adulthood, with the postnatal development of reflexes and maturation of central regulating areas proceeding until

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*,
https://doi.org/10.1007/978-3-030-28008-6_60

adolescence. One key moment of this maturational process is the shift from sympathetic to parasympathetic balance that occurs during infancy, when the myelinated fibers subserving vagal tone become strong enough to determine the resting heart rate. This maturational process is extremely important for the acquirement of social skills but also leads to periods of developmental instability that could play a significant role in the pathogenesis of either benign conditions such as breath-holding spells or extreme outcomes such as sudden infant death syndrome (SIDS). Conversely, the presence of congenital heart disease may affect deeply brain development, ultimately resulting in a worse neurological outcome in adulthood.

Keywords

Autonomic nervous system · Development · Sympathovagal balance · Breath-holding spells · Children · Social engagement system · Congenital heart disease

Introduction

Embryogenesis is a complex, peculiar process, during which the prenatal organism progressively develops in a genetically predetermined fashion all the structures that will allow and facilitate its extrauterine survival. It is well known that the development of those structures, from an ontogenetic perspective, is function of the phylogenetic, evolutionary-driven development [1, 2].

These axioms are extremely important in the study of the development of the brain-heart axis, since they offer a framework that facilitates the comprehension of the rationale behind the orderly maturation of reflexes and anatomical structures that permit and optimize the interaction between the most important organs in vertebrates.

The heart and brain are closely interconnected from their very emergence, since they develop simultaneously [3], share precursor cells deriving from the neuronal crests and show similar gene expression and analogous response to numerous signaling pathways. The nature of their connection, however, is not limited to the molecular level as they also show a strong reciprocal physiological influence. The brain is highly dependent on the heart for oxygen and nutrient delivery, and heart function is in turn greatly influenced by the action of the central nervous system (CNS) [4]. Despite its intrinsic characteristics and pacemaker activity, the heart physiological parameters are always the result of the delicate balance of counter-opposing forces, and the CNS itself is a key player in the regulation of this balance.

The main structure through which the CNS exercises its action on the heart is the vegetative (Reil, 1857) or autonomic nervous system (ANS), as defined by Langley and Dickinson in 1896. The ANS, in addition to the somatic nervous system, is one of the two main branches of the peripheral nervous system and it regulates the function of internal organs. It determines the activation state of the organism since it can shift the balance between a state of high responsiveness and activation, known as the "fight or flight" response, and a state of reduced metabolic consumption and increased visceral activity, sometimes called "rest and digest." Its action on the heart is of particular importance since its sympathetic and parasympathetic arms exert a cardioexcitatory and a cardioinhibitory effect, respectively, whereby increasing or decreasing their action can determine heart rate (HR) and contractile force [5]. The nervous regulation of the heart is extremely relevant since it is responsible for all the rapid, phasic adjustments that occur in the timespan of mere seconds.

Despite being part of the peripheral nervous system, the ANS output is controlled by the CNS, and in particular by a network of bulbar and pontine nuclei that generates a basal autonomic tone. This network itself is regulated by higher-level structures, such as the hypothalamus, the amygdala, and portions of the cortex, but also peripheral sensors, such as the carotid body and the carotid sinus. These structures contain receptors that provide a constant feedback on various parameters of interest and allow for a fine regulation. The action of the ANS is unconscious, but since it can be synergic and overlapping with that

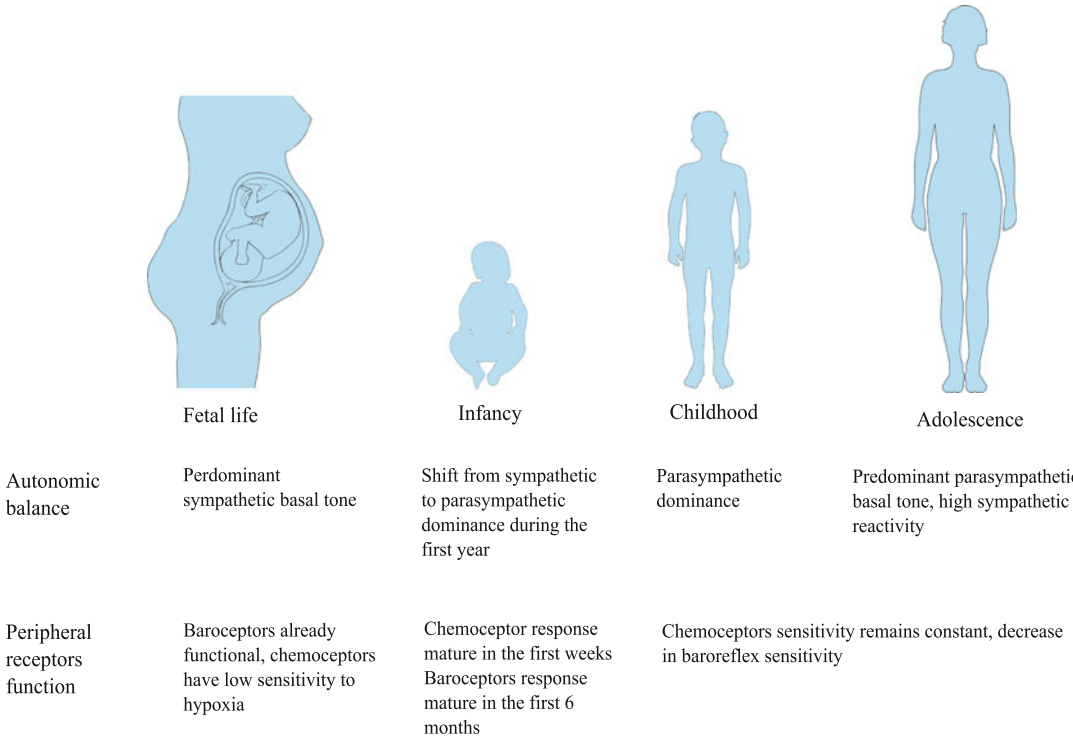

Fig. 1 Autonomi nervous sysgem balance during development

of the somatic nervous system a certain degree of voluntary control over its action is still possible.

During development, the elements at all levels of this system change dramatically (Fig. 1), and so does the overall output of the system. An individual and the environment it lives in go through tremendous changes from fetal life to adulthood, and the system that regulates its visceral function needs to adapt to all these changes.

Fetal Life

The ANS originates from neuronal crest cells that migrate along specific routes under the action of both extra- and intracellular signals, such as bone morphogenetic proteins (BMP), neurotrophic factors, and second messengers such as cAMP. All regions of the neural crest can provide the entire spectrum of the autonomic ganglion cells, but the axial level of origin [5] limits the differentiation possibilities of those neuron precursors due to differences in the signals they receive [7]. Those signals determine both the differentiation of a neural precursor into an ANS cell and its neurotransmitter phenotype. During this process an interchange of signals between the developing heart and the ANS takes place. On one hand BMPs originating from the dorsal aorta are in fact responsible for upregulation of the proteins necessary for the synthesis of catecholamines, a necessary feature of sympathetic nerves [5, 8]. At the same time, studies on tachyarrhythmias [6, 9] show evidences of how the cardiac sympathetic innervation shapes the electrophysiological phenotype of myocardium cells.

The development of the autonomic innervation of the myocardium is a particularly complex process involving maturation in both the neurons and the target cells [6]. This process begins quite early in gestation, with cardiac ganglia and nerves being present since the 7th week, and lasts until at least the 24th week, when the distribution resembles that of the adult [10]. Neurons appear initially in the atria, with a higher density in proximity of sinoatrial and atrioventricular nodes, as

well as the conduction system; then, progressing along the coronary vasculature, they start to enter the ventricular myocardium [11].

The maturation of the sympathetic and parasympathetic systems occurs during different periods in pregnancy [12], with the development of parasympathetic fibers occurring first. During the third trimester of gestation, the ANS progressively becomes organized enough to start exercising its action on the heart. In this period, in fact, both the higher-order control centers and the afferent structures become developed enough to provide coherent inputs [13]. The periods between the 26th and the 28th and between the 30th and 32nd weeks are critical because of the rapid maturation of the brain-heart axis. This period is characterized by a decrease in fetal heart rate accompanied by an increase in heart rate variability [14]. During the same weeks, the fetus becomes able to couple motor activity and phasic heart rate acceleration [1] and since the 28th week holds a cardiac activity coupled with its function energetics. In this period, moreover, it becomes possible to distinguish diverse functional states (activity, rest, wakefulness, sleep), a sign that the CNS has reached a significant maturational level. An example of this maturation and its consequences can be found analyzing the arterial baroreceptor, a structure that plays a key role in the regulation of sympathetic outflow [15]. In the sheep, it has been demonstrated that the baroreceptor already exerts a control on the autonomic output during fetal life and that during development its operating point shifts to maintain its basal output constant despite the changes in pressure of the developing fetus [16].

Another important player in autonomic regulation is the carotid body, the main peripheral chemoreceptor. This structure develops early during prenatal development from neural crest cells and becomes an independent structure from the aorta as early as in the 9th week, already showing a structure very similar to the adult one during the 14th week. During the 23rd week, it is even possible to see synapses between the chemoreceptors and the afferent neurons. Since its main role is to monitor O_2 levels, its role during fetal life is likely of lesser importance [17].

Studies on animal models suggest that in this period, the CNS is already able to deeply modulate the activity of the ANS, since variation in electroencephalographic activity between a REM-like state and a wakefulness-like state corresponds to a variation in the heart resting frequency and thus in the sympathetic and parasympathetic tone that determines it [18].

During the fetal life, the sympathetic basal tone is predominant in determining heart rate, and only near term the parasympathetic activity becomes progressively more important [14, 19]. Compared to the sympathetic arm, the maturation of the parasympathetic arm, in fact, seems more complex. For example, the differentiation of the lateral zone of the hypothalamus, a region extremely important in determining the parasympathetic function, occurs only at the end of the second trimester [20]. From a phylogenetic perspective, it is possible to distinguish an evolutionarily older unmyelinated vagus from a more recent myelinated vagus that is more relevant in humans. The myelinated vagus develops from the 24th week through adolescence, and the highest developmental speed occurs between the 30th week of gestational age and the 6th month postpartum [21].

Some studies on animal models support the idea that the autonomic control of circulation during gestation is not necessary to maintain homeostasis. This hypothesis would endorse the idea that during fetal life the organism is only training the system to be as functional as possible after birth. However, the increase in catecholamines at birth [22] suggests that ANS activity, and sympathetic activity in particular, is essential in the complex changes associated with birth and with the start of autonomous respiration [23].

Infancy

Children at birth are not independent and able to survive without a caregiver and do not need to be able to self-regulate completely from an evolutionary prospective. Thus, likely, no evolutionary pressure operates toward a mature autonomic nervous system at this stage. Having only a structured

backbone to control roughly the autonomic functions necessary for survival and then tuning reflexes more precisely based on external and internal clues is much more effective than developing the same reflexes during intrauterine life. There are evidences that the extrauterine environment provides the necessary stimuli for a correct development of autonomic reflexes such as the deep breath vasoconstriction, the reflex peripheral vasoconstriction that occurs after a deep breath, whose appearance is related to postnatal age and not postconceptional age [24]. The same extrauterine stimuli could lead to maturation at the central level. It is indeed possible to see differences in the central nervous system response to a classical cardiovascular challenge, the head up tilting test, between newborns and 2- to 4-month old infants, a sign that the maturation process proceeds substantially after birth, and in some fashion due to birth, at all levels of the heart-brain axis [25]. Another important example of how the extrauterine environment determines the maturation of autonomic reflexes concerns the carotid body. At birth this structure shows a scarce response toward hypoxia, and during the first few weeks of extrauterine life, perhaps due to the fourfold increase in oxygen tension, it undergoes a resetting of O_2 sensitivity thanks to various modifications at all the levels of the transduction cascade initiaded by O_2 variations. All these changes lead to a substantial increase in hypoxia perception and consequently to a more elicited response [26].

In addition, at birth the innervation of the heart is still undergoing a process of maturation. The pattern of innervation of the conduction system is different from that reached in the adult, and its cells are not yet capable of synthetizing all neurotransmitters [27]. In the newborn heart, the parasympathetic innervation is scarce in the ventricles and moderate in the atria, being prevalent at the sinoatrial node level only. The sympathetic fibers are less concentrated in the conduction system but, differently from vagal fibers, innervate uniformly the myocardium [28] and are almost the only nerve population in the ventricles. The development of sympathetic innervation seems correlated with a progressive decrease in the sensibility toward circulating epinephrine [29]. The immaturity of the innervation is particularly evident for the vagus nerve. This structure is probably still underdeveloped, because it begins to mature only in the last trimester [30]. Therefore, it would not be surprising for preterm infants born between the 32nd and 37th weeks to show a significantly less prominent maturation of the vagus nerve [31] and a reduced high-frequency peak at the spectrum analysis of heart rate variability, associated with sinus respiratory arrhythmia, a well-known index of vagal output.

The shift from sympathetic to parasympathetic dominance [32–34] is extremely important for the infant, because it allows for a more precise and efficient control of heat rate. In a potentially dangerous situation, in addition to an increased sympathetic discharge, there will also be a faster and more effective option: the removal of the basal inhibition [35]. This phenomenon, called vagal brake removal, leads to a rapid mobilization of the individual [30]. Therefore, the immaturity of the vagus nerve in the first months of life, when the myelinated component is still incomplete, could cause increased sensibility to adverse conditions such as hypotensive states and lowered oxygen saturation and would explain the exaggerated cardiac responses observed in infants [36]. The cardiac rate of the newborn can shift from an average of 120–140 beats per minute to 170 or higher during stressing situations such as crying and falls to 70–90 or to bradycardic conditions during sleep [37].

The maturation of the brain-heart axis can be appreciated looking at variations in physiological cardiac parameters, the most exemplary being heart rate (HR) (Table 1). Analyzing an electrocardiogram it is possible to deduce the activity of the heart-brain axis. An aspect that is of utmost importance is the frequency domain of beat-to-beat variability, which is the end result of many different interplaying factors. The high-frequency domain (with a tight association with the respiratory rate as for its central frequency, 0.15–0.4 Hz in adults) reflects rapid and constant beat-to-beat adjustments on a very short time scale, while the low-frequency domain (0.1 Hz) is mainly affected by fluctuations associated with vasomotion. The main factor determining high-frequency variations is breathing. Heart rate is constantly

Table 1 Heart rate variation from birth to adolescence

Years	Mean HR (bpm)
Newborn	125
1	120
2	110
4	100
6	100
8	90
10	90
12	85–90
14	80–85
16	75–80
18	70–75

HR heart rate, *bpm* beats per minute
Data from: Bernstein [37]

synchronized with respiratory rate in order to improve the efficiency of every breath, increasing heart rate in inspiration and decreasing it during expiration [4, 38]. This phenomenon can be quantified by respiratory sinus arrhythmia (RSA), an index which is highly dependent on the myelinated vagus action and is considered one of the best indicators of nucleus ambiguus activity. Many classical studies considered an increase in HR or variations in the spectral power of low frequencies in blood pressure and heart rate variability (HRV), as measured based of the R-R interval, a reliable index of sympathetic activity [39]. However, this parameter is affected by parasympathetic control as well; thus recently the pre-ejection period (PEP, defined as the time interval between ventricular electrical depolarization and the beginning of ventricular ejection) has become the main index for evaluating sympathetic stimulation [40–42].

Considering the absence of an effective vagal output, observing that the newborn heart rate is rapid and subject to wide fluctuations is not surprising [37]. The parameters describing heart activity change strongly with aging, with a progressive decrease of HR [42–45], while the HRV increases and loses the wide fluctuations characteristic of newborn heart. The highest decrease of the HR and increase in the HRV occurs between 4 and 9 months, when it reaches a phase of developmental instability [46]. Thereafter it slows down but continues until at least 7 years of age [47] and probably even further since the highest level of HRV is observed in early adolescents [48, 49]. Most of those variations are explained by the maturation of the parasympathetic arm [39] that shows stability at the end of the first year under resting conditions. The rapid maturation of parasympathetic activity is in part related to the maturation and integration of baroreflex response in the first 6 months of life [50]. Animal models also suggest that changes in the orexin-mediated inhibitory circuits on the cardiac vagal neurons in the nucleus ambiguus are fundamental in the maturation of the parasympathetic cardiac control system [51].

Although there is general consensus on the decline of the sympathetic influence on heart, there is still controversy on the role played by the sympathetic system during the first year of life. Some authors suggest that in this early phase, the role of sympathetic activation is more relevant than parasympathetic withdrawal [45], while others [46] believe that the variations attributed to sympathetic activity may be due to the maturational increase in activity of brainstem respiratory centers.

The infant spends most of the day sleeping; therefore observing how the ANS exerts its function on the heart during sleep is important to understand how its control mechanisms work and evolve during life. Furthermore, this period of rapid evolution carries the risk of sudden infant death syndrome (SIDS), which often occurs during sleep. It is possible to differentiate two sleep phases in the fetus and the newborn, defined as quiet and active sleep. During quiet sleep all the parameters of parasympathetic function are increased [52–54]. The modifications of sleep patterns that characterize aging, with active sleep progressively diminishing in favor of quiet sleep, are accompanied by a change in cardiovascular control, with a decrease in sympathetic vascular modulation and an increase in parasympathetic control [53], probably caused by the maturation of the system as a whole [52].

Childhood

The maturation of the ANS proceeds from infancy into adolescence through all childhood, as it can be seen by changes in indexes of

Table 2 Autonomic indexes variation during early life

	Resting RSA		RSA reactivity		Resting PEP		PEP reactivity	
	Mean	Population size	Mean difference	Population size	Mean	Population size	Mean difference	Population size
6 months	3.32	158	0.01	157	66.26	149	0.31	147
1 year	3.74	154	0.10	152	66.69	146	0.54	142
3.5 years	6.44	136	−0.33	136	74.07	133	-0.03	133
5 years	6.80	294	−0.18	294	78.23	293	-0.23	295

RSA respiratory sinus arrhythmia, *PEP* pre-ejection period
Data from Alkon et al. [44]

autonomic activation [39, 40]. The most important variation is a progressive decrease in resting HR that can be explained by an increase in both resting RSA and resting PEP (Table 2) [44], corresponding to an increase in parasympathetic basal tone strength and a decrease in sympathetic activation. This is in turn accompanied by an increase in indexes of sympathetic reactivity, a term describing the physiological response to an external stressor or challenge. Those findings show that a parasympathetic predominance during resting conditions coupled with a strong sympathetic response to stressors is characteristic of late childhood. The resulting configuration is much closer to the codominance typical of adulthood. For the adult individual, having a dynamic balance of autonomic regulation is extremely important since a static imbalance leads to vulnerability to pathologies [55]. This balance is measurable observing the ratio between changes in the low-frequency power spectrum peak of HRV over changes in the high-frequency peak [56].

Different elements underlie the increase in sympathetic reactivity. One factor is the decrease of arterial baroreflex sensitivity [57]. The arterial baroreceptor is one of the strongest activators of the parasympathetic system and thus, in addition to being fundamental for rapid adjustments in blood pressure and heart rate, is important in reducing the sympathetic output by decreasing the amplitude of a responsive activation. This decrease in sensitivity from childhood to adolescence is accompanied by a marked change in the maturation trajectory around the 10-year age that correlates with changes in gray matter volumes in the region of interest for cardiocirculatory regulation [56]. A hypothesis sustains that the amplitude of the response is increased because the sympathetic system is already predominant in early childhood and therefore the response to an external stimulus would not be as significant as it could in a parasympathetic dominated heart. This hypothesis can be translated in terms of physiological parameters in the observation that basal PEP is already close to its physiological minimum in young children and thus decrements are difficult [39].

Despite this increase and refinement of the sympathetic response, the parasympathetic maturation continues as well, as it can be seen in the increase in cholinergic innervation of the human heart from childhood to adulthood [36].

The maturational process that characterizes the heart-brain axis culminates in a system in which higher order cortical areas, such as the prefrontal cortex, inhibit cardioactivatory subcortical circuits, and therefore impose on the heart a parasympathetic mediated tonic inhibitory control, that leads to energy preservation. Losing this tonic inhibition is considered to favor pathology. After a cold pressor challenge, a stimulation used to challenge the autonomic system and measure its activation profile [58], healthy adolescents demonstrate responses that involve both cortical and subcortical structures. Brain areas are recruited in a systematic and lateralized pattern and cortical areas, as well as cerebellum, show an important role in modulating subcortical responses and thus control of the ANS [59]. Knowing the process of autonomic activation is particularly important in adolescence since ANS deficits are common in multiple diseases typical of this age [59].

A Period of Vulnerability, Breath-Holding Spells, and Sudden Infant Death Syndrome

The development of a functionally efficient brain-heart axis, as we have seen, is neither a homogeneous process nor a rapid one. Thus, when the system is still immature or when its development is passing through a critical stage, it is possible for abnormal conditions to emerge, particularly if the child has comorbidity such as the long QT syndrome [52, 60, 61].

An example of a condition strictly related to an immature ANS can be found in breath-holding spells, a benign [62], paroxysmal, non-epileptic condition characterized by an intense response to an emotional stimulus resulting in a brief, involuntary cessation of breathing. They affect about 4% of children in the preschool age and are especially frequent in the breast-feeding period [63, 64]. It is possible to classify them as either cyanotic or pallid. There are evidences of parasympathetic reflex, cardiorespiratory inhibition, and autonomic dysregulation in both types of breath-holding spells. Probably the parasympathetic system plays a major role in both types of breath-holding spells, and the role of the sympathetic system is minor, if any.

In pallid breath-holding spells, the central dysregulation of the ANS is probably exerted directly on the cardiorespiratory system, while in the cyanotic type, the consequences are more prominent in peripheral vascular sites.

A predisposing factor for their insurgence is iron deficiency, and a possible reason why iron deficiency could be a contributory cause in the insurgence could be the role that this element plays in catecholamine synthesis and myelination processes [65]. There are indeed evidences that delayed myelination or synaptic maturation in the brain stem [63], the anatomical site of nucleus ambiguus and dorsal motor nucleus of the vagus nerve, which respectively control the myelinated and unmyelinated portions of vagus nerve, could play a role in the pathogenesis of breath-holding spells.

Cardiorespiratory control immaturity appears to play a role also in the final event of SIDS. This condition is defined as the death of an infant, aged less than 1 year, unexplained after autopsy. The incidence of this condition is highest between 2 and 4 months of age [65], and this period corresponds to the nadir of blood pressure in the infant [50] as well as to a period of immaturity of the arterial baroreflex [48]. Moreover, this period is usually characterized by prone sleep, the major risk factor for this pathology. Pre-existing abnormalities in brainstem areas regulating autonomic cardiorespiratory and blood pressure control [50], together with the immaturity of the baroreflex, suggest that the infant is unable to respond properly to a life-threatening hypotension [31]. Electroencephalographic studies show how baroreflex stimulation in an infant elicits a stronger response compared to an adult subject.

Infants that succumb to SIDS show a higher HR and a decreased HRV [66] as well as smaller changes in HRV high-frequency power [67], which, taken together, are typical signs of inadequate parasympathetic function. For these reasons, it has been suggested that an impaired parasympathetic function and/or sympathetic predominance occurs prior to death.

The Social Engagement System

From a behavioral prospective, the regulation of the autonomic state, and thus the regulation of heart rate and contractility, is a key process for emotion control and social interaction [30, 39, 55]. Among the phylogenetically organized circuits that regulate the ANS, the most recently developed, and most frequently used, is considered closely connected to language and communication [30]. The vagus plays a major role in social interactions during early life, since it is fundamental in rapid adjustments of the physiological states, a condition extremely important in establishing an interaction for an infant. Moreover, it also regulates ingestive behaviors, one of the main interactions between the infant and the mother or care provider.

The increase in the neural regulation of the ANS is a key feature in the progressive achievement of independence and is indispensable in

order to start and conduct social interactions. Many evidences suggest that the ANS has an even bigger impact in child development, since it provides a physiological substrate to habituation [68], a process that determines the decrement in attention toward a constantly present stimulus and one of the most important indexes of information processing in children as well as a major index of the learning process in infants. Infants with high RSA, and thus also rapid habituation, require less time to inspect a visual stimulus and exhibit enhanced attention and abilities to deal with novel situations [69]. Fox showed that infants who had a more mature vagal tone at 40-week conceptional age had a better intellectual outcome compared to those exhibiting lower vagal activity [43].

Considering that the measure of activation of the nucleus ambiguus indicates the child's ability of self-regulation [43], it will not be surprising that measures collected during the first months of life can predict the child's behavioral profile [59, 70]. Children with a higher index of parasympathetic activity are prone to better controlling their responses and are thus friendlier and more outgoing. On the other hand, children who lack variability in the high frequencies spectrum but show high variations in the low-frequency power often appear to be much insecure and reserved once grown up [45, 70, 71]. The role played by the sympathetic system is not a minor one either, as children with little or no PEP reactivity toward an unfamiliar person show a poorer emotional regulation [35] but at the same time a greater sympathetic response to a cognitive challenge is a typical feature of behaviorally inhibited children [72]. The reason of these differences in temperament has been linked to variations in the limbic sites, monitoring cardiac and motor responses, first of all the amygdala [45]. Physiological regulation, however, is a primitive way of self-regulation [73], and as the child develops a larger repertoire of self-regulation tools, the burden on the sole ANS decreases [74].

However, the relationship between social interactions and the ANS is not unidirectional: mental stress [75] and deprivation of adequate social interaction could cause variations in the autonomic indexes. For example, orphans, who usually have a socially poor and stressful infancy, exhibit functional and structural brain variations that impact and shape brain development [76, 77]. Other confirmations of the bidirectionality of this process derive from observations suggesting that children from low-income families who grow in a harsh environment show worse cardiovascular indexes [78] than controls that lived a less stressful life and children with chronic pain conditions exhibit lower parasympathetic indexes [79].

Although the behavioral and emotional regulation process continues to develop long after the achievement of a mature ANS, the role of autonomic regulation would probably become less prominent as the maturational process progresses.

When Something Goes Wrong, Congenital Heart Disease and the Brain

The relationship between the heart and brain, as we said, is not unidirectional, and an alteration in heart functioning negatively affects brain development. This is particularly true for congenital heart diseases (CHD), since in these conditions the brain may receive an inadequate blood flow during a period of high vulnerability, as demonstrated by the high morbidity due to neurological complications observed in patients with CHD [80]. Most studies report adverse short- and long-term outcomes, spanning from mild cognitive impairment to more severe conditions.

Adverse neurological outcomes in patients that underwent cardiac surgery have often been considered a consequence of surgery itself, but the presence of similar outcomes in patients with no surgical history and evidences of neurological manifestations pre-dating surgery highlight how CHD by itself can be responsible for all deficits observed [81, 82]. The neurological implications can appear even early during gestation, which is not surprising if we consider that the brain is highly demanding during the intrauterine life, accounting for up to 50% of fetal oxygen consumption [83]. This needful state, which is particularly enhanced in the third trimester, is largely

dictated by the surge in synapsis formation [78] and myelination [84] typical of this period.

Therefore, the brain is naturally highly prioritized [83] and receives up to 25% of the fetal blood flow. Given the structure of the arteriovenous shunts, the blood directed to the brain is much richer in both oxygen and nutrients, compared to the rest of the circulatory system. Any alteration leading to a dysfunctional shunt of oxygenated blood often has consequences on brain development [85]. Most serious outcomes are associated with single ventricle pathology, probably due to more serious modifications of the blood flow toward the brain.

The deprivation of an adequate blood flow leads to reduced brain volume [86] and metabolism during the third intrauterine trimester [80], to an abnormal cerebral microstructure [81] with altered indexes of brain development, and to an increased risk of brain injury (e.g., after heart surgery) [82, 87]. Smaller postnatal brain volume in CHD is associated with an abnormal neurobehavioral status [88]. Injuries that are more often associated with CHD are periventricular leukomalacia, reflecting an altered structure of the white matter located in a vascular watershed zone adjacent to the lateral ventricles [87], and other focal or multifocal injuries of the white matter.

In school age and later adolescence, young people with CHD continue to show lower executive function indexes and a reduced IQ score. The most striking consequences of CHD, however, are a reduced attention span and impaired executive functions. In the adult, there are evidences of a shift from neurodevelopmental delays to cognitive decline and a higher risk for dementia [89].

References

1. Belich AI, Konstantinova NN. Formation of Coordinational function of the central nervous System: Phylo and ontogenetic aspects. J Evol Biochem Physiol. 2003;39(3):375–87.
2. Schmidt A, Schukat-Talamazzini EG, Zöllkau J, Pytlik A, Leibl S, Kumm K, et al. Universal characteristics of evolution and development are inherent in fetal autonomic brain maturation. Auton Neurosci. 2018;212:32–41. Available from: https://doi.org/10.1016/j.autneu.2018.02.004
3. Mcquillen PS, Miller SP. Congenital heart disease and brain development. Ann N Y Acad Sci. 2010;1184:68–86.
4. Taylor EW, Leite CAC, Sartori MR, Wang T, Abe AS, Crossley DA. The phylogeny and ontogeny of autonomic control of the heart and cardiorespiratory interactions in vertebrates. J Exp Biol. 2014;217(5):690–703. Available from: http://jeb.biologists.org/cgi/doi/10.1242/jeb.086199
5. Vincentz JW, Rubart M, Firulli AB. Ontogeny of cardiac sympathetic innervation and its implications for cardiac disease. Pediatr Cardiol. 2013;33(6):923–8.
6. Smith J. Ontogeny of the autonomic nervous System. In: Gootman PM, editor. Developmental neurobiology of the autonomic nervous System. New York: Springer Science; 1987. p. 18–37. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC469751/.
7. Kim C-H, Kim K-S. Development and differentiation of autonomic neurons. In: Robertson D, Biaggioni I, Burnstock G, Low PA, JFR P, editors. Primer on the autonomic nervous system. 3rd ed. Amsterdam: Elsevier; 2012. p. 10–6.
8. Ieda M, Fukuda K. Cardiac innervation and sudden cardiac death. Curr Cardiol Rev. 2009;5(4):289–95. Available from: http://openurl.ingenta.com/content/xref?genre=article&issn=1573-403X&volume=5&issue=4&spage=289
9. Rubart M, Zipes DP. Mechanisms of sudden cardiac death. J Cllinical Investig. 2005;115(9):2305–15.
10. Gordon L, Polak JM, Moscoso GJ, Smith A, Kuhn DM, Wharton J. Development of the peptidergic innervation of human heart. J Anat. 1993;183(Pt 1):131–40.
11. Navaratnam V. Development of the nerve supply to the human heart. Br Heart J. 1965;27(5):640–50.
12. Pappano AJ. Ontogenetic development of autonomic neuroeffector transmission and transmitter reactivity in embryonic and fetal hearts. Pharmacol Rev. 1977;29(1):3–33.
13. Schneider U, Bode F, Schmidt A, Nowack S, Hoyer D, Rudolph A, et al. Developmental milestones of the autonomic nervous system revealed via longitudinal monitoring of fetal heart rate variability. PLoS One. 2018;13(7):1–13.
14. Gagnon R, Campbell K, Ph D, Hunse C, Patrick J. Patterns of human fetal heart rate accelerations from 26 weeks to term. Am J Obstet Gynecol. 1987;157(3):743–8.
15. Bartolome J, Mills E, Lau C, Slotkin AT. Maturation of sympathetic neurotransmission in the rat heart. V. Development of baroreceptor control of sympathetic. J Pharmacol Exp Ther. 1980;215(3):596–600.
16. Segar JL, Hajduczok G, Smith BA, Merrill DC, Merrill C, Hajduczok G, et al. Ontogeny of baroreflex control of renal sympathetic nerve activity and heart rate. Am J Physiol Heart Circ Physiol. 1992;263(6):H1819–6.
17. Hempleman SC, Warburton SJ. Comparative embryology of the carotid body. Respir Physiol Neurobiol.

2013;185(1):3–8. Available from: http://linkinghub.elsevier.com/retrieve/pii/S156990481200225X
18. Zhu Y. Shan, Szeto HH. Cyclic variation in fetal heart rate and sympathetic activity. Am J Obstet Gynecol. 1987;156(4):1001–5.
19. Karin J, Hirsch M, Akselrod S. An estimate of fetal autonomic state by spectral analysis of fetal heart rate fluctuations. Pediatr Res. 1993;34(2):3–7.
20. Koutcherov Y, Mai JK, Paxinos G. Hypothalamus of the human fetus. J Chem Neuroanat. 2003;26:253–70.
21. Sachis PN, Armstrong DL, Becker LAE, Bryan C. Myelination of the human Vagus nerve from 24 weeks postconceptional age to adolescence. J Exp Neurobiol. 1982;41(4):466–72.
22. Lagercrantz H. Catecholamine release in the newborn infant at birth. Pediatr Res. 1977;11(8):889–93.
23. Ogundipe OA, Kullama LK, Stein H, Nijland MJ, Ervin MG, Padbury J, et al. Fetal endocrine and renal responses to in utero ventilation and umbilical cord occlusion. Am J Obstet Gynecol. 1993;169(6):1479–86. Available from: https://doi.org/10.1016/0002-9378(93)90422-F
24. Inwald D, Hathorn MKS, Costeloe K. The deep breath vasoconstriction reflex – a new tool for autonomic assessment in infancy? David Early Hum Dev. 1996;45:55–61.
25. Grieve PG, Stark RI, Isler JR, Housman SL, Fifer WP, Myers MM. Electrocortical functional connectivity in infancy: response to body tilt. Pediatr Neurol. 2007;37(2):91–8. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0887899407001543
26. Carroll JL, Kim I. Postnatal development of carotid body glomus cell O2 sensitivity. Respir Physiol Neurobiol. 2005;149(1–3):201–15. Available from: http://linkinghub.elsevier.com/retrieve/pii/S1569904805001187
27. Chow LT, Chow SS, Anderson RH, Gosling JA, Elizabeth Q. Innervation of the human cardiac conduction system at birth. Br Heart J. 1993;69:430–5.
28. Chow LT, Chow SS, Anderson RH, Gosling JA. The innervation of the human myocardium at birth. J Anat. 1995;187:107–14.
29. Ziyatdinova NI, Dement RE, Khisamieva LI, Ze TL. Age-related peculiarities of adrenergic regulation of cardiac chronotropic action after I f blockage. Bull Exp Biol Med. 2013;156(1):7–9.
30. Porges SW, Furman SA. The early development of the autonomic nervous system provides a neural platform for social behaviour: a polyvagal perspective. Infant Child Dev. 2011;20(1):106–18. Available from: http://doi.wiley.com/10.1002/icd.688
31. Hunt CE. Ontogeny of autonomic regulation in late preterm infants born at 34-37 weeks postmenstrual age. Semin Perinatol. 2006;30(2):73–6. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0146000506000310
32. Massin M. Normal ranges of heart rate variability during infancy and childhood. Pediatr Cardiol. 1997;18(4):297–302.
33. Cohen HL. Development of autonomic innervation in mammalian myocardium. In: Gootman PM, editor. Neurobiology of the autonomic nervous system: Springer Science; 1987. p. 159–91. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC469751/.
34. Kirjavainen J, Jahnukainen T, Huhtala V, Lehtonen L, Kirjavainen T, Korvenranta H, et al. The balance of the autonomic nervous system is normal in colicky infants. Acta Paediatr. 2001;15:250–4.
35. Stifter CA, Dollar JM, Cipriano EA. Temperament and emotion regulation: the role of autonomic nervous System reactivity. Dev Psichobiology. 2013;53(3):266–79.
36. Tsun L, Chow C, Sau S, Chow M, Anderson RH, Gosling JA. Autonomic innervation of the human cardiac conduction System: changes from infancy to senility — an Immunohistochemical and. Anat Rec. 2001;182(February):169–82.
37. Bernstein D. Developmental biology of the cardiovascular system. In: Nelson textbook of pediatrics. Philadelphia: W.B. Saunders Co; 2011. p. 1527–36.
38. Giardino ND, Glenny RW, Borson S, Chan L. Respiratory sinus arrhythmia is associated with efficiency of pulmonary gas exchange in healthy humans. Am J Physiol Circ Physiol. 2003;284(5):H1585–91. Available from: http://www.physiology.org/doi/10.1152/ajpheart.00893.2002
39. Quigley KS, Stifter CA. A comparative validation of sympathetic reactivity in children and adults. Psychophysiology. 2006;43(4):357–65. Available from: http://doi.wiley.com/10.1111/j.1469-8986.2006.00405.x
40. Bush NR, Caron ZK, Blackburn KS, Alkon A. Measuring cardiac autonomic nervous System (ANS) activity in toddlers – resting and developmental challenges. J Vis Exp. 2016;25(108):1–12. Available from: http://www.jove.com/video/53652/measuring-cardiac-autonomic-nervous-system-ans-activity-toddlers
41. Alkon A, Lippert S, Vujan N, Rodriquez ME, Boyce WT, Eskenazi B. The ontogeny of autonomic measures in 6- and 12-month-old infants. Dev Psychobiol. 2006;48(3):197–208. Available from: http://doi.wiley.com/10.1002/dev.20129
42. Salomon K, Matthews KA, Allen MT. Patterns of sympathetic and parasympathetic reactivity in a sample of children and adolescents. Psychophysiology. 2000;37:842–9.
43. Fox NA, Porges SW. The relation between neonatal heart period patterns and developmental outcome author (s): Nathan a. Fox and Stephen W. Porges published by: Wiley on behalf of the Society for Research in child development stable. Child Dev. 1985;56(1):28–37.. http://www.jstor.org/stable/1130
44. Alkon A, Boyce WT, Davis NV, Eskenazi B. Developmental changes in autonomic nervous System resting and reactivity measures in Latino children from 6 to 60 months of age. J Dev Behav Pediatr. 2011;32(9):668–77.
45. Snidman N, Kagan J, Riordan L, Shannon DC. Cardiac function and behavioral reactivity during infancy. Psychophysiology. 1995;32:199–207.

46. Bar-Haim Y, Marshall PJ, Fox NA. Developmental changes in heart period and high- frequency heart period variability from 4 months to 4 years of age. Dev Psychobiol. 2000;37(1):44–56.
47. Marshall PJ, Stevenson-Hinde J. Behavioral inhibition, heart period, and respiratory sinus arrhythmia in young children. Dev Psychobiol. 1998;33(3): 283–92.
48. Korkushko OV, Shatilo VB, Plachinda YI, Shatilo TV. Autonomic control of cardiac chronotropic function in man as a function of age: assessment by power spectral analysis of heart rate variability. J Auton Nerv Syst. 1991;32:191–8.
49. Finley John P, System NSTAN. Heart rate variability in infants, children and young adults. J Auton Nerv Syst. 1995;51(2):103–8.
50. Yiallourou SR, Sands SA, Walker AM, Horne RSC. Postnatal development of baroreflex sensitivity in infancy. J Physiol. 2010;588(12):2193–203. Available from: http://doi.wiley.com/10.1113/jphysiol.2010.187070
51. Dergachevaa O, Batemana R, Byrnea P, Mendelowitza D. Orexinergic modulation of GABAergic neurotransmission to cardiac vagal neurons in the brainstem nucleus ambiguus changes during development. Neuroscience. 2013;202:12–20.
52. Horne RSC. Cardio-respiratory control during sleep in infancy. Paediatr Respir Rev. 2014;15(2):163–9. Available from: https://doi.org/10.1016/j.prrv.2013.02.012
53. Yiallourou SR, Sands SA, Walker AM, Horne RSC. Maturation of heart rate and blood pressure variability during sleep in term-born infants. Sleep. 2012;35: 177–86. Available from: https://academic.oup.com/sleep/article-lookup/doi/10.5665/sleep.1616
54. Schechtman VL, Henslee JA, Harper RM. Developmental patterns of heart rate and variability in infants with persistent apnea of infancy. Early Hum Dev. 1998;50:251–62.
55. Thayer JF, Brosschot JF. Psychosomatics and psychopathology: looking up and down from the brain. Psychoneuroendocrinology. 2005;30(10):1050–8. Available from: http://linkinghub.elsevier.com/retrieve/pii/S030645300500106X
56. DiFrancesco MW, Shamsuzzaman A, McConnell KB, Ishman SL, Zhang N, Huang G, et al. Age-related changes in baroreflex sensitivity and cardiac autonomic tone in children mirrored by regional brain gray matter volume trajectories. Pediatr Res. 2018;83(2):498–505. Available from: http://www.nature.com/doifinder/10.1038/pr.2017.273
57. Huang C, Sandroni P, Sletten DM. Effect of age on adrenergic and vagal baroreflex sensitivity in normal subjects. Muscle Nerve. 2007;36:637–42.
58. Harper RM, Macey PM, Henderson LA, Woo MA, Macey KE, Frysinger RC, et al. fMRI responses to cold pressor challenges in control and obstructive sleep apnea subjects. Brain Behav. 2018;8(6):1583–95.
59. Richardson HL, Macey PM, Kumar R, Valladares EM, Woo MA, Harper RM. Neural and physiological responses to a cold pressor challenge in healthy adolescents. J Neurosci Res. 2013;91(12):1618–27. Available from: http://doi.wiley.com/10.1002/jnr.23283
60. Yoshinaga M, Kucho Y, Ushinohama H, Ishikawa Y, Ohno S, Ogata H. Autonomic function and QT interval during night-time sleep in infant long QT syndrome. Circ J. 2018;82(8):2152–9. Available from: https://www.jstage.jst.go.jp/article/circj/82/8/82_CJ-18-0048/_article
61. Tomoum H, Habeeb N, Elagouza I, Mobarez H. Paediatric breath-holding spells are associated with autonomic dysfunction and iron deficiency may play a role. Acta Paediatr. 2018;107:653–7.
62. Calik M, Dokumaci DS, Demir M, Isik I, Kazanasmaz H, Kandemir H. Brain metabolite values in children with breath- holding spells. Neuropsychiatr Dis Treat. 2017;13:1655–60.
63. Vurucu S, Karaoglu A, Paksu SM, Oz O, Yaman H, Gulgun M, et al. Breath-holding spells may be associated with maturational delay in myelination of brain stem. J Clin Neurophysiol. 2014;31(1):99–101.
64. Orii KE, Kato Z, Osamu F, Funato M, Kubodera K, Inoue R, et al. Changes of autonomic nervous system function in patients with breath-holding spells treated with iron. J Child Neurol. 2002;17(5):337–40.
65. Moon RY, Horne RSC, Hauck FR. Sudden infant death syndrome. The Lancet. 2007;370:1578–87.
66. Harper RM, Leake B, Hodgman E. Developmental patterns of heart rate and heart rate variability during sleep and waking in normal infants and infants at risk for the sudden infant death syndrome. Sleep. 1982;5:28–38.
67. Grieve PG, Myers MM, Stark RI, Housman S, Fifer WP. Topographic localization of electrocortical activation in newborn and two- to four-month-old infants in response to head-up tilting. Acta Paediatr Int J Paediatr. 2005;94(12):1756–63.
68. Bornstein MH, Suess PE. Physiological self-regulation and information processing in infancy: cardiac vagal tone and habituation. Child Dev. 2000;71(2):273–87.
69. Richards JE, Cameron D. Infant heart rate variability and behavioral developmental status. Infant Behav Dev. 1989;12:42–58.
70. Burgess KB, Marshall PJ, Rubin KH, Fox NA. Infant attachment and temperament as predictors of subsequent externalizing problems and cardiac physiology. J Psychol Psychiatry. 2003;6:819–31.
71. Izard CE, Porges SW, Simons RF, Haynes OM, et al. Infant cardiac activity: developmental changes and relations with attachment. Dev Psychol. 1991;27 (3):432–9. Available from: http://doi.apa.org/getdoi.cfm?doi=10.1037/0012-1649.27.3.432
72. Kagan J, Reznick JS, Snidman N, Kagan J, Reznick JS, Snidman N. The physiology and psychology of behavioral inhibition in children. Child Dev. 1987;58(6): 1459–73.
73. Porges SW, Doussard-Roosevelt JA, Maiti AK. Vagal tone and the physiological regulation of emotion. Monogr Soc Res Child Dev. 1994;59:167–86.

74. Calkins SD, Keane SP. Cardiac vagal regulation across the preschool period: stability, continuity, and implications for childhood adjustment. Dev Psychobiol. 2004;45(3):101–12. Available from: http://doi.wiley.com/10.1002/dev.20020
75. Moore GA. Parent conflict predicts infants' vagal regulation in social interaction. Dev Psychopathol. 2010;22(1):23–33.
76. Chugani HT, Behen ME, Muzik O, Juha C. Local brain functional activity following early deprivation: a study of Postinstitutionalized Romanian orphans. NeuroImage. 2001;14(6):1290–301.
77. Eluvathingal TJ, Chugani HT, Behen ME, Juhász C, Maqbool M, Chugani DC, et al. Abnormal brain connectivity in children after early severe socioemotional deprivation: a diffusion. Pediatrics. 2006;117(6):2093–100.
78. Lehman BJ, Taylor SE, Kiefe CI, Seeman TE. Relationship of early life stress and psychological functioning to blood pressure in the CARDIA study. Health Psychol. 2009;28(3):338–46. Available from: http://doi.apa.org/getdoi.cfm?doi=10.1037/a0013785
79. Evans S, Tsao JCI, Lung KC, Zeltzer LK, Naliboff BD. Heart rate variability as a biomarker for autonomic nervous system response differences between children with chronic pain and healthy control children. J Pain Res. 2013;2013:449–57.
80. Limperopoulos C, Tworetzky W, McElhinney DB, Newburger JW, Brown DW, Robertson RL, et al. Brain volume and metabolism in fetuses with congenital heart disease: evaluation with quantitative magnetic resonance imaging and spectroscopy. Circulation. 2010;121(1):26–33. Available from: http://circ.ahajournals.org/cgi/doi/10.1161/CIRCULATIONAHA.109.865568
81. Dimitropoulos A, Xu D, Brant R, Azakie A, Campbell A, Barkovich AJ, et al. Brain injury and development in newborns with critical congenital heart disease. Am Acad Neurol. 2013;81(3):241–8.
82. Miller SP, McQuillen PS, Hamrick S, Xu D, Glidden DV, Charlton N, et al. Abnormal brain development in newborns with congenital heart disease. N Engl J Med. 2007;357(19):1928–38. Available from: http://www.nejm.org/doi/abs/10.1056/NEJMoa067393
83. Prsa M, Sun L, Van Amerom J, Yoo S. Reference ranges of blood flow in the major vessels of the normal human fetal circulation at term by phase-contrast magnetic resonance imaging. Circ Cardiovasc Imaging. 2014;7(4):663–70.
84. Kinney HC, Brody BANN, Ph D, Kloman AS, Gilles FH. Sequence of central nervous System myelination in human infancy II. Patterns of myelination in autopsied infants. J Neuropathol Exp Neurol. 1988;47(3):217–34.
85. Claessens NHP, Kelly CJ, Counsell SJ, Benders MJNL. Neuroimaging, cardiovascular physiology, and functional outcomes in infants with congenital heart disease. Dev Med Child Neurol. 2017;59(9):894–902. Available from: http://doi.wiley.com/10.1111/dmcn.13461
86. Menteer J, Macey PM, Woo MA, Panigrahy A, Harper RM. Central nervous System changes in pediatric heart failure: a volumetric study. Pediatr Cardiol. 2010;31(7):969–76. Available from: http://link.springer.com/10.1007/s00246-010-9730-9
87. Licht DJ, Shera DM, Clancy RR, Wernovsky G, Montenegro LM. Brain maturation is delayed in infants with complex congenital heart defects. J Thorac Cardiovasc Surg. 2008;137(3):529–37. Available from: https://doi.org/10.1016/j.jtcvs.2008.10.025
88. Owen M, Shevell M, Donofrio M, Majnemer A, Mccarter R, Vezina G, et al. Brain volume and Neurobehavior in newborns with complex congenital heart defects. J Pediatr. 2014;164(5):1121–1127.e1. Available from: https://doi.org/10.1016/j.jpeds.2013.11.033
89. Morton PD, Ishibashi N, Jonas RA. Neurodevelopmental abnormalities and congenital heart disease. Circ Res. 2017;120(6):960–77. Available from: http://circres.ahajournals.org/lookup/doi/10.1161/CIRCRESAHA.116.309048

Gender Differences in Brain-Heart Connection

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Caterina Trevisan, Giuseppe Sergi, and Stefania Maggi

Contents

Abstract

The brain-heart connection is characterized by sex- and gender-related differences that tend to modify over an individual's lifetime, thus in relation to age. However, since the need for a gender-specific approach has had growing attention only in the latest years, this issue has not yet been fully elucidated. The knowledge gap is especially marked for pathologies that have historically been considered pertaining mostly to men, e.g., cardiovascular diseases, or to women, e.g., neuropsychiatric conditions, and it is even more pronounced with regard to the relationship that exists between these dysfunctions. This chapter will present an overview of the current evidence on the sex- and gender-related aspects that could influence the brain-heart connection and the possible effect of aging on such features. Sex- and gender-related aspects will, in particular, be evaluated in regard to (1) individual

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*,
https://doi.org/10.1007/978-3-030-28008-6_61

vulnerability and the risk factor patterns associated with the development and co-occurrence of cardiovascular and neuropsychiatric pathologies; (2) the mechanisms by which the nervous and cardiovascular systems interact with one another; (3) the bidirectional connection between neuropsychiatric disorders and cardiovascular diseases; and (4) the disparities in how cardiovascular and neuropsychiatric conditions are recognized and treated that can affect the course and the co-occurrence of these diseases.

Keywords

Cardiovascular diseases · Neuropsychiatric disorders · Gender · Sex · Aging

Introduction

A fascinating, growing chapter of biomedical research concerns *gender medicine*, i.e., the science that aims to study "the differences in the normal physiology of men and women and the ways that they experience disease" [1]. In clinical practice in particular, gender medicine focuses on how diseases differ in the male and female populations in terms of prevention, pathology, clinical presentation, treatment, and prognosis [2]. In this context, two main concepts need, of course, to be defined. *Sex* refers to the biological differences between males/females such as their anatomic reproductive systems and secondary sex characteristics. *Gender*, which primarily refers to personal, societal, and cultural perceptions of being female or male, is defined by the World Health Organization (WHO) as "the socially constructed characteristics of women and men, such as norms, roles, and relationships of and between groups of women and men from the social and cultural roles" [3].

Despite growing awareness of the importance of a gender-specific approach in research and clinical practice particularly with regard to some medical specialties, a substantial knowledge gap still exists, especially for pathologies that have historically been considered male diseases, such as cardiovascular ones. The idea that individuals of the female sex have per se a lower risk of cardiovascular diseases (CVDs) due to estrogen's protective action has led investigators to underestimate the occurrence of those diseases in women and to exclude them from the first large clinical trials [4]. The guidelines for the management of CVDs were thus developed on the basis of studies exclusively investigating men and, until only recently, have rarely considered possible sex- and gender-related features that need be taken into consideration for a *personalized medicine* approach.

Just as research on CVDs was thought to apply exclusively to the male population, some neuropsychiatric conditions, such as depression, have been studied mainly in women. These mis-/preconceptions have led to the creation of a gender gap in scientific knowledge and to the under-identification and undertreatment of some diseases in clinical practice [5]. If this is true with regard to a single medical specialty or disease, it is all the more so for the sex or gender differences affecting the interaction between these systems and the relationship(s) between various dysfunctions. This chapter will focus, in particular, on the sex- and gender-related factors that may influence the brain-heart connection and on the possible interaction of age on such issue.

Investigating the Brain-Heart Dynamics from an Epidemiologic Perspective: the Relevance of Age and Gender Characteristics

Age- and gender-related features affecting the brain-heart dynamics have been studied from epidemiological and pathophysiological points of view. With regard to the *age effect*, the aging process leads to a gradual impairment in the functioning of multiple organ systems, often beginning early in life and progressing over the course of a lifetime [6]. The lengthening of life expectancy especially in high-income countries has given epidemiological research the opportunity to explore the phenomenon of the accumulation of deficits and diseases. As a result, the prevalence

of individuals over 60 who have more than one chronic condition is estimated to fall between 55% and 98% [7], and different comorbidity patterns of types and severity of diseases have been identified [8]. The growing knowledge about underlying causal and non-causal pathways leading to specific dysfunction patterns may help investigators and clinicians to identify interventions that can prevent or delay the development and progression of some chronic diseases. Among these, recent studies have confirmed that cardiovascular and neuropsychiatric disorders, which have marked effects on personal independence, quality of life, and mortality, are very prevalent conditions in older people [9]. Although these disorders generally tend to present themselves individually in younger individuals, the situation seems to change in older people who have a higher probability of being affected by a combination of cardiovascular diseases (CVDs) and neuropsychiatric pathologies [10]. Disease patterns continue to mutate over the course of a lifetime, e.g., CVDs seem to cluster with depression in the youngest old, but with dementia in the oldest old [8]. The co-occurrence of these conditions could be explained by the fact that they share pathophysiological pathways (i.e., stress or inflammation) or by an age-related higher vulnerability that makes impairment in one system more likely to trigger alterations in other organs or tissues.

In addition to the effect of age, the brain-heart dynamics are characterized by *sex- and gender-specific features* that can mutate over the life course and may influence the distribution of CVDs and neuropsychiatric disorders in men and women. Indeed, the prevalence of CVDs is higher in adult men with respect to women, but this gender difference gradually attenuates with advancing age. Conversely, many cognitive and mood disorders, such as Alzheimer's dementia and depression, are more frequent in women with respect to men. In addition, although men and women show similar patterns in the overall accumulation of chronic diseases in older age [11], some gender differences have been noted in the co-occurrence of cardiovascular and neuropsychiatric conditions. These findings suggest that even *gender* affects the brain-heart connection, and this hypothesis could be supported by several issues.

First, individual vulnerability and risk factor patterns that favor the development or co-occurrence of impairments in the nervous and cardiovascular systems seem to present some important sex- and gender-related features. Second, the mechanisms through which the nervous and cardiovascular systems interact with one another could be different in men and women. Third, irrespective of the underlying mechanism, the impact that neuropsychiatric disorders have on cardiovascular functions, and vice versa, might differ in men and women. Finally, the relationship between neuropsychiatric and cardiovascular conditions could be influenced by sex- and gender-related aspects linked to diagnosis and treatment of such disorders.

The following sections will review current findings that focused on the sex and gender differences in connection to these points.

Sex and Gender Differences in the Factors Influencing Neurologic and Cardiovascular Systems

Differences in *structural neurologic and cardiovascular features* have been noted in men and women even at the prenatal phase. Indeed, evidence concerning the development of the autonomic nervous system, which is strictly correlated with cardiac functions, has emerged from a number of animal studies. Those works, for example, found a sex-related variability in the distribution of neuropeptides in the brain as well as in the number of ganglionic neurons and in the enzymatic activity regulating the clearance of neurotransmitters [12]. Although a more detailed explanation of these mechanisms goes beyond the scope of this chapter, they need to be taken into consideration when sex differences in the brain-heart connection are being examined.

With reference to sex-related features characterizing some pathophysiological processes in children, young adults, and in older adults, *gonadal hormones* play a primary role due to their systemic actions, which involve also the

cardiovascular and nervous systems. As is well-known, in addition to sex hormone patterns distinguishing men and women, there are variations in hormonal levels in each sex over the course of a lifetime. In particular, while the fall in testosterone levels is gradual in middle-aged and older men, women experience periodic fluctuations in ovarian hormones in the premenopausal age and a more drastic reduction in hormonal levels after menopause [12]. As far as the cardiovascular system is concerned, the controversial effects of estrogen on hemodynamic parameters and atheroma formation have been amply investigated over the past 30 years. Although several studies have produced findings supporting the cardioprotective role of ovarian hormones at the cellular and human levels [13], the Women's Health Initiative trial has reported contrasting data [14, 15]. In fact, the study found a higher risk of coronary heart diseases in healthy postmenopausal women who used estrogen plus progestin with respect to that in a placebo group [14]. Instead, hysterectomized women treated with conjugated equine estrogen alone showed an increased incidence of stroke but not of ischemic heart diseases [15]. These results paved the way for further investigations examining a timing hypothesis: i.e., hormonal therapy could lower cardiovascular risk if it is administered close to menopause, but the effect may prove detrimental at a more advanced age [16]. Just as for estrogen, endogenous androgens could both directly and indirectly affect the cardiovascular system in both men and women. While the majority of studies uncovered an association between low levels of circulating testosterone and higher cardiovascular risk in males, the situation is not clear in women as both reduced and increased androgen concentrations have been shown to be related to CVD [17].

In addition to their cardiovascular effects, sex hormones seem to have an important influence on the nervous system due to their impact on several mechanisms linked to neural plasticity and their interactions with the most common neurotransmitters [18]. Estrogens' neuroprotective effects, which have been noted in animal models, have been supported by observational and experimental studies involving women who underwent oophorectomy before menopause [19]. But trials carried out on postmenopausal women to test the effectiveness of estrogen therapy uncovered nonsignificant or even worse cognitive outcomes in the patients who had initiated treatment with respect to the placebo group [20]. These apparent discordant results can probably be explained by the time estrogen therapy was initiated, and this suggests that timing may have an effect also on the neurologic actions of sex hormones [21]. Indeed, estrogen may play a neuroprotective role when vascular or degenerative lesions have not yet developed but seem to be unable to reverse the process once lesions have formed.

Another factor influencing differences in men and women in the brain-heart connection and in the way neuropsychiatric and cardiovascular conditions co-occur may be linked to the frequency of *risky behaviors and diseases*. Gender plays a vital role in determining lifestyle characteristics, and health-related behaviors are largely shaped by an individual's educational level and sociocultural context, which are, in turn, linked to female and male roles. It is well-known, for example, that smoking, drinking, following an unhealthy diet, and physical inactivity can negatively affect both the neurologic and cardiovascular systems [22, 23]. At an individual level, these factors could promote the onset of *both* neurologic and cardiovascular dysfunctions, or they could primarily influence one of these systems, leading thus to impairments in the other. The gender-specific differences in the frequency of these behaviors can therefore partially explain the distinctive patterns of system dysfunction noted in men and women and may affect several pathophysiological aspects of the brain-heart connection. The higher prevalence of smoking and heavy alcohol consumption noted in men, for example, makes them more vulnerable to atherosclerosis, thus to ischemic or non-ischemic heart failure, carotid artery diseases, and specific forms of encephalopathy, psychosis, and dementia [24]. Unhealthy diets and low levels of physical activity can also contribute to the development of obesity characterized by different fat distribution patterns in men and women [25].

A higher concentration of adipose tissue in the abdominal compartment, for example, is particularly common in middle-aged and older men [25]. These findings are particularly interesting not only because abdominal obesity has been associated with a number of cardiovascular and metabolic diseases and may affect brain health [26] but also because fat distribution seems to modulate sympathetic tone [12]. In fact, when considered together with age, sex and body fat percent, the waist-to-thigh ratio as a measure of abdominal obesity appeared to be the only factor independently associated with sympathetic tone [27]. The correlation between waist-to-thigh ratio and muscle sympathetic activity was more marked in men than in women, supporting the hypothesis that fat distribution could at least partially explain the higher sympathetic activity observed in the former [37], a subject that will be discussed below.

The distribution of some comorbid clinical conditions connected to the nervous and cardiovascular systems may also present differences between male and female populations. Diseases affecting the thyroid gland, for example, are more prevalent in women [28], while men more frequently present conditions such as hypertension and type 2 diabetes [29]. These disorders may increase the risk of arrhythmias, heart failure, and ischemic heart diseases, and they can lead to a reduction in blood supply or to the development of cognitive deficits or peripheral neuropathy, all affecting brain health [30, 31].

Sex Differences in the Mechanisms Underlying the Brain-Heart Dynamics

One of the principal communication channels between the brain and the heart is constituted by the *autonomic nervous system*. By regulating the sympathetic and parasympathetic responses, the system can control vital cardiovascular parameters such as blood pressure and heart rate. Interestingly, although men and women have the same adrenaline and noradrenaline plasma and urinary concentrations in physiological conditions, most studies have reported more marked resting sympathetic activity to muscle in men, especially in younger men, while women tend to show higher parasympathetic activity [12]. Consistent with this evidence, several studies have reported that noradrenaline-induced vasoconstriction and baroreflex sensitivity are lower in women with respect to men and that these differences are influenced by hormonal levels [32, 33]. Sex disparities have also emerged in connection to exposure to some stressors. Men have demonstrated greater cardiovascular and catecholamine responses with respect to women during exercise, while women have shown increased lipolytic and ketogenic responses [34]. Women, in particular premenopausal ones, have a more pronounced and prolonged sympathetic neural activity with respect to men when they are directly exposed to cooling [35]. The effect can probably explain why there is a higher prevalence of Raynaud's phenomenon in the female population, a condition which has been found to be due to an increase in sympathetic tone and not to structural factors [12]. Similar sex-related differences have been uncovered in individuals with hypertension and in response to stimuli such as hypoglycemia or hypo-/hyperoxia [12]. Although neuroendocrine mechanisms have been shown to be activated in response to similar reductions in glycaemia in men and women, the former have demonstrated greater sympathetic activity and adrenaline plasma concentrations [36]. Women, instead, show shorter latency in activating the sympathetic system and in recovering in the event of isocapnic hypoxia [37]. Overall, these sex-related features may modulate the response to critical clinical conditions such as ischemic heart diseases, which activate both the sympathetic and parasympathetic nervous systems. Indeed, women have a vagal predominance that makes more likely that in case of acute coronary syndrome they present atypical symptoms, unexplained syncope, hypotension or bradycardia, and they have an increased risk of hemodynamic complications after acute angioplasty [38]. Conversely, at the onset of myocardial infarction, men often tend to show more severe arrhythmias than women probably due to a higher sympathetic tone that, as demonstrated in animal models, increases the risk of ventricular tachyarrhythmia [39].

It is noteworthy that sex differences in the interplay between autonomic nervous control and the cardiovascular system seem to attenuate with advancing age. In particular, the greater preponderance of sympathetic nervous activity and responsiveness observed in the male sex compared with the female one appears to decline after 50, and no substantial sex differences are observed after that age [33]. These findings may be explained by the age-related sex hormone changes in the two populations affecting the autonomic nervous system at the central and peripheral levels. Indeed, genomic and non-genomic pathways can mediate the effects of sex hormones by increasing the expression and affinity of receptors, e.g., the muscarinic ones induced by estrogens, and by regulating the clearance of neurotransmitters [40]. While estrogens increase acetylcholine content and uptake, testosterone mainly affects catecholamine and neuropeptide Y synthesis and clearance, enhancing sympathetic activity [41]. Similar effects have been reported at the peripheral level and have been shown to be more marked in young and middle-aged adults but are attenuated with the age-related reduction of gonadal hormones [12]. An additional mechanism that could be involved here is linked to estrogen's antiapoptotic role which could also concern the nervous cells [42]. The higher exposition of women to estrogen over the course of their lifetime could mitigate the loss of autonomic nervous cells and explain the greater reduction in autonomic activity that occurs in men with aging [12].

Another pathway by which the nervous and cardiovascular systems can influence one another is *inflammation*. Some CVDs, such as hypertension, acute myocardial infarction, heart failure, and atrial fibrillation, are associated with local and systemic inflammatory pathways, which can affect the nervous system through detrimental structural and functional effects [43]. Inflammation is also linked to hypercoagulability that can trigger cerebrovascular ischemic events [44] and increases the risk of long-term cognitive impairment [30, 45]. Neurological diseases, such as stroke, or psychological conditions, such as depression, anxiety, or psychosocial stress, may also be associated with a chronic inflammatory status that can increase cardiovascular risk [46, 47]. In addition to the direct effect of inflammation on cardiovascular cells, even a mild inflammation can affect the autonomic nervous system [48], which modulates the immune response [49] and cardiovascular parameters and may increase the risk of ischemic heart diseases. As far as sex differences in the inflammatory pathway are concerned, it is well-known that each sex tends to present distinctive patterns of immune response and that such variability could in part be explained by an interaction between the sex hormones and immune cells [50]. In response to the same stimulus, women have, in fact, higher antibody responses by the B lymphocytes, making them more vulnerable to autoimmune diseases, and a predominant T helper 2 response [50]. Conversely, some studies have suggested that androgens in men could enhance the T helper 1 cell activity, but downregulate humoral and cell-mediated immune responses [50]. Despite the greater immune activation generally observed in the female sex, gonadal hormones, especially estrogens, may have pro-inflammatory or anti-inflammatory actions depending on a multitude of factors, including the type of immune-stimulus, the target organ and microenvironment, the reproductive period, and the estrogen concentrations [51]. All of this means that their roles in the context of local or systemic inflammations in several cardiovascular and nervous conditions could substantially vary in the two populations [52]. For example, although there is a scarcity of studies on this subject, psychosocial stress and sleep disturbances seem to induce higher inflammation in women than in men [53]. However, as far as the detrimental effects of inflammation on brain health are concerned, the inverse association between peripheral inflammatory markers and total brain volume seems to be more marked in men, especially in the oldest old [54]. This effect could be due to the intrinsic neuroprotection that women have due to their longer exposition to the anti-apoptotic action of estrogens, but further investigations are warranted to clarify this point.

A further mechanism by which heart diseases may, in particular, affect neuronal health concerns *cerebral hypoperfusion*. Indeed, CVD with an

acute or chronic reduction in cerebral blood flow can have important consequences for the nervous system, determining structural and functional neuronal loss. The detrimental effects of chronic hypoperfusion might involve several brain regions, including those that regulate autonomic system, mood, and cognitive functions [55]. Sex differences in the frequency of conditions such as heart failure or some arrhythmias could contribute to variability in the onset of neuropsychiatric diseases. Heart failure, for example, can both increase the risk of stroke and, in cases of reduced ejection fraction, could lead to chronic brain hypoperfusion [30]. This condition seems more frequent in men as they present a twofold higher prevalence of heart failure with reduced ejection fraction with respect to women, although the disparity tends to attenuate with aging [56]. Regarding arrhythmias, the most common chronic arrhythmia in adults and older people, namely, atrial fibrillation, has been recently associated with a higher risk of cognitive decline not only due to thromboembolism and inflammation but also to reduced cardiac output that, even intermittently, can lead to cerebral hypoperfusion [57]. Although atrial fibrillation more frequently affects men, women's longer life expectancy and the fact that this arrhythmia tends to present at an advanced age imply that the absolute number of patients with atrial fibrillation is similar or even higher in women than in men [58]. However, a recent study has shown that, although women have a higher incidence of stroke and dementia than men, the risk of dementia associated to atrial fibrillation does not differ between the two populations [59].

Sex and Gender Differences in the Bidirectional Relationship Between Cardiovascular Diseases and Neuropsychiatric Conditions

One of the most interesting aspects regarding gender differences in brain-heart dynamics is represented by the bidirectional relationship between CVD and psychological/psychosocial stress, including conditions such as anxiety and depression. Several investigations have recently set out to examine the link between CVD and depression. As it has been amply demonstrated, CVD increases the risk of developing depressive symptoms. At the same time, persons with depression have a higher risk and a worse prognosis of CVD [60, 61]. The mechanisms by which depression as well as other stressful psychological conditions can increase the risk of developing CVD are linked to inflammation, the activation of the sympathetic autonomous system and of the hypothalamus-pituitary-adrenal axis, unhealthy behavioral habits, and scarce adherence to medical recommendations [61]. In turn, the psychological burden linked to the experience of living with CVD, chronic inflammation, and the activation of neuroendocrine pathways associated with CVD could facilitate the onset or worsening of depressive symptoms [62]. The involvement of both biological and behavioral mechanisms suggests that this complex relationship could be influenced, respectively, by sex- and gender-related aspects.

Considering depression as a risk factor for CVD and particularly of ischemic heart diseases, some studies have demonstrated that it can increase the risk of coronary heart diseases in a similar way in men and women [63], but others have reported that the risk is higher for the latter [64, 65], especially at younger ages or in the presence of other cardiovascular risk factors, such as diabetes [66]. As regards the prevalence of depression in CVD patients, the estimated figure is consistent with the higher frequency of depression in women throughout the course of their lifetime and probably linked to hormonal and psychosocial factors. In individuals with coronary artery diseases, for example, the prevalence of depression is approximately twice as high in females of all age classes [67, 68], and women seem to have more severe and prolonged depressive symptoms than men [69]. Nonetheless, the impact of depression on CVD prognosis shows gender differences only when young women with suspected or established CAD are compared with their older counterparts or with men [70]. Conversely, after myocardial infarction, the influence of depression on CVD prognosis was similar

between the two populations, especially when disease severity was accounted for [68].

Similarly to depressive symptoms, other psychosocial factors have been found to influence CVD outcomes, and some gender differences do seem to exist. Concerning the impact of stressful conditions, for example, a large body of evidence has shown that work stress can increase the risk of coronary heart disease in men [71]; in women the same effect seems to be mostly caused by marital stress alone or combined with work stress [72]. On the other hand, lower general negative affect and the presence of numerous social support levels seemed to reduce the risk of coronary events in both genders in persons with no history of coronary heart disease [73], but depending on some features regarding the quality and quantity of social relationships [74]. In fact, the lack of social integration has been shown to independently predict recurrent cardiac events and disease progression [75] in women with coronary heart disease, but the results in men continue to be mixed [74]. In this regard, Takotsubo syndrome is a distinctive model of stress-related CVD showing marked gender differences, and it consists in a non-ischemic transient dysfunction of the left ventricle that is typically triggered by physical or emotional stress [76]. In 90% of cases it affects women, especially postmenopausal. So far, the sex- and gender-related features underlying such disparity in the disease's pathophysiology have not yet been fully elucidated, and this syndrome continues to be a relevant confounder in identifying an acute coronary syndrome in women, as its clinical presentation resembles that of myocardial infarction [76].

The relationship between cardiovascular and neuropsychiatric conditions and the presence of potential gender differences in this context are important factors for geriatric medicine, due to their high prevalence and impact on independence and quality of life in older adults. As it has emerged in recent findings, the prevalence of both cardiovascular and neurologic diseases surpasses 20% in persons over 60, and cardiovascular and neurological diseases co-occur in one third of these individuals [10]. Although the total prevalence of concurrent cardiovascular and neuropsychiatric diseases seems to be similar in the two genders, one study reported that older women with CVD had a higher frequency of neuropsychiatric comorbidities than men, but the situation was reversed when neuropsychiatric disorders were considered the index disease [10]. Moreover, slight gender differences were observed when the burden of multiple cardiovascular and neuropsychiatric diseases on functional decline was calculated, with women seeming more burdened with respect to men [10].

Recognizing and Treating Cardiovascular and Neuropsychiatric Diseases: Gender Differences and the Impact on the Brain-Heart Connection

Gender differences in the brain-heart connection can also be influenced by the way CVD and neuropsychiatric conditions are faced by patients and healthcare providers. The difficulty in recognizing the disease, the type of treatment prescribed, and the patient's attitude and determination to recover can all influence the course of the disease, as well as the extent to which it can promote the development of concurrent pathologies.

As far as recognizing the disease is concerned, as previously mentioned, both CVD and neuropsychiatric conditions have been associated with gender-related bias, which may hinder the recognition of the former in women and of the latter in men. Although the growing number of studies investigating gender medicine has increased physicians' awareness, misconceptions still exist even from the patient's point of view. It has been shown, for example, that women with acute coronary syndrome seek medical attention much later with respect to men [77]. This pattern seems to be due to the high frequency of atypical symptoms that women present and to their unawareness of their cardiovascular risk and of the peculiar symptoms of CVD [4]. On the other hand, men tend to be less inclined to seek medical attention for psychological disturbances such as

depressive mood or anxiety leading to higher rates of under-identification and undertreatment [5, 78].

As regards gender differences in the treatment of CVD or neuropsychiatric disorders, some studies have indeed found disparities, but the tendency seems to be attenuating since the last decades [79]. Nevertheless, although invasive and noninvasive procedures for ischemic heart diseases seem to produce similar benefits for men and women, the latter are still more likely to receive conservative treatment [80]. Cardiac rehabilitation programs also seems to present some gender-specific features: compared to men, women are less frequently admitted to rehabilitation after ischemic heart diseases, while the opposite is true for those who undergo heart valve surgery or experience heart failure [81]. Women are less likely to receive anticoagulation for atrial fibrillation irrespective of the thromboembolic risk [82], and, even when they are prescribed direct oral anticoagulants, they frequently receive a lower drug dose [83]. These differences can affect the prognosis of the disease and seem to be only partially explained by the fact that women seek medical attention for CVD at more advanced stages, at an older age, and with a higher number of chronic diseases, compared to men [4, 83].

Another important variable in the brain-heart connection concerns the use of drugs for CVD that could interact with cerebral functions and could present some gender-specific features. Women with chronic heart failure, for example, are less likely to be prescribed ACE inhibitors, angiotensin receptor blockers, or beta-blockers than men [84]. The use of these drugs could affect the autonomic nervous system and neuropsychiatric status, although findings on the latter are still inconsistent [30]. Neuroleptic drugs, such as antidepressants and acetylcholinesterase inhibitors, might instead have cardiovascular effects triggering dysrhythmias or blood pressure variations [30]. Gender differences in the use of antidepressants, more commonly prescribed to women, have been noted [5], while disparities in the use of pharmacological treatments for cognitive impairment have not yet emerged [85].

Finally, the success of treatments prescribed depends on some patient-related factors that may also reflect some gender differences. First of all, the capability of facing the challenges of a disease or a condition of psychosocial stress is largely influenced by means of coping strategies, and, in this regard, women seem to have greater resources with respect to men [69, 86]. The two populations differ also in the way they become involved with their family members for support and assistance. In accordance with traditional gender roles, women tend to minimize the burden of the disease and are less inclined to seek support and assistance. Men, instead, tend to ask their partners for help particularly when they are physically impaired and report receiving more support with respect to women [86]. Second, adherence to treatments and to lifestyle recommendations also seems to reflect some gender-related features. Although findings on this topic are contrasting, women seem to show worse adherence to some pharmacological (e.g., statins, antihypertensive drugs [87, 88]) and non-pharmacological interventions, such as increasing physical activity [89] but demonstrate greater achievement of some dietary targets [90]. As regards the use of psychotropic drugs, adherence to antidepressants also seems to be linked to gender differences [91]: men tend to show a lower adherence and greater risk of discontinuing, especially in case of occupational, social, or family functioning improvements, while in women, discontinuation of the therapy seems to be related to improvement in family functioning [91, 92].

Conclusions

The brain-heart connection is characterized by sex and gender differences that can influence the main mechanisms by which the cardiovascular and nervous systems interact and by which CVD and neuropsychiatric diseases affect one another and co-occur. Sex hormones play a fundamental role in modulating these mechanisms, and their alterations are partially responsible for the variability of the sex-related differences in brain-heart

dynamics that are present over the life course. Gender differences could affect health behaviors and the ways cardiovascular and neuropsychiatric disorders are recognized and treated, another variable that can affect the brain-heart interaction. Although the awareness about the need of a gender-specific approach is increasing, further investigations are needed to fully elucidate the distinctive features and mechanisms of brain-heart dynamics in the male and female populations.

Cross-References

- Brain-Heart Communication
- Cardiovascular Adverse Effects of Psychotropic Drugs
- Dementia and Cerebrovascular Disease
- Depression and Cardiovascular Diseases
- Genetic Determinants Affecting the Relationship Between the Autonomic Nervous System and Sudden Death
- Heart Activity and Cognition
- Immune System and Mind-Body Medicine: An Overview
- The Role of Emotions, Stress, and Mental State in Inflammatory Processes Perturbing Brain-Heart Dialogue

References

1. Legato MJ. Beyond women's health the new discipline of gender-specific medicine. Med Clin North Am [Internet]. 2003 [cited 2019 Sep 9];87:917–37, vii. Available from: http://www.ncbi.nlm.nih.gov/pubmed/14621324
2. Baggio G, Corsini A, Floreani A, Giannini S, Zagonel V. Gender medicine: a task for the third millennium. Clin Chem Lab Med [Internet]. 2013 [cited 2019 Sep 9];51:713–27. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23515103
3. WHO|Gender. WHO [Internet]. World Health Organization; 2019 [cited 2019 Sep 9]; Available from: https://www.who.int/gender-equity-rights/understanding/gender-definition/en/
4. Trevisan C, Maggi S, Manzato E, Sergi G, Veronese N. Geriatric insights on elderly women and heart disease. Curr Cardiovasc Risk Rep. 2017;11:8. https://doi.org/10.1007/s12170-017-0532-y
5. Kilmartin C. Depression in men: communication, diagnosis and therapy. J Men's Heal Gend [Internet]. 2005 [cited 2019 Sep 17];2:95–9. Available from: http://online.liebertpub.com/doi/pdfplus/10.1016/j.jmhg.2004.10.010
6. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci [Internet]. 2001 [cited 2014 Aug 27];56:M146–56. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11253156
7. Marengoni A, Angleman S, Melis R, Mangialasche F, Karp A, Garmen A, et al. Aging with multimorbidity: a systematic review of the literature. Ageing Res Rev [Internet]. 2011 [cited 2019 Sep 10];10:430–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21402176
8. Marengoni A, Rizzuto D, Wang H-X, Winblad B, Fratiglioni L. Patterns of chronic multimorbidity in the elderly population. J Am Geriatr Soc [Internet]. 2009 [cited 2019 Sep 10];57:225–30. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19207138
9. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, et al. Heart disease and stroke statistics – 2019 update: a report from the American Heart Association. Circulation [Internet]. 2019 [cited 2019 Sep 18];139:e56–528. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30700139
10. Vetrano DL, Rizzuto D, Calderón-Larrañaga A, Onder G, Welmer A-K, Bernabei R, et al. Trajectories of functional decline in older adults with neuropsychiatric and cardiovascular multimorbidity: a Swedish cohort study. Steinhubl SR, editor. PLOS Med. [Internet]. Public Library of Science; 2018 [cited 2019 Sep 16];15:e1002503. Available from: https://dx.plos.org/10.1371/journal.pmed.1002503
11. Calderón-Larrañaga A, Vetrano DL, Onder G, Gimeno-Feliu LA, Coscollar-Santaliestra C, Carfí A, et al. Assessing and measuring chronic multimorbidity in the older population: a proposal for its operationalization. J Gerontol Ser A Biol Sci Med Sci [Internet]. 2016 [cited 2017 May 29];glw233. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28003375
12. Dart A, Du X-J, Kingwell BA. Gender, sex hormones and autonomic nervous control of the cardiovascular system. Cardiovasc Res [Internet]. Narnia; 2002 [cited 2019 Sep 10];53:678–87. Available from: https://academic.oup.com/cardiovascres/article-lookup/doi/10.1016/S0008-6363(01)00508-9
13. Collins P, Rosano GM, Sarrel PM, Ulrich L, Adamopoulos S, Beale CM, et al. 17 beta-estradiol attenuates acetylcholine-induced coronary arterial constriction in women but not men with coronary heart disease. Circulation [Internet]. 1995 [cited 2016 Dec 30];92:24–30. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7788912
14. Writing Group for the Women's Health Initiative Investigators WG for the WHI. Risks and benefits of estrogen plus progestin in healthy postmenopausal

women: principal results from the women's health initiative randomized controlled trial. JAMA J Am Med Assoc [Internet]. American Medical Association; 2002 [cited 2019 Sep 10];288:321–33. Available from: http://jama.ama-assn.org/cgi/doi/10.1001/jama.288.3.321
15. Anderson GL, Limacher M, Assaf AR, Bassford T, Beresford SAA, Black H, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy. JAMA [Internet]. 2004 [cited 2019 Sep 18];291:1701. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15082697
16. Mehta JM, Chester RC, Kling JM. The timing hypothesis: hormone therapy for treating symptomatic women during menopause and its relationship to cardiovascular disease. J Women's Heal [Internet]. 2019 [cited 2019 Sep 10];28:705–11. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30484736
17. Armeni E, Lambrinoudaki I. Androgens and cardiovascular disease in women and men. Maturitas [Internet]. 2017 [cited 2019 Sep 10];104:54–72. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28923177
18. Barth C, Villringer A, Sacher J. Sex hormones affect neurotransmitters and shape the adult female brain during hormonal transition periods. Front Neurosci [Internet]. Frontiers; 2015 [cited 2019 Sep 10];9:37. Available from: http://journal.frontiersin.org/Article/10.3389/fnins.2015.00037/abstract
19. Rocca WA, Bower JH, Maraganore DM, Ahlskog JE, Grossardt BR, de Andrade M, et al. Increased risk of cognitive impairment or dementia in women who underwent oophorectomy before menopause. Neurology [Internet]. 2007 [cited 2019 Sep 12];69:1074–83. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17761551
20. Lethaby A, Hogervorst E, Richards M, Yesufu A, Yaffe K. Hormone replacement therapy for cognitive function in postmenopausal women. Cochrane Database Syst Rev [Internet]. 2008 [cited 2019 Sep 12];CD003122. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18254016
21. Rocca WA, Grossardt BR, Shuster LT. Oophorectomy, menopause, estrogen, and cognitive aging: the timing hypothesis. Neurodegener Dis [Internet]. Karger Publishers; 2010 [cited 2019 Sep 10];7:163. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2859235/
22. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016 European guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J [Internet]. 2016 [cited 2019 Jul 2];37:2315–81. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27222591
23. Peters R, Booth A, Rockwood K, Peters J, D'Este C, Anstey KJ. Combining modifiable risk factors and risk of dementia: a systematic review and meta-analysis. BMJ Open [Internet]. 2019 [cited 2019 Sep 18];9:e022846. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30782689
24. Linardakis M, Smpokos E, Papadaki A, Komninos ID, Tzanakis N, Philalithis A. Prevalence of multiple behavioral risk factors for chronic diseases in adults aged 50 +, from eleven European countries – the SHARE study (2004). Prev Med (Baltim) [Internet]. Academic Press; 2013 [cited 2019 Sep 18];57:168–72. Available from: https://www.sciencedirect.com/science/article/pii/S0091743513001539
25. Mansour MF, Chan C-WJ, Laforest S, Veilleux A, Tchernof A. Sex differences in body fat distribution. Adipose Tissue Biol [Internet]. Cham: Springer International Publishing; 2017 [cited 2019 Sep 18]. p. 257–300. Available from: http://link.springer.com/10.1007/978-3-319-52031-5_8
26. Jagust W, Harvey D, Mungas D, Haan M. Central obesity and the aging brain. Arch Neurol [Internet]. American Medical Association; 2005 [cited 2019 Sep 18];62:1545–8. Available from: http://archneur.jamanetwork.com/article.aspx?doi=10.1001/archneur.62.10.1545
27. Tank J, Heusser K, Diedrich A, Hering D, Luft FC, Busjahn A, et al. Influences of gender on the interaction between sympathetic nerve traffic and central adiposity. J Clin Endocrinol Metab [Internet]. 2008 [cited 2019 Sep 18];93:4974–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18782878
28. Vanderpump MPJ. The epidemiology of thyroid disease. Br Med Bull [Internet]. Narnia; 2011 [cited 2019 Sep 18];99:39–51. Available from: https://academic.oup.com/bmb/article-lookup/doi/10.1093/bmb/ldr030
29. Millett ERC, Peters SAE, Woodward M. Sex differences in risk factors for myocardial infarction: cohort study of UK Biobank participants. BMJ [Internet]. British Medical Journal Publishing Group; 2018 [cited 2019 Sep 18];363:k4247. Available from: https://www.bmj.com/content/363/bmj.k4247
30. Doehner W, Ural D, Haeusler KG, Čelutkienė J, Bestetti R, Cavusoglu Y, et al. Heart and brain interaction in patients with heart failure: overview and proposal for a taxonomy. A position paper from the Study Group on Heart and brain interaction of the Heart Failure Association. Eur J Heart Fail [Internet]. 2018 [cited 2019 Sep 15];20:199–215. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29280256
31. Yanai H. Thyroid hormone and dementia. J Endocrinol Metab [Internet]. 2019 [cited 2019 Sep 18];9:81. Available from: https://jofem.org/index.php/jofem/article/view/592/284284375#R06
32. Kneale BJ, Chowienczyk PJ, Brett SE, Coltart DJ, Ritter JM. Gender differences in sensitivity to adrenergic agonists of forearm resistance vasculature. J Am Coll Cardiol [Internet]. J Am Coll Cardiol; 2000 [cited 2019 Sep 18];36:1233–8. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0735109700008494
33. Barnes JN, Matzek LJ, Charkoudian N, Joyner MJ, Curry TB, Hart EC. Association of cardiac baroreflex sensitivity with blood pressure transients: influence of sex and menopausal status. Front Physiol [Internet]. Frontiers; 2012 [cited 2019 Sep 18];3:187. Available

from: http://journal.frontiersin.org/article/10.3389/fphys.2012.00187/abstract
34. Davis SN, Galassetti P, Wasserman DH, Tate D. Effects of gender on neuroendocrine and metabolic counterregulatory responses to exercise in normal man. J Clin Endocrinol Metab [Internet]. 2000 [cited 2019 Sep 18];85:224–30. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10634391
35. Bartelink ML, De Wit A, Wollersheim H, Theeuwes A, Thien T. Skin vascular reactivity in healthy subjects: influence of hormonal status. J Appl Physiol [Internet]. 1993 [cited 2019 Sep 18];74:727–32. Available from: https://www.physiology.org/doi/10.1152/jappl.1993.74.2.727
36. Davis SN, Shavers C, Costa F. Differential gender responses to hypoglycemia are due to alterations in CNS drive and not glycemic thresholds. Am J Physiol Metab [Internet]. 2000 [cited 2019 Sep 18];279:E1054–63. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11052960
37. Jones PP, Snitker S, Skinner JS, Ravussin E. Gender differences in muscle sympathetic nerve activity: effect of body fat distribution. Am J Physiol [Internet]. American Physiological Society Bethesda, MD; 1996 [cited 2019 Sep 14];270:E363–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8779960
38. Mehta LS, Beckie TM, DeVon HA, Grines CL, Krumholz HM, Johnson MN, et al. Acute myocardial infarction in women. Circulation [Internet]. 2016 [cited 2019 Sep 18];133:916–47. Available from: https://www.ahajournals.org/doi/10.1161/CIR.0000000000000351
39. Du X, Cox HS, Dart AM, Esler MD. Sympathetic activation triggers ventricular arrhythmias in rat heart with chronic infarction and failure. Cardiovasc Res [Internet]. Narnia; 1999 [cited 2019 Sep 18];43:919–29. Available from: https://academic.oup.com/cardiovascres/article-lookup/doi/10.1016/S0008-6363(99)00139-X
40. McEwen BS, Akama KT, Spencer-Segal JL, Milner TA, Waters EM. Estrogen effects on the brain: actions beyond the hypothalamus via novel mechanisms. Behav Neurosci. [Internet]. NIH Public Access; 2012 [cited 2019 Sep 18];126:4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22289042
41. Kopp J, Collin O, Villar M, Mullins D, Bergh A, Hökfelt T. Regulation of neuropeptide Y Y1 receptors by testosterone in vascular smooth muscle cells in rat testis. Neuroendocrinology [Internet]. Karger Publishers; 2008 [cited 2019 Sep 18];88:216–26. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18535365
42. Gollapudi L, Oblinger MM. Estrogen and NGF synergistically protect terminally differentiated, ERα-transfected PC12 cells from apoptosis. J Neurosci Res [Internet]. John Wiley & Sons, Ltd; 1999 [cited 2019 Sep 18];56:471–81. Available from: http://doi.wiley.com/10.1002/%28SICI%291097-4547%2819990601%2956%3A5%3C471%3A%3AAID-JNR3%3E3.0.CO%3B2-1
43. Thackeray JT, Hupe HC, Wang Y, Bankstahl JP, Berding G, Ross TL, et al. Myocardial inflammation predicts remodeling and neuroinflammation after myocardial infarction. J Am Coll Cardiol [Internet]. 2018 [cited 2019 Sep 18];71:263–75. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29348018
44. Anrather J, Iadecola C. Inflammation and stroke: an overview. Neurotherapeutics [Internet]. Springer; 2016 [cited 2019 Sep 18];13:661–70. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27730544
45. Pendlebury ST, Rothwell PM. Prevalence, incidence, and factors associated with pre-stroke and post-stroke dementia: a systematic review and meta-analysis. Lancet Neurol [Internet]. Elsevier; 2009 [cited 2019 Sep 18];8:1006–18. Available from: https://www.sciencedirect.com/science/article/abs/pii/S1474442209702364
46. Mattina GF, Van Lieshout RJ, Steiner M. Inflammation, depression and cardiovascular disease in women: the role of the immune system across critical reproductive events. Ther Adv Cardiovasc Dis [Internet]. 2019 [cited 2019 Sep 15];13:175394471985195. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31144599
47. Chen Z, Venkat P, Seyfried D, Chopp M, Yan T, Chen J. Brain-heart interaction: cardiac complications after stroke. Circ Res [Internet]. NIH Public Access; 2017 [cited 2019 Sep 15];121:451–68. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28775014
48. Felder RB. Mineralocorticoid receptors, inflammation and sympathetic drive in a rat model of systolic heart failure. Exp Physiol [Internet]. NIH Public Access; 2010 [cited 2019 Sep 15];95:19–25. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19648480
49. Bellinger DL, Millar BA, Perez S, Carter J, Wood C, ThyagaRajan S, et al. Sympathetic modulation of immunity: relevance to disease. Cell Immunol [Internet]. 2008 [cited 2019 Sep 15];252:27–56. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18308299
50. Gilliver SC. Sex steroids as inflammatory regulators. J Steroid Biochem Mol Biol [Internet]. 2010 [cited 2019 Sep 18];120:105–15. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20045727
51. Straub RH. The complex role of estrogens in inflammation. Endocr Rev [Internet]. 2007 [cited 2019 Sep 15];28:521–74. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17640948
52. Fairweather D. Sex differences in inflammation during atherosclerosis. Clin Med Insights Cardiol [Internet]. Sage Publications; 2014 [cited 2019 Sep 15];8:49–59. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25983559
53. Dolsen MR, Crosswell AD, Prather AA. Links between stress, sleep, and inflammation: are there sex differences? Curr Psychiatry Rep [Internet]. 2019 [cited 2019 Sep 15];21:8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30729328
54. Jefferson AL, Massaro JM, Wolf PA, Seshadri S, Au R, Vasan RS, et al. Inflammatory biomarkers are associated with total brain volume: the Framingham Heart Study. Neurology [Internet]. 2007 [cited 2019 Sep 15];68:1032–8. Available from: http://www.neurology.org/cgi/doi/10.1212/01.wnl.0000257815.20548.df

55. Woo MA, Kumar R, Macey PM, Fonarow GC, Harper RM. Brain injury in autonomic, emotional, and cognitive regulatory areas in patients with heart failure. J Card Fail [Internet]. 2009 [cited 2019 Sep 18];15:214–23. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19327623
56. Scantlebury DC, Borlaug BA. Why are women more likely than men to develop heart failure with preserved ejection fraction? Curr Opin Cardiol [Internet]. 2011 [cited 2019 Sep 15];26:562–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21993357
57. Silva RMFL Da, Miranda CM, Liu T, Tse G, Roever L. Atrial fibrillation and risk of dementia: epidemiology, mechanisms, and effect of anticoagulation. Front Neurosci [Internet]. Frontiers Media SA; 2019 [cited 2019 Sep 15];13:18. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30766470
58. Heeringa J, van der Kuip DAMM, Hofman A, Kors JA, van Herpen G, Stricker BHCC, et al. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. Eur Heart J [Internet]. Narnia; 2006 [cited 2016 Apr 20];27:949–53. Available from: https://academic.oup.com/eurheartj/article/27/8/949/2887153
59. Golive A, May HT, Bair TL, Jacobs V, Crandall BG, Cutler MJ, et al. The impact of gender on atrial fibrillation incidence and progression to dementia. Am J Cardiol [Internet]. 2018 [cited 2019 Sep 15];122:1489–95. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30195396
60. Hare DL, Toukhsati SR, Johansson P, Jaarsma T. Depression and cardiovascular disease: a clinical review. Eur Heart J [Internet]. Narnia; 2014 [cited 2019 Sep 18];35:1365–72. Available from: https://academic.oup.com/eurheartj/article-lookup/doi/10.1093/eurheartj/eht462
61. Nemeroff CB, Goldschmidt-Clermont PJ. Heartache and heartbreak – the link between depression and cardiovascular disease. Nat Rev Cardiol [Internet]. Nature Publishing Group; 2012 [cited 2019 Sep 15];9:526–39. Available from: http://www.nature.com/articles/nrcardio.2012.91
62. Carney RM, Freedland KE. Depression and coronary heart disease. Nat Rev Cardiol [Internet]. Nature Publishing Group; 2017 [cited 2019 Sep 15];14:145–55. Available from: http://www.nature.com/articles/nrcardio.2016.181
63. Gan Y, Gong Y, Tong X, Sun H, Cong Y, Dong X, et al. Depression and the risk of coronary heart disease: a meta-analysis of prospective cohort studies. BMC Psychiatry [Internet]. BioMed Central; 2014 [cited 2019 Sep 15];14:371. Available from: http://bmcpsychiatry.biomedcentral.com/articles/10.1186/s12888-014-0371-z
64. Whang W, Kubzansky LD, Kawachi I, Rexrode KM, Kroenke CH, Glynn RJ, et al. Depression and risk of sudden cardiac death and coronary heart disease in women. J Am Coll Cardiol [Internet]. 2009 [cited 2019 Sep 15];53:950–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19281925
65. Wyman L, Crum RM, Celentano D. Depressed mood and cause-specific mortality: a 40-year general community assessment. Ann Epidemiol [Internet]. NIH Public Access; 2012 [cited 2019 Sep 15];22:638–43. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22835415
66. Clouse RE, Lustman PJ, Freedland KE, Griffith LS, McGill JB, Carney RM. Depression and coronary heart disease in women with diabetes. Psychosom Med [Internet]. 2003 [cited 2019 Sep 15];65:376–83. Available from: https://insights.ovid.com/crossref?an=00006842-200305000-00009
67. Shanmugasegaram S, Russell KL, Kovacs AH, Stewart DE, Grace SL. Gender and sex differences in prevalence of major depression in coronary artery disease patients: a meta-analysis. Maturitas [Internet]. Elsevier; 2012 [cited 2019 Sep 15];73:305–11. Available from: https://www.sciencedirect.com/science/article/abs/pii/S0378512212002794
68. Doyle F, McGee H, Conroy R, Conradi HJ, Meijer A, Steeds R, et al. Systematic review and individual patient data meta-analysis of sex differences in depression and prognosis in persons with myocardial infarction. Psychosom Med [Internet]. 2015 [cited 2019 Sep 15];77:419–28. Available from: https://insights.ovid.com/crossref?an=00006842-201505000-00009
69. Naqvi TZ, Naqvi SSAA, Merz CNB. Gender differences in the link between depression and cardiovascular disease. Psychosom Med [Internet]. Lippincott Williams and Wilkins; 2005 [cited 2016 Oct 22];67 Suppl 1:S15–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15953793
70. Shah AJ, Ghasemzadeh N, Zaragoza-Macias E, Patel R, Eapen DJ, Neeland IJ, et al. Sex and age differences in the association of depression with obstructive coronary artery disease and adverse cardiovascular events. J Am Heart Assoc [Internet]. 2014 [cited 2019 Sep 15];3:e000741. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24943475
71. Sara JD, Prasad M, Eleid MF, Zhang M, Widmer RJ, Lerman A. Association between work-related stress and coronary heart disease: a review of prospective studies through the job strain, effort-reward balance, and organizational justice models. J Am Heart Assoc [Internet]. 2018 [cited 2019 Sep 15];7. Available from: https://www.ahajournals.org/doi/10.1161/JAHA.117.008073
72. Orth-Gomér K, Wamala SP, Horsten M, Schenck-Gustafsson K, Schneiderman N, Mittleman MA. Marital stress worsens prognosis in women with coronary heart disease. JAMA [Internet]. 2000 [cited 2019 Sep 15];284:3008. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11122587
73. Nabi H, Kivimaki M, De Vogli R, Marmot MG, Singh-Manoux A, Whitehall II Prospective Cohort Study. Positive and negative affect and risk of coronary heart disease: Whitehall II Prospective Cohort Study. BMJ [Internet]. British Medical Journal Publishing Group; 2008 [cited 2019 Sep 15];337:a118. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18595926

74. Low CA, Thurston RC, Matthews KA. Psychosocial factors in the development of heart disease in women: current research and future directions. Psychosom Med [Internet]. NIH Public Access; 2010 [cited 2019 Sep 15];72:842–54. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20841557
75. Wang H-X, Mittleman MA, Leineweber C, Orth-Gomer K. Depressive symptoms, social isolation, and progression of coronary artery atherosclerosis: the Stockholm Female Coronary Angiography Study. Psychother Psychosom [Internet]. 2006 [cited 2019 Sep 15];75:96–102. Available from.: http://www.ncbi.nlm.nih.gov/pubmed/16508344
76. Lyon AR, Bossone E, Schneider B, Sechtem U, Citro R, Underwood SR, et al. Current state of knowledge on Takotsubo syndrome: a position statement from the taskforce on Takotsubo syndrome of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail [Internet]. John Wiley & Sons, Ltd; 2016 [cited 2019 Sep 18];18:8–27. Available from: http://doi.wiley.com/10.1002/ejhf.424
77. Nguyen HL, Gore JM, Saczynski JS, Yarzebski J, Reed G, Spencer FA, et al. Age and sex differences and 20-year trends (1986 to 2005) in prehospital delay in patients hospitalized with acute myocardial infarction. Circ Cardiovasc Qual Outcomes [Internet]. 2010 [cited 2016 Dec 31];3:590–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20959564
78. Seidler ZE, Rice SM, Ogrodniczuk JS, Oliffe JL, Shaw JM, Dhillon HM. Men, masculinities, depression: implications for mental health services from a Delphi Expert Consensus Study. Prof Psychol Res Pract [Internet]. 2019 [cited 2019 Sep 17];50:51–61. Available from: http://doi.apa.org/getdoi.cfm?doi=10.1037/pro0000220
79. Ruiz-Pizarro V, Ferrera C, Gómez-Polo JC, Palacios-Rubio J, Rico-García Amado C, Fernández-Ortiz A, et al. Sex differences in treatment and prognosis of acute coronary syndrome with interventional management. Cardiovasc Revasc Med [Internet]. Elsevier; 2019 [cited 2019 Sep 17];20:183–6. Available from: https://www.sciencedirect.com/science/article/pii/S1553838918302707
80. Haimi I, Lee HJ, Mehta S, Salwan R, Zambahari R, Chen Y, et al. CRT-200.92 Gender disparities in ST-elevation myocardial infarction care and outcomes in emerging countries: a Global Lumen Organization for Women (GLOW) initiative and call to action. JACC Cardiovasc Interv [Internet]. J Am Coll Cardiol; 2016 [cited 2016 Oct 22];9:S31. Available from: http://linkinghub.elsevier.com/retrieve/pii/S1936879815021123
81. De Feo S, Tramarin R, Ambrosetti M, Riccio C, Temporelli PL, Favretto G, et al. Gender differences in cardiac rehabilitation programs from the Italian survey on cardiac rehabilitation (ISYDE-2008). Int J Cardiol [Internet]. 2012 [cited 2019 Sep 17];160:133–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21531469
82. Thompson LE, Maddox TM, Lei L, Grunwald GK, Bradley SM, Peterson PN, et al. Sex differences in the use of oral anticoagulants for atrial fibrillation: a report from the National Cardiovascular Data Registry (NCDR®) PINNACLE registry. J Am Heart Assoc [Internet]. 2017 [cited 2019 Sep 17];6. Available from: https://www.ahajournals.org/doi/10.1161/JAHA.117.005801
83. Mohanty S, Trivedi C, Gianni C, Natale A. Gender specific considerations in atrial fibrillation treatment: a review. Expert Opin Pharmacother [Internet]. 2018 [cited 2019 Sep 17];19:365–74. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29424249
84. Baumhäkel M, Müller U, Böhm M. Influence of gender of physicians and patients on guideline-recommended treatment of chronic heart failure in a cross-sectional study. Eur J Heart Fail [Internet]. John Wiley & Sons, Ltd; 2009 [cited 2019 Sep 17];11:299–303. Available from: http://doi.wiley.com/10.1093/eurjhf/hfn041
85. Canevelli M, Quarata F, Remiddi F, Lucchini F, Lacorte E, Vanacore N, et al. Sex and gender differences in the treatment of Alzheimer's disease: a systematic review of randomized controlled trials. Pharmacol Res [Internet]. Academic Press; 2017 [cited 2019 Sep 17];115:218–23. Available from: https://www.sciencedirect.com/science/article/abs/pii/S1043661816307538
86. Kristofferzon M-L, Lofmark R, Carlsson M. Myocardial infarction: gender differences in coping and social support. J Adv Nurs [Internet]. 2003 [cited 2019 Sep 15];44:360–74. Available from: http://www.ncbi.nlm.nih.gov/pubmed/14651708
87. Lewey J, Shrank WH, Bowry ADK, Kilabuk E, Brennan TA, Choudhry NK. Gender and racial disparities in adherence to statin therapy: A meta-analysis. Am Heart J [Internet]. Mosby; 2013 [cited 2019 Sep 17];165:665–78.e1. Available from: https://www.sciencedirect.com/science/article/abs/pii/S0002870313001385
88. Tang L, Patao C, Chuang J, Wong ND. Cardiovascular risk factor control and adherence to recommended lifestyle and medical therapies in persons with coronary heart disease (from the National Health and Nutrition Examination Survey 2007–2010). Am J Cardiol [Internet]. Excerpta Medica; 2013 [cited 2019 Sep 18];112:1126–32. Available from: https://www.sciencedirect.com/science/article/abs/pii/S0002914913012897
89. Nieuwenhuis MMW, Jaarsma T, van Veldhuisen DJ, Postmus D, van der Wal MHL. Long-term compliance with nonpharmacologic treatment of patients with heart failure. Am J Cardiol [Internet]. Excerpta Medica; 2012 [cited 2019 Sep 17];110:392–7. Available from: https://www.sciencedirect.com/science/article/abs/pii/S0002914912010557
90. Chung ML, Moser DK, Lennie TA, Worrall-Carter L, Bentley B, Trupp R, et al. Gender differences in adherence to the sodium-restricted diet in patients with heart failure. J Card Fail [Internet]. 2006 [cited 2019 Sep 17];12:628–34. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17045182

91. Rivero-Santana A, Perestelo-Perez L, Pérez-RamosJ, Serrano-Aguilar P, De Las Cuevas C. Socio-demographic and clinical predictors of compliance with antidepressants for depressive disorders: systematic review of observational studies. Patient Prefer Adherence [Internet]. Dove Press; 2013 [cited 2019 Sep 18];7:151–69. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23487319
92. Demyttenaere K. Compliance and acceptance in antidepressant treatment. Int J Psychiatry Clin Pract [Internet]. 2001 [cited 2019 Sep 18];5:29–35. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24936994

Vascular Risk Factors and Cognitive Function

60

The Effect of Aging Process

Enrico Mossello and Niccolò Marchionni

Contents

Abstract

During the last 20 years, several epidemiological and experimental studies have linked vascular risk factors with cognitive decline and dementia, including Alzheimer's disease, in old age. Yes, this association changes across lifetime. In fact, high blood pressure and obesity at midlife have been associated with greater age-associated cognitive decline,

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*,
https://doi.org/10.1007/978-3-030-28008-6_62

while dementia onset in old age is often heralded by lowering of blood pressure and body mass index. Part of this seemingly paradoxical association can be explained by reverse causation, as damage of specific brain areas can impair blood pressure (insula, amygdala) and fat mass (hypothalamus) control. On the other hand, autonomic nervous system dysfunction, mainly age-associated baroreflex response impairment and orthostatic hypotension, may have a pathogenic role in brain damage. Other vascular risk factors maintain their cognitive prognostic role lifelong, harmful for insulin resistance and protective for aerobic physical activity. Age-associated loss of muscle mass (sarcopenia) can contribute to insulin resistance, resulting in faster neurodegeneration, and, conversely, accumulation of neuropathological lesion has been associated with muscle mass decline over time. Pharmacological treatment of vascular risk factors at midlife is warranted to prevent cognitive decline, but should be less aggressive in older, cognitively impaired patients, more vulnerable to adverse events. Physical activity should be recommended lifelong, both as primary prevention and as adjuvant treatment in dementia.

Keywords

Hypertension · Obesity · Overweight · Diabetes mellitus · Insulin resistance · Exercise · Physical activity · Dementia · Mild cognitive impairment (MCI) · Aging

Introduction

The dramatic expansion of the older population that occurred mainly in developed countries over the last decades has led to an increased prevalence of age-associated cognitive impairment and dementia. According to the World Alzheimer Report [1], 47 million people were living with dementia worldwide in 2015, with about 10 million new cases every year, estimated as 1 new case every 3 s. Dementia prevalence among the 900 million subjects aged 60+ years worldwide is about 5% and increases exponentially with age, doubling every 5 years, with a prevalence peaking to 25–30% in subjects aged 85+ years. The number of cases is expected to almost double during the next 20 years, with most future cases expected to arise in middle- and low-income countries. Dementia obviously has a profound negative impact on functional competence and life expectancy of affected subjects, causes a huge care burden on their families, and impacts with direct and indirect costs on the society as a whole. Global costs associated with dementia were estimated US$ 818 billion in 2015, representing about 1% of global gross domestic product [1].

Unfortunately, no curative treatment is yet available for Alzheimer's disease (AD) that, as the sole cause or together with other pathologic conditions, contributes to the genesis of 50–75% of dementia cases [2]. In this context, the identification of potentially modifiable factors is being increasingly recognized as a public health priority, with the aim of preventing or delaying the onset of new cases and therefore limiting the forecasted increase in the incidence of cognitive disorders. Indeed, about half of dementia cases in the world have been attributed to potentially modifiable risk factors [3]. Several European and American population-based cohort studies recently have given support to the preventive approach, showing in fact that the age-specific incidence and prevalence of dementia has decreased over the past 20 years [4]. Therefore, while no single risk or protective factor has been identified that fully explains the observed trends, a primary prevention process seems actually ongoing, with improvements in living conditions, education, and healthcare claimed as the main protective factors of cognitive health throughout life course [4].

During the last two decades, many epidemiological and experimental studies have proven that the association of vascular risk factors (VRF) with cognitive impairment may be mediated by the development of not only vascular but also neurodegenerative pathology [5]. On the other hand, neuropathological features of AD often coexist with vascular damage particularly in older dementia cases, with both pathologies synergistically

contributing to cognitive decline [6]. Three of the classical VRF, namely, high blood pressure (HBP), diabetes (DM), and obesity, are presently regarded as potentially modifiable risk factors involved in the pathogenesis of cognitive disorders [3], and a fourth one, physical inactivity, is strictly associated with them.

Yet, it has to be highlighted that the increased dementia risk associated with VRF is typically observed during life course and that, compared to cardiovascular events (stroke, myocardial infarction, heart failure), a longer exposure time is necessary to observe the association. In fact, midlife exposure is more strongly associated with increased risk of later cognitive decline and dementia than late life exposure [5, 7]. In accordance with this observation, the CAIDE score has been validated to estimate the 20-year risk of dementia, based on presence of VRF at midlife [8]. Yet, in a life-course perspective, the association of VRF with cognitive impairment seems sometimes reverted in the oldest old, as is the case for obesity and possibly for HBP, as discussed below.

The time-dependent direction of the association is further complicated by the fact that, through the autonomic nervous system, specific brain areas have a role in the control of the cardiovascular system, including blood pressure (BP), and that alterations of the autonomic control may in turn increase the risk of cognitive decline [9]. Evidence regarding the role of altered autonomic control in determining cognitive decline will be discussed below, although a "reverse causation" is also likely to occur, as neurodegeneration and vascular brain damage also have been identified as concurrent causes of autonomic impairment [9].

Therefore, the role of VRF in predicting the risk of cognitive decline, including the risk-to-benefit ratio of their treatment, is likely to be strongly age-dependent. In keeping with previously cited data [10], a cut-off can be identified around the age of 80, with 80+ subjects deserving a different approach to the prevention of cognitive decline through the management of VRF. Moreover, management should probably differ between cognitively intact subjects (*primary prevention*) and those who already show some degree of cognitive decline (*secondary prevention*). In this latter group, it is of paramount importance to further separate cases with mild cognitive impairment (MCI) from those with overt dementia. MCI affects 10–20% of older subjects, is characterized by a mild impairment of one or more cognitive domains without an overt impact on everyday functioning, can be stable over time or even revert, and only in some cases represents the prodromal phase of a subsequent dementia [11]. Conversely, dementia is defined by persistent and multiple cognitive-behavioral disorders with a decline in everyday functioning [12], and typically progresses from phases of mild impairment to severe disability. In every stage of cognitive impairment, from MCI to severe dementia, secondary prevention approaches are conceivable, although targets and intensity of treatment should again be reasonably different, as discussed in the last section of the chapter.

Vascular Risk Factor and Cognitive Damage: Epidemiologic Association During Life Course

Arterial Hypertension

Since the 1990s, several studies have identified an association between BP values and cognitive decline and/or dementia [13]. Although with moderately heterogeneous results, several longitudinal studies with over 20 years of follow-up, including the Honolulu-Asia Aging Study [14] and the Finnish CAIDE [15], have observed that HBP at midlife is associated with an increased risk of cognitive decline and dementia, including AD, in late life. Consistently, in the US Atherosclerosis Risk in Communities cohort, a dose-response relationship was observed between systolic blood pressure (SBP) at midlife, especially in untreated hypertensives, and a composite score of cognitive deterioration over a 20-year follow-up. Of notice, no association was observed between BP at the end of follow-up and cognitive decline [16]. This observation confirms the pioneering results published by Skoog et al. in

1996 [17], showing for the first time, in subjects aged 70 at enrolment, that HBP at baseline was associated with a 15-year higher risk of not only vascular but also of AD dementia. Yet, those developing dementia at follow-up showed a greater BP decline over time, and low BP at follow-up was associated with a more severe brain atrophy [18]. Subsequent lifetime studies, which have followed BP and cognitive function trajectories for over 30 years, have confirmed this bimodal association, as subjects developing dementia had higher BP values until the age of 75, especially if not receiving antihypertensive drugs, and then showed a sharper BP decline than those maintaining a normal cognitive function [19].

These data explain the reason of the inconsistent association observed in late life between BP values and cognitive function and suggest that the "window of opportunity" for antihypertensive treatment preventing subsequent cognitive decline possibly ranges from midlife to "young old" age. In fact, the predictive role of BP for cognitive decline and AD at older ages is more uncertain, and several data, including a meta-analysis [20], suggest that it is possibly reverted. Comparing the data from two Dutch epidemiological studies, an association between HBP and cognitive decline after an 11-year follow-up has been observed for subjects aged 65–75, while the reverse association has been observed for subjects aged 85+ after 5 years [21]. Biological aging and functional status might modulate the BP-cognition association in old age. Indeed, in subjects aged 85+ years, the protective effect of higher BP on cognition seems particularly evident among subjects who already showed a baseline disability in activities of daily living [22].

This observation is consistent with the hypothesis that in the presence of physical frailty, a less stringent BP target might preserve brain perfusion, a concept reinforced by a recent joint statement of the European Society of Hypertension and the European Union Geriatric Medicine Society [23]. Evidence for beneficial effects and possible harms of antihypertensive treatment is discussed in the last section of the chapter.

Diabetes Mellitus

Only few studies have addressed the cognitive outcome of type 1 diabetes mellitus (DM), a condition of absolute lack of insulin secretion, often arising in young age subjects, who may have a mildly decreased cognitive function lifetime, but do not show an increased risk of clinically relevant cognitive decline. Conversely, several longitudinal and cross-sectional studies have associated the condition of insulin resistance, and its full-blown expression represented by type 2 DM (T2DM), with a higher risk of cognitive decline and dementia [24, 25]. This association seems largely independent of other VRF associated with T2DM and is supported not only by more severe white matter changes but also by more severe atrophy in areas that are strategic for onset of AD, such as mesial temporal structures (hippocampus, amygdala) [26], apparently explaining the higher risk of incident cognitive decline in T2DM patients [5].

Different from HBP, the association of T2DM with reduced cognitive performance can be observed in a reproducible fashion also in cross-sectional studies and apparently includes the full spectrum of cognitive impairment: from subjective cognitive impairment, to MCI not necessarily prone to further deterioration, up to overt dementia, including AD, vascular dementia, and mixed forms [25]. Again different from HBP, which represents a risk factors for cognitive decline mainly at midlife, hyperglycemia and T2DM seem to retain their predictive role for cognitive impairment also in old age and after relatively short follow-up [7]. This is confirmed by the observation that even a new diagnosis of T2DM in "young old" subjects is associated with a greater 10-year risk of dementia, at least in subsets with clinical atherosclerosis and chronic kidney disease [27].

Moreover, a clear association with AD risk has been observed for older subjects with MCI who also show T2DM [28]. Potentially relevant to the clinical practice, the coexistence of other VRF, the presence of micro- and macrovascular complications, and a poor glycometabolic control, all have been associated with a worse cognitive

functioning in T2DM, especially for memory, attention, and executive functions [29].

Obesity

Consistently with studies showing an association of HBP, T2DM, and atherosclerotic disease with dementia, several longitudinal studies have tested the association between obesity and risk of dementia. While several studies have observed an association between midlife obesity and increased dementia risk in old age, others, including the largest one with more than 2,000,000 subjects, did not confirm this association. Rather, in the abovementioned study, overweight and obesity were overall protective against the risk of dementia [30]. In a recent meta-analysis of all available longitudinal studies, a global association between greater body mass index (BMI) and lower dementia risk has been observed, but with a large heterogeneity according to length of follow-up. Indeed, excluding studies with shorter follow-ups, the association between BMI and risk of dementia changed in a stepwise manner, with risk of dementia increasing for greater BMI when follow-up was 20 years or longer [31]. Consistently, in a different meta-analysis, obesity and overweight were risk factors for incident dementia in subjects younger than 65, whereas they resulted to be protective in older individuals [32]. Moreover, a greater weight loss over a 20-year period from midlife to late life was associated with increased incident MCI cases [33]. Finally, in a sample of older subjects (mean age 75) included in a research on AD biomarkers, fewer overweight subjects with no cognitive impairment or MCI had a biomarker pattern suggestive of AD [34].

Together, these data strongly suggest that midlife overweight and obesity are true dementia risk factors after 20 years or more, but that weight loss precede dementia onset, possibly over a long pre-symptomatic period, leading to an apparent protective effect of overweight and obesity during the years preceding dementia. It has been hypothesized that weight loss might be a non-cognitive sign of pre-symptomatic AD [35] and that the protective association between overweight and BMI might be a case of reverse causation [31]. Part of this mechanism can be explained by changes in the neural control of energy expenditure, as it will be discussed below.

Physical Inactivity

The role of physical inactivity in the pathogenesis of several chronic conditions, especially cardiovascular diseases, and of physical activity (PA) as a factor promoting successful aging is well known. During the last 15 years, several evidence have accumulated regarding the possible neuroprotective role of PA during lifetime, both in primary and in secondary prevention [36]. Of notice, among potentially modifiable dementia risk factors, inactivity was identified as the single factor with greater attributable risk, accounting for as many as 12.7% of dementia diagnoses [3]. Systematic reviews and meta-analysis of observational studies have identified a global protective effect of PA against the risk of cognitive decline and dementia [37], including AD [38]. A high heterogeneity is present for baseline age, follow-up duration, activity assessment instruments, and covariates included as adjustment factors. Generally speaking, the protective association seems stronger in studies with a follow-up shorter than 10 years, thus making the case for reverse causation, i.e., physical activity might decrease some years before dementia diagnosis due to prodromal disease [37]. Therefore, long-term studies might be more informative, yet heterogeneity of results exists. In fact, PA at midlife has been identified as a protective factors for dementia, including AD, after a 20-year follow-up in the CAIDE cohort [39]. As an additional factor, irrespectively of midlife assessment, maintaining or increasing PA level during follow-up was associated with a decreased risk of dementia and AD at follow-up [40]. Nonetheless, a subsequent 27-year follow-up study in the UK observed that the association between greater PA and lower dementia risk was limited to the last 10 years before diagnosis, suggesting that reverse causation might play a major role in the observed

association [41]. Yet, studies including biomarkers, especially neuroradiological ones, support the pathophysiological plausibility of the observed association. In fact, PA at midlife has been associated with brain atrophy, and extent of white matter changes at follow-up [36]. Moreover, several cross-sectional studies have shown an association between engagement in PA, cardiorespiratory fitness, and neuroradiological measures of gray matter atrophy and white matter changes [42]. Of notice, the protective effect of PA might be specific for brain areas most often associated with age-associated loss, and, from a statistical standpoint, this was more evident when analyzed as an interaction with age [42]. Moreover, in a group of midlife subjects with high polygenic dementia risk but who were free of cognitive impairment, higher level of cardiorespiratory fitness were associated with lower levels of AD biomarkers in the cerebrospinal fluid [43].

Overall, the available data identify inactivity as a risk factor for age-related cognitive decline, beyond the effect of associated VRF, and lifelong PA as a protective agent reducing the risk of cognitive decline and dementia. In contrast with HBP and obesity, the protective effect of intense PA seems to extend over the whole lifespan, and might be even more evident in older subjects and in subjects with higher risk of neurodegeneration.

Aging, Brain Damage, and Vascular Risk Factors: Pathophysiological Link

Aging, Vascular Changes, and Cognition: Focus on Vascular Stiffness

A part of the negative effect of VRF on cognition might well be explained by increased risk of cerebrovascular disease that has been identified for HBP, T2DM, and obesity. This risk includes both stroke due to atherosclerosis or to cardioembolic events secondary to atrial fibrillation (whose risk is increased at least by advanced age, HPB, and obesity) and microvascular brain pathology leading to lacunar infarcts and white matter lesions (WMLs). Both conditions can be the pathogenic factors of vascular dementia [44] and contribute to the genesis of mixed dementia, mainly AD with associated cerebrovascular disease, which represents the most common form of dementia in the oldest old [6].

However, other age-associated vascular changes can lead to brain damage and increased risk of cognitive dysfunction. The most important of such mechanisms is represented by the age-associated increase in large arteries stiffness, caused by degeneration of elastin fibers, which progressively affects pulse wave propagation along the arterial bed and is typically enhanced by the coexistence of VRF, including HBP, T2DM, and obesity [45]. In young adults, the aorta is highly compliant compared with its first-order branches. When the pulse wave encounters such impedance discontinuity, a portion of the pulsatile energy stored in that wave is not transmitted into the distal vessels but is reflected back to the heart, thus protecting them from the transmission of excessive pulsatility into the microcirculation. Increased age-associated aortic stiffness reduces the reflected wave and increases the transmission of pulsatile energy further into the periphery and microcirculation, including the brain [46].

Moreover the speed of reflected waves, known as pulse wave velocity, increases as a function of arterial stiffness. When pulse wave velocity increases, the reflected pressure waves are anticipated from the diastolic to the systolic period, and thus augment central SBP, which is directly transmitted to brain circulation. Increased brain BP pulsatility may induce microvascular changes with consequent impaired autoregulation of blood flow and tissue damage due to hypoperfusion [47].

In a cross-sectional study, increased aortic stiffness and pulse wave velocity were associated with greater prevalence of subcortical brain infarcts, increased extension of WMLs, lower gray and white matter volumes, and worse cognitive performance in the domains of memory, processing speed, and executive functions [46]. Subsequent studies have associated increased vascular stiffness also to age-associated brain amyloid deposition in cognitively normal individuals, as measured with PET [48]. In a different study, greater aortic stiffness was also associated with lower brain volumes in AD-susceptible regions,

especially the precuneus, more severe WMLs, and a higher risk of odds of concomitant WMLs and amyloid deposition at PET scan [49]. The latter association might be explained by a disrupted transport of amyloid fragments out of the brain, with increased vascular stiffness being the common link to the two pathophysiological distinct pathways of amyloid-associated neurodegeneration and microvascular damage [49].

The clinical relevance of aortic stiffness is confirmed by longitudinal data from the Framingham Offspring cohort (mean age 69), showing that increased stiffness is associated with increased 10-year risk of incident MCI, dementia, and AD. While part of the effect is explained by associated VRF, in multivariate models aortic stiffness remains independently associated with dementia risk, thus suggesting that this pathogenic process might act independently of other VRF. Conversely, in the same study, pulse pressure failed to reach statistical significance in predicting MCI and dementia risk [50]. This suggests that vascular stiffness has probably a larger predictive role on dementia risk than BP values per se.

Aging, Neural Blood Pressure Control and Cognition: Baroreceptor Function, Orthostatic Hypotension

As previously discussed, structural vascular change may affect brain function. A large amount of research is also available regarding neural control of vascular function, and how this can be modified during physiological aging and in pathological conditions. Some of these changes have been clearly associated with cognitive function, although the causal pathway of the association is often unclear. In fact, brain aging and neurodegeneration may obviously affect the autonomic function, but on the other hand impaired vascular control may produce subtle brain damage, ultimately accelerating cognitive decline.

The aging process is characterized by typical changes in the neural control of vascular function, including increased sympathetic nerve activity, especially in women, associated with increased vascular resistance, contributing to age-associated BP increase [51]. The baroreflex sensitivity is often decreased, contributing on one hand to increased BP and on the other to diminished heart rate and BP homeostatic regulation in response to stand-up and other stressors. In fact a decreased parasympathetic tone is associated with less vagal withdrawal on standing, resulting in reduced cardioacceleration and orthostatic hypotension on brisk standing [9, 52].

Moreover, decreased parasympathetic tone results in age-associated alteration of sympathovagal balance with consequent reduced heart variability. This alteration is typically enhanced in pathological conditions, such as obesity, obstructive sleep apnea, coronary artery disease, and heart failure, and represents a negative prognostic marker, including increased risk factor for sudden cardiac death [51].

All the cited parameters have been associated also with cognitive function. Specifically, impaired baroreflex sensitivity has been associated with greater impairment of cognitive function in a sample of subjects aged 67, and its decrease over an 8-year follow-up was associated with a parallel decrease of memory function [53]. Moreover, baroreceptor reflex was reduced in a sample of AD patients in comparison with age-matched controls, thus leading to preliminary suggestion of its use as a biomarker for the disease [54]. In the latter study, baroreflex impairment improved with cholinesterase inhibitors treatment, in agreement with the positive role of cholinergic stimulation in autonomic balance. Reduced heart rate variability has been associated with impaired cognitive function as well. This was observed since midlife in the large CARDIA cohort (mean age 45), which showed an association between reduced heart rate variability and impaired executive functions measured 5 years later, independently of other VRF and comorbidities [55]. These data are consistent with secondary results of PROSPER study, which showed an association between reduced heart rate variability and processing speed both in the a cross-sectional analysis, at a mean age of 75, and in the longitudinal 3-year follow-up [56]. Moreover, in the PROSPER study reduced heart variability was associated with a worse global

functional outcome, in terms of disability in activities of daily living, independently of incident vascular events and baseline cognitive profile [57]. Moreover, small clinical samples of subjects with AD have shown a reduced heart rate variability in comparison with individuals with MCI who, in turn, had a lower heart rate variability than cognitively normal subjects [58]. Finally, lower heart rate variability was associated with lower cognitive function also within subjects with overt AD [59].

The most likely explanation of the observed associations is represented by disease-associated degeneration of areas controlling autonomic function. Beyond the brainstem, which directly controls sympathovagal innervation of the vascular system, autonomic nervous system activity is modulated by cortical regions, including the insula and anterior cingulate cortex, and subcortical structures, including the amygdala. Insular cortex, in particular, is a frequent site of vascular damage, and may be involved in a brain-heart axis increasing the risk of future brain vascular damage [60]. Moreover, amygdala is affected by AD neuropathology early in the neurodegenerative process (Braak stages II–III), possibly before the onset of overt cognitive impairment, and insula and anterior cingulate cortex are involved too, in a slightly later stage (Braak stages III–IV) [61]. As an alternative explanation, higher heart rate variability might be a marker of healthier cardiovascular system, which is a protective factor for brain aging and functional decline. Finally, longitudinal observation is consistent with a pathogenic role of autonomic dysfunction on cognitive decline.

The latter hypothesis has received a strong support by studies on orthostatic hypotension. In an analysis of the HYVET cohort, including relatively high-functioning subjects aged 80+ ($n = 3121$), the presence of orthostatic hypotension at baseline was associated with increased risk of cognitive decline or dementia at the 2-year follow-up, after adjusting for possible confounders [62]. Even more strikingly, in a large sample of the epidemiological ARIC study ($n = 11{,}709$), orthostatic hypotension at midlife (mean age 55) was associated with an increased risk of dementia and ischemic stroke at 25-year follow-up [63]. In the Rotterdam Study (6,204 participants mean age 69), orthostatic hypotension was associated with an increased risk of dementia at 15-year follow-up, being similar for AD and vascular dementia. Among subjects with orthostatic hypotension, the risk of dementia was highest in those who lacked the compensatory heart rate response after standing, a pattern that is typical of neurogenic orthostatic hypotension [64]. A meta-analysis of all published cohort studies estimates a significant 21% increase of dementia risk associated with orthostatic hypotension [62].

The association of orthostatic hypotension with dementia in the cited studies appears to be independent of known VRF and remains significant after exclusion of known causes of autonomic failure at baseline and of incident stroke during follow-up. Although residual confounding cannot be excluded, this finding strongly suggests that chronic brain hypoperfusion has a pathogenic role in the development of dementia, possibly inducing brain damage through hypoxia, inflammatory mechanisms, or accelerated neurodegeneration [65]. The latter hypothesis is consistent with data that have associated impaired autonomic function to hypoperfusion of the hippocampus, the initial site of neurodegeneration in AD, already at midlife [66]. Again, reverse causation cannot be excluded, but this is likely insufficient to explain all the observed association due to the long follow-up time, which in ARIC cohort [63] was even longer than the estimated presymptomatic phase of AD.

The Role of Blood Pressure Variability

Although with some inconsistence across studies, increased BP variability is typically associated with aging. Impaired baroreflex sensitivity is one of the main determinants of BP variability and has been shown to have opposite influences in resting/supine vs. stress conditions, including tilt test and mental stress. In supine conditions, impaired parasympathetic function has been associated with reduced beat-to-beat BP variability, mirroring reduced heart rate variability, while it has been associated with greater BP variability during 24-h activity [52]. Consistent with these data, heart rate

and BP variability decrease with aging when measured at rest, while they increase over the life span when assessed during sit-to-stand maneuvers. Of notice, in the same study, cerebral blood flow variability during postural changes, which represents a negative prognostic factor for cardiovascular events and mortality, is also positively correlated with aging [67].

BP fluctuations can be measured both in the short-term (e.g., beat-to-beat, or within 24 h) and over long-term fluctuations (e.g., across different days, or even months or years). They result from a complex interaction between cardiovascular regulatory mechanisms, vascular stiffness, and environmental and behavioral factors. Most importantly, several observational studies have associated BP variability with a greater risk of cardiovascular events, stroke, renal failure, cardiovascular, and total mortality, well beyond the risk associated with absolute BP values. Among variability parameters that have been studied in the last decade, visit-to-visit BP variability has shown a particularly strong predictive value for cardiovascular morbidity and mortality [68].

During last years, visit-to-visit BP variability in older subjects also has been also identified as a predictor of future onset of cognitive impairment and dementia, including AD. Neurological studies support its role as predictor of subcortical white matter changes and, to a lesser extent, cerebral atrophy [69]. It has been hypothesized that the age-associated autonomic dysfunction can result in higher BP variability and, that this, in turn, can increase arterial stiffness [70]; conversely, increased arterial stiffness can induce a further decrease of baroreflex sensitivity [71]. This can lead to a negative feedback, leading to increased brain damage, including both ischemic and neurodegenerative changes (see above). Moreover, the associated vascular remodeling can induced a further brain damage through impaired vascular autoregulation, which may facilitate hypoperfusion during hypotensive phases.

A simplified scheme of reciprocal interconnections between autonomic dysfunction, vascular remodeling, and brain damage is reported in Fig. 1.

Methods to interrupt such a negative feedback loop have been hypothesized and are discussed in the next section of the chapter. In particular, regular aerobic exercise has been associated with increased baroreflex cardiovagal response [52], reduced vascular stiffness [72], and increased cerebral blood flow among older adults [73]. Among antihypertensives, calcium-channel blockers have been identified as the most effective agents in reducing BP variability, which would account for their greater efficacy in stroke prevention [74].

The Role of Cerebral Blood Flow Autoregulation

Cerebral autoregulation is the process through which cerebral blood is maintained constant in front of changes in systemic BP. The main control mechanism of the process is represented by sensitivity of parietal vascular smooth cells to CO_2, resulting in vasodilation. The control of large arteries, arterioles, and capillaries is also under the influence of endothelial cells, astrocytes, neurons, and pericytes [75] that interact functionally in the so-called neurovascular unit [76]. Although it was previously observed that cerebral blood flow can remain relatively unchanged within a mean arterial BP range 60–150 mmHg, recent data show a much narrower range of autoregulation, especially evident for hypotensive conditions. The ability of maintaining a stable cerebral blood flow is further reduced by the ageing process [9]. As a consequence of reduced regulatory ability, cerebral blood flow variability during sit-to-stand maneuvers increases with aging [67]. A history of HBP has been associated with impaired autoregulation, resulting in a shift to the right of the autoregulation curve and a decrease of cerebral blood flow [77]. However, the precise mechanism of this association is yet unclear. In fact, a recent study has associated increased arterial stiffness, a well-known consequence of long-standing HBP, with reduced cerebral blood flow, in spite of preserved autoregulation [78].

It has been shown that subjects with subcortical vascular lesions, ultimately leading to vascular dementia, show altered vasoreactivity and reduced cerebral blood flow in the affected areas [79]. In agreement with the role of VRF in AD

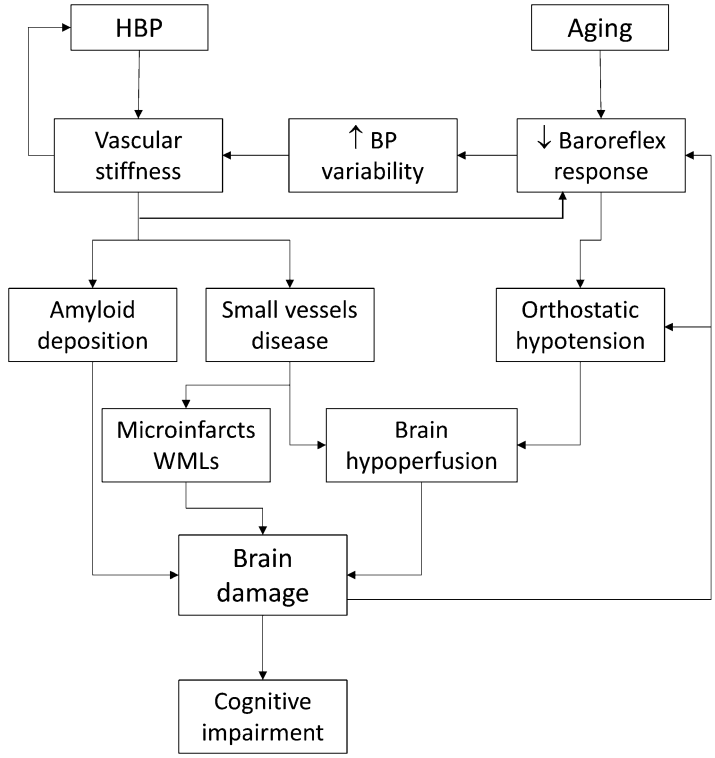

Fig. 1 Reciprocal interconnections between autonomic dysfunction, vascular remodeling, and brain damage. Age-associated impaired baroreflex response may increases blood pressure variability, thus increasing vascular remodeling associated with aging and high blood pressure. Orthostatic hypotension, associated with small vessels disease, may increase the risk of brain hypoperfusion. Brain damage associated with neurodegeneration and chronic ischemic lesions may impair autonomic function (reverse causation), possibly inducing a negative feedback. *HBP* high blood pressure, *BP* blood pressure, *WMLs* white matter lesions

pathogenesis, several experimental and clinical evidences point to the presence of a neurovascular unit impairment also in AD [75]. In a small sample of subjects with AD, vasomotor reactivity to CO_2 and cerebral blood flow autoregulation were reduced in comparison with age- and HBP-matched controls [80]. The impaired vasomotor reactivity seems to be linked to ApoE genotype, the most important genetic risk factor for sporadic AD, as it has been observed in a sample of cognitively normal older subjects with the ApoE4 allele. Presence of ApoE4 allele and a history of HBP were independently associated with a reduced CO_2 vasoreactivity, in keeping with the view of a synergistic effect of the two factors on cerebral blood flow impairment [81]. Vascular amyloid deposition, as is observed in hereditary cerebral amyloid angiopathy [82], has also been associated with impaired cerebrovascular reactivity and may be involved in impaired cerebral blood flow control in AD as well. Several studies have found a reduced cerebral blood flow in subjects with AD. Although part of the association can be the effect of reduced neuronal activity due to neurodegeneration, cerebral blood flow decrease was associated with an increased risk of incident dementia and accelerated cognitive decline in a 7-year follow-up of the Rotterdam Study. The effect was attenuated but still present after adjusting for baseline small vessel disease, thus suggesting a role of hypoperfusion also in the neurodegenerative process [83]. In spite of these data, several links between altered autoregulation and neurodegeneration still need to be clarified. A recent study, although confirming a reduced cerebral blood flow associated with increased

cerebrovascular resistance in subjects with AD compared with MCI and healthy controls, did not identify any across-group difference in baroreflex sensitivity and cerebral blood flow autoregulation during sit-to-stand maneuvers [84]. This finding reinforces the view of a large pathophysiological variability of vascular function control in neurodegenerative conditions, and calls for further studies.

Body Composition, Insulin Resistance, and Age-Associated Cognitive Decline

Aging is associated with changes in body composition, resulting in decreased muscle mass/fat mass ratio. Both increased fat mass, typical of obesity [85], and decrease of muscle mass, the key feature of sarcopenia [86], are associated with increased insulin resistance, defined as an impaired cellular response to insulin action. Moreover, insulin resistance has been identified as a condition of increased risk of muscle mass loss, therefore further increasing sarcopenia [87].

Insulin resistance is the pathophysiological basis of T2DM and is identified both as a vascular risk factor and as a major pathological player of neurodegeneration, including AD, through multiple molecular pathways [88]. Beyond its metabolic actions, insulin plays a crucial role as a trophic factor in the central nervous system, promoting neuron growth and survival. When peripheral insulin resistance develops, insulin transport into SNC through blood-brain barrier receptors is reduced. Moreover, signal transduction after insulin-receptor binding is impaired, resulting in impaired GSK-3 (glycogen synthase kinase-3) inhibition: this leads to an increased tau protein phosphorylation, promoting its aggregation into neurofibrillary tangles, which possess a neurotoxic activity and constitute one of the neuropathological features of AD [89]. In agreement with this hypothesis, features of insulin resistance have been identified at autopsy in AD patients' brains, showing an impairment of insulin and IGF-1 receptor signaling, especially evident in neurons with neurofibrillary tangles [89]. Based on results of experimental models, some authors have even proposed the existence of a "type 3 diabetes mellitus," characterized by the presence of insulin resistance inside the brain, as the pathophysiological basis of AD [88]. Besides insulin resistance, both obesity and T2DM are associated with an enhanced inflammatory response, possibly resulting in a condition of subclinical neuroinflammation, which is considered one of the pathogenic mechanisms of age-associated cognitive decline and AD [88, 90]. Indeed, increased levels of proinflammatory cytokines, especially IL6, have been found in AD and MCI, although large interindividual variations make them probably useless as cognitive biomarkers [91].

On the other hand, some recent studies have proposed that brain changes can influence body composition, especially muscle mass. Cachexia, including muscle mass loss, is a well-known consequence of all severe chronic diseases, including dementia. Of interest, a decrease of lean mass has been observed since the early stages of AD, and its extent was correlated with severity of brain atrophy [92]. This association might well be explained by upstream pathophysiological mechanisms, e.g., systemic inflammation, but is also consistent with an influence of central nervous system pathology on muscle function. This hypothesis is supported by a further study, in which a cohort of older subjects ($n = 791$, mean baseline age 81) has been followed until death (mean observation time: 7 years), with autoptic assessment of neuropathological lesions, especially AD-type, parkinsonian, and vascular lesions. The presence of AD-type neuropathological lesions, independent of demographics and comorbidities, including dementia, was significantly associated with the decline of muscle strength, the functional correlate of muscle mass [93]. These data suggest that the accumulation of lesions in the central nervous system may impair muscle mass and function.

A reverse-causation pathway regarding body composition and brain function has been hypothesized also for adipose tissue, in order to explain the apparent "BMI paradox," represented by the role of obesity at midlife as a risk factor for dementia and of low BMI and weight loss as risk factors for AD during the years immediately preceding the diagnosis. In a group of healthy older subjects (mean age 75, $n = 363$) undergoing biomarker dosage in the ADNI initiative research, subjects with a weight loss $\geq$5% over a 4-year follow-up

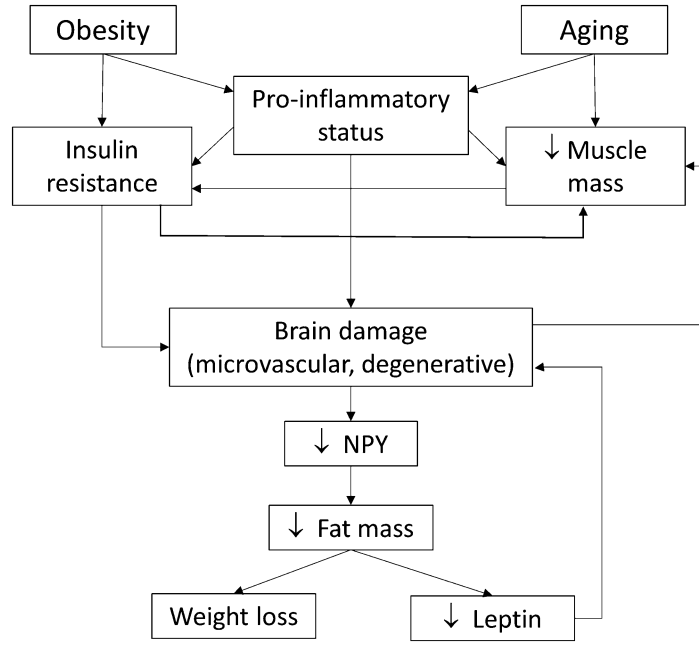

Fig. 2 Reciprocal interconnections between body composition, insulin resistance, reduced leptin activity, and brain damage. Age-associated muscle mass loss (sarcopenia) may increase insulin resistance and in turn can be enhanced by insulin resistance; both conditions are associated with increased inflammation. Chronic brain damage is associated with enhanced muscle damage and decreased fat mass (reverse causation), with reduced leptin level possibly inducing a negative feedback. *NPY* neuropeptide Y

had higher AD biomarkers at baseline: lower Abeta-42/total tau ratio in the CSF, greater amyloid deposition measured with PET, and more severe right temporal atrophy at MRI. Moreover, subjects with weight loss also had a slight decline of global cognitive function over the follow-up, globally suggesting a condition of preclinical AD [35]. The mechanism potentially involved has been identified in a transgenic APP-mutated mice model, in which a clear weight loss occurred before amyloid plaques formation. In the same model, a decrease of hypothalamic neuropeptide Y (NPY, neuromediator whose effects include increased appetite and decreased energy expenditure) was observed together with reduced leptin levels and reduced responsiveness of hypothalamic arcuate nuclei to leptin induced by beta-amyloid fragment. The authors hypothesize that a hypothalamic impairment occurs early in the disease process, with impaired expression of NPY resulting in decrease of fat mass, with consequent reduced leptin secretion not balanced by increased NPY, thus leading to a further weight loss [94]. Of notice, as leptin has been identified as a neuroprotective agent in several experimental and clinical studies [95], the observed weight loss might be not only an early effect of neurodegeneration but a true pathogenic mechanism contributing to AD progression with a negative feedback.

A scheme of possible reciprocal interconnections between body composition, insulin resistance, reduced leptin activity, and brain damage is reported in Fig. 2.

Biological Role of Physical Activity

Several mechanisms can explain the positive effect of PA across the continuum of age-associated cognitive decline. As discussed before, a regular aerobic physical training has been associated with an improvement of neuroautonomic function and of baroreflex cardiovagal response [52]. Moreover a meta-analysis of intervention studies has confirmed that aerobic, but not resistance training, is able to decrease vascular stiffness, with a dose-response relationship and with more beneficial effects in subjects with greater baseline stiffness [72]. Intervention studies have also shown that a program of aerobic exercise in older adults can increase cerebral blood flow in the anterior cingulate area and in those included in the default mode network, whose connectivity is typically impaired in AD [73].

Other beneficial effect of physical activity on cognitive function can be associated with the increased release of neurotrophic factors, including brain-derived neurotrophic factor (BDNF), which is released by the brain in response to exercise and has a trophic action on the hippocampus, promotes long-term potentiation, and enhances memory. Moreover, regular PA is associated with a decrease of inflammatory response, thus possibly further increasing neuroprotection [96].

Treatment of Vascular Risk Factor: The Effect of Aging and Cognitive Impairment

Antihypertensive Treatment

Ethical reasons linked with the well-known protective effects of antihypertensives on many other health outcomes, together with logistic issues, prevent from conducting long-term placebo-controlled randomized trials of antihypertensive treatment at midlife with a primary cognitive outcome. Nevertheless, some trials that enrolled older subjects included cognitive measures as secondary outcomes. Yet, also in this case randomized clinical trials have a limited statistical power, as follow-up times necessary to observe a cognitive protection are longer than those needed to demonstrate a beneficial effect on of vascular events or all-cause mortality. The open-label extension of the randomized controlled Syst-Eur was the only single study showing a statistically significant benefit of antihypertensive treatment against dementia, with a 55% decreased incidence at 4-year follow-up, which translates into an estimate of 20 cases of dementia prevented for 1000 patients treated for 5 years [97]. The placebo-controlled HYVET study included subjects aged 80+ with isolated systolic hypertension but, being stopped after about 2 years only for the clear superiority of active treatment on vascular outcomes and all-cause mortality, was unable to show a significant effect on cognition [98]. The meta-analysis of Syst-Eur, HYVET, and other available placebo-controlled trials showed a borderline significant, protective effect of antihypertensives against incident dementia, with large heterogeneity among different studies [98].

Until now, there are no clear data regarding the effect of different drug classes on cognitive function. A large observational study has shown a greater efficacy of angiotensin receptor blockers in reducing the progression of dementia, mortality, and nursing home admission in the subgroup of subjects previously diagnosed with dementia [99]. A subsequent meta-analysis did not show significant differences between ACE inhibitors and angiotensin receptor blockers on cognitive outcomes, but suggested a better cognitive outcome in subjects with dementia treated with those ACE inhibitors able to cross the blood-brain barrier [100]. Finally, as already mentioned, calcium-channel blockers have been identified as the most effective agents in reducing BP variability, thus accounting for a greater efficacy in stroke prevention [74], but data on their efficacy in preventing cognitive decline and dementia are not available [101].

A further issue regarding the role of advanced age and cognition in antihypertensive treatment choice is associated with the assessment of patient's vulnerability. In fact, it has been proposed that the presence of functional disability, motor impairment, and cognitive impairment might be markers of increased susceptibility to adverse events associated with antihypertensive treatment [102]. In particular, the large group of older subjects already suffering from cognitive impairment might represent a subpopulation at high risk for brain hypoperfusion. In fact, available data show a high prevalence of "neurocardiovascular instability" [9] and of impaired vasoreactivity in older subjects with cognitive impairment and both AD [75] or vascular dementia [79], although a recent study did not confirm an impairment in autoregulation of cerebral blood flow in AD and MCI subjects [84]. Clinical data in this setting are still inconsistent. In an epidemiological Chinese study including 837 subjects aged 55+ with MCI (mean age 67.8, baseline MMSE 26/30), high BP increased the risk of conversion to AD at 5 years, and antihypertensive treatment reduced that risk [103]. Conversely, in an Italian clinical sample of 172 subjects with dementia or MCI aged 65+ (mean age 79, MMSE 22/30) in whom BP was carefully assessed with 24-hour

ambulatory monitoring, the risk of cognitive decline at 9 months was increased in subjects with lower mean daytime SBP (<129 mmHg) actively treated with antihypertensive drugs [104]. A treatment discontinuation randomized trial of 385 older subjects 75+ with mild cognitive decline (mean age 81, MMSE 26/30) included subjects who were taking at least one antihypertensive drug and had a SBP ≤160 mmHg. After 16 weeks, SBP increased from 149 mmHg to 154 mmHg, without any positive effect on cognitive function, psychological profile, or daily functioning [105]. The relatively high BP of subjects included in that trial (well above cerebral blood flow autoregulation lower limits) and the high prevalence of white coat hypertension, resulting in a low concordance between office BP and mean daytime BP values [106], might explain the negative results.

In summary, further research is needed to identify the optimal BP target in subjects who already have some degree of cognitive impairment. Moreover, due to reduced life expectancy, any potential protective effect of BP lowering on cognition may be blunted, while potential adverse effects of an aggressive treatment can be enhanced, in cognitively impaired older subjects. For example, dementia patients have a higher risk of hip fracture, a powerful determinant mortality in these patients [107], and antihypertensives represent a risk factor for fall injuries in advanced age [108]. Accordingly, older patients with cognitive decline might be the right target for the de-intensification clinical trials that have been proposed for antihypertensive treatment [109].

Antidiabetic Treatment

While epidemiologic and experimental studies have clearly associated insulin resistance and T2DM with cognitive decline and dementia, no strong evidence is yet available regarding the capacity of antidiabetic treatment to prevent cognitive decline. The ACCORD trial has examined the effect of an intensive (target HbA1c 42 mmol/mol) versus a standard target (53–63 mmol/mol) glycemic control in almost 3,000 diabetics aged 55+, and was interrupted after 3.5 years due to increased mortality in the intensive treatment arm. In a secondary analysis of the cited trial, no significant between-group difference was observed in cognitive outcome, despite a less severe atrophy progression in the intensive treatment group [110], and no cognitive or neuroradiological between-group difference was observed at the 80-month open-label assessment [111]. In agreement with these data, a meta-analysis of ACCORD-MIND with clinical trials including a cognitive outcome (ADVANCE, ADDITION, ORIGIN) was unable to show any beneficial effect of different glycometabolic targets on cognition [112]. These negative results might in part be explained by the higher risk of hypoglycemia associated with a more aggressive glycometabolic control. In fact, hypoglycemic events are associated with a higher risk of incident dementia in diabetes, and, conversely, cognitively impaired older subjects have a higher risk of drug-associated hypoglycemia [113], possibly due to difficulties in drug management and inability to early recognize symptoms of hypoglycemia. Moreover, insulin treatment has been identified as an independent risk factors of unexplained falls in subjects with dementia, suggesting that undiagnosed hypoglycemic episodes might increase the risk of injuries in this vulnerable population [114].

For this reason, insulin-sensitizing agents that possess a negligible risk of hypoglycemia and can improve this neurotoxic metabolic dysfunction potentially represent a first choice of neuroprotection in subjects without diabetes [115]. These molecules include metformin, which is also able to reduce tau protein hyperphosphorylation, and thiazolidinediones, which through PPAR-gamma activation can decrease the secretion of microglial inflammatory mediators. A pilot intervention study has shown a beneficial effect of metformin on episodic memory in overweight, nondiabetic subjects [116], and a large observational study has shown a lower dementia incidence with a second-line pioglitazone treatment compared with other oral hypoglycemic agents in diabetics treated with metformin [117]. Another class of antidiabetic agents is represented by Glp-1 (glucagon-like peptide 1) agonists that, beyond increasing

glucose-dependent insulin secretion, have shown a direct cerebral activity, inducing a significant improvement of neuropathological, neurophysiological, and behavioral impairment in experimental models of insulin resistance and AD [118]. A pilot study in AD has shown a positive effect of one of such molecules, liraglutide, on 6-month cerebral metabolism decline in a sample of AD patients [119]. Finally, the use of intranasal insulin has been proposed to directly counteract brain insulin resistance while avoiding insulin systemic effects, and pilot studies have shown improvement in episodic memory in subjects with T2DM [120], MCI, and AD [121].

Physical Exercise

In agreement with the observational studies cited above, showing an association between physical activity and lower risk of cognitive decline, several clinical trials have tested the effect of physical exercise on cognitive outcome in different settings.

Small randomized controlled studies including "young old" subjects have found that, after a 6–12-month program of aerobic exercise, the volume of some cortical regions, especially the anterior hippocampus, increased in comparison with controls and that this was associated with better episodic memory [122, 123]. A meta-analysis of 42 small intervention studies including a total of 1,627 individuals in a wide (19–72 years) age range has shown a significant decrease of measures of arterial stiffness after a median of 12 weeks of aerobic exercise. The effect was enhanced with higher intensity of aerobic exercise and in participants with greater baseline arterial stiffness [72]. A pilot intervention study conducted in sedentary older adults has shown, after 12 weeks of regular 3 h/week physical exercise, an improvement in cerebral blood flow in anterior cingulate cortex and in episodic memory [124].

Unfortunately, the LIFE randomized controlled study, which enrolled 1,635 frail sedentary older adults and included cognitive measures among its secondary outcomes, did not observe any cognitive benefit of a 2-year program of structured aerobic and strength training [125]. Yet, beneficial effects on executive functions were observed among subjects aged 80+ and with more severe physical frailty (Short Physical Performance Battery <8). Moreover, it can be hypothesized that the control intervention, which consisted of a structured health education and social stimulation program, might have produced some beneficial cognitive effect partially shadowing the effect of physical activity [125]. Since the cardiovascular effects of the intervention, mainly aimed at counteracting sarcopenia, were small and clinically negligible [126], this also might explain the lack of cerebral blood flow-mediated neuroprotective effect.

Several intervention studies have tested the effect of physical exercise in older subjects with overt dementia. Overall, those studies have shown an association between intervention and smaller cognitive decline over time, with beneficial effects that were independent of clinical diagnosis and frequency of intervention, but were evident only in studies testing interventions that included aerobic exercise [127]. Similarly, a meta-analysis of studies testing the efficacy of aerobic exercise in older subjects with MCI found an overall benefit on measures of global cognitive function [128]. The specific effect of aerobic exercise supports the hypothesis that the neuroprotective effect of physical activity is mediated by vascular mechanisms, possibly increasing cerebral blood flow. Nonetheless, in older subjects with overt dementia, the association of strength training is warranted, due to the beneficial effect on muscle function, resulting in reduced functional decline [129] and risk of falling [130].

Conclusion

Available epidemiological and pathophysiological evidences strongly support the association of vascular risk factors and neuroatonomic dysfunction with cognitive decline and dementia in old age. Yet, this association changes across lifetime, and differs across different parameters. In particular, high blood pressure and obesity at midlife

have been associated with greater age-associated cognitive decline, while dementia onset in old age is often heralded by lowering of blood pressure and body mass index. Pharmacological treatment of vascular risk factors at midlife is warranted to prevent cognitive decline. While the same approach should be followed in non-frail older subjects, due to beneficial cardiovascular effect clearly shown in clinical trials, a less aggressive approach is reasonable for older, cognitively impaired patients, more vulnerable to treatment adverse events. Physical activity should be recommended lifelong, both as primary prevention and as adjuvant treatment in cognitively impaired older subjects.

References

1. International AsD. World Alzheimer report. London: Alzheimer's Disease International; 2015.
2. Lane CA, Hardy J, Schott JM. Alzheimer's disease. Eur J Neurol. 2018;25(1):59–70.
3. Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C. Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. Lancet Neurol. 2014;13(8):788–94.
4. Wu YT, Beiser AS, Breteler MMB, Fratiglioni L, Helmer C, Hendrie HC, et al. The changing prevalence and incidence of dementia over time – current evidence. Nat Rev Neurol. 2017;13(6):327–39.
5. Roberts RO, Knopman DS, Przybelski SA, Mielke MM, Kantarci K, Preboske GM, et al. Association of type 2 diabetes with brain atrophy and cognitive impairment. Neurology. 2014;82(13): 1132–41.
6. Schneider JA, Arvanitakis Z, Bang W, Bennett DA. Mixed brain pathologies account for most dementia cases in community-dwelling older persons. Neurology. 2007;69(24):2197–204.
7. Kloppenborg RP, van den Berg E, Kappelle LJ, Biessels GJ. Diabetes and other vascular risk factors for dementia: which factor matters most? A systematic review. Eur J Pharmacol. 2008;585(1):97–108.
8. Kivipelto M, Ngandu T, Laatikainen T, Winblad B, Soininen H, Tuomilehto J. Risk score for the prediction of dementia risk in 20 years among middle aged people: a longitudinal, population-based study. Lancet Neurol. 2006;5(9):735–41.
9. O'Callaghan S, Kenny RA. Neurocardiovascular instability and cognition. Yale J Biol Med. 2016;89(1):59–71.
10. Vos SJB, van Boxtel MPJ, Schiepers OJG, Deckers K, de Vugt M, Carrière I, et al. Modifiable risk factors for prevention of dementia in midlife, late life and the oldest-old: validation of the LIBRA index. J Alzheimers Dis. 2017;58(2):537–47.
11. Langa KM, Levine DA. The diagnosis and management of mild cognitive impairment: a clinical review. JAMA. 2014;312(23):2551–61.
12. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7:263–9.
13. Qiu C, Winblad B, Fratiglioni L. The age-dependent relation of blood pressure to cognitive function and dementia. Lancet Neurol. 2005;4(8):487–99.
14. Launer LJ, Ross GW, Petrovitch H, Masaki K, Foley D, White LR, et al. Midlife blood pressure and dementia: the Honolulu-Asia aging study. Neurobiol Aging. 2000;21:49–55.
15. Kivipelto M, Helkala EL, Laakso MP, Hanninen T, Hallikainen M, Alhainen K, et al. Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. BMJ. 2001;322: 1447–51.
16. Gottesman RF, Schneider AL, Albert M, Alonso A, Bandeen-Roche K, Coker L, et al. Midlife hypertension and 20-year cognitive change: the atherosclerosis risk in communities neurocognitive study. JAMA Neurol. 2014;71(10):1218–27.
17. Skoog I, Lernfelt B, Landahl S, Palmertz B, Andreasson LA, Nilsson L, et al. 15-year longitudinal study of blood pressure and dementia. Lancet. 1996;347:1141–5.
18. Skoog I, Andreasson LA, Landahl S, Lernfelt B. A population-based study on blood pressure and brain atrophy in 85-year-olds. Hypertension. 1998;32(3): 404–9.
19. Joas E, Backman K, Gustafson D, Ostling S, Waern M, Guo X, et al. Blood pressure trajectories from midlife to late life in relation to dementia in women followed for 37 years. Hypertension. 2012;59:796–801.
20. Power MC, Weuve J, Gagne JJ, McQueen MB, Viswanathan A, Blacker D. The association between blood pressure and incident Alzheimer disease: a systematic review and meta-analysis. Epidemiology. 2011;22(5):646–59.
21. Euser SM, van Bemmel T, Schram MT, Gussekloo J, Hofman A, Westendorp RG, et al. The effect of age on the association between blood pressure and cognitive function later in life. J Am Geriatr Soc. 2009;57: 1232–7.
22. Sabayan B, Oleksik AM, Maier AB, van Buchem MA, Poortvliet RK, de Ruijter W, et al. High blood pressure and resilience to physical and cognitive decline in the oldest old: the Leiden 85-plus study. J Am Geriatr Soc. 2012;60:2014–9.
23. Benetos A, Bulpitt CJ, Petrovic M, Ungar A, Agabiti Rosei E, Cherubini A, et al. An expert

opinion from the European Society of Hypertension-European Union Geriatric Medicine Society working group on the management of hypertension in very old. Frail Subjects Hypertens. 2016;67(5):820–5.
24. Biessels GJ, Staekenborg S, Brunner E, Brayne C, Scheltens P. Risk of dementia in diabetes mellitus: a systematic review. Lancet Neurol. 2006;5(1):64–74.
25. Koekkoek PS, Kappelle LJ, van den Berg E, Rutten GE, Biessels GJ. Cognitive function in patients with diabetes mellitus: guidance for daily care. Lancet Neurol. 2015;14(3):329–40.
26. Manschot SM, Biessels GJ, de Valk H, Algra A, Rutten GE, van der Grond J, et al. Metabolic and vascular determinants of impaired cognitive performance and abnormalities on brain magnetic resonance imaging in patients with type 2 diabetes. Diabetologia. 2007;50(11):2388–97.
27. Haroon NN, Austin PC, Shah BR, Wu J, Gill SS, Booth GL. Risk of dementia in seniors with newly diagnosed diabetes: a population-based study. Diabetes Care. 2015;38(10):1868–75.
28. Li JQ, Tan L, Wang HF, Tan MS, Xu W, Zhao QF, et al. Risk factors for predicting progression from mild cognitive impairment to Alzheimer's disease: a systematic review and meta-analysis of cohort studies. J Neurol Neurosurg Psychiatry. 2016;87(5):476–84.
29. Reijmer YD, van den Berg E, Ruis C, Kappelle LJ, Biessels GJ. Cognitive dysfunction in patients with type 2 diabetes. Diabetes Metab Res Rev. 2010;26(7):507–19.
30. Qizilbash N, Gregson J, Johnson ME, Pearce N, Douglas I, Wing K, et al. BMI and risk of dementia in two million people over two decades: a retrospective cohort study. Lancet Diabetes Endocrinol. 2015;3(6):431–6.
31. Kivimäki M, Luukkonen R, Batty GD, Ferrie JE, Pentti J, Nyberg ST, et al. Body mass index and risk of dementia: analysis of individual-level data from 1.3 million individuals. Alzheimers Dement. 2018;14(5):601–9.
32. Pedditzi E, Peters R, Beckett N. The risk of overweight/obesity in mid-life and late life for the development of dementia: a systematic review and meta-analysis of longitudinal studies. Age Ageing. 2016;45(1):14–21.
33. Alhurani RE, Vassilaki M, Aakre JA, Mielke MM, Kremers WK, Machulda MM, et al. Decline in weight and incident mild cognitive impairment: Mayo Clinic study of aging. JAMA Neurol. 2016;73(4):439–46.
34. Vidoni ED, Townley RA, Honea RA, Burns JM, Initiative ADN. Alzheimer disease biomarkers are associated with body mass index. Neurology. 2011;77(21):1913–20.
35. Jimenez A, Pegueroles J, Carmona-Iragui M, Vilaplana E, Montal V, Alcolea D, et al. Weight loss in the healthy elderly might be a non-cognitive sign of preclinical Alzheimer's disease. Oncotarget. 2017;8(62):104706–16.
36. Macpherson H, Teo WP, Schneider LA, Smith AE. A life-long approach to physical activity for brain health. Front Aging Neurosci. 2017;9:147.
37. Blondell SJ, Hammersley-Mather R, Veerman JL. Does physical activity prevent cognitive decline and dementia?: a systematic review and meta-analysis of longitudinal studies. BMC Public Health. 2014;14:510.
38. Stephen R, Hongisto K, Solomon A, Lönnroos E. Physical activity and Alzheimer's disease: a systematic review. J Gerontol A Biol Sci Med Sci. 2017;72(6):733–9.
39. Rovio S, Kareholt I, Helkala EL, Viitanen M, Winblad B, Tuomilehto J, et al. Leisure-time physical activity at midlife and the risk of dementia and Alzheimer's disease. Lancet Neurol. 2005;4(11):705–11.
40. Tolppanen AM, Solomon A, Kulmala J, Kåreholt I, Ngandu T, Rusanen M, et al. Leisure-time physical activity from mid- to late life, body mass index, and risk of dementia. Alzheimers Dement. 2015;11(4):434–443.e6.
41. Sabia S, Dugravot A, Dartigues JF, Abell J, Elbaz A, Kivimäki M, et al. Physical activity, cognitive decline, and risk of dementia: 28 year follow-up of Whitehall II cohort study. BMJ. 2017;357:j2709.
42. Erickson KI, Leckie RL, Weinstein AM. Physical activity, fitness, and gray matter volume. Neurobiol Aging. 2014;35(Suppl 2):S20–8.
43. Schultz SA, Boots EA, Darst BF, Zetterberg H, Blennow K, Edwards DF, et al. Cardiorespiratory fitness alters the influence of a polygenic risk score on biomarkers of AD. Neurology. 2017;88(17):1650–8.
44. Román GC, Tatemichi TK, Erkinjuntti T, Cummings JL, Masdeu JC, Garcia JH, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. Neurology. 1993;43(2):250–60.
45. Blacher J, Safar ME. Large-artery stiffness, hypertension and cardiovascular risk in older patients. Nat Clin Pract Cardiovasc Med. 2005;2(9):450–5.
46. Mitchell GF, van Buchem MA, Sigurdsson S, Gotal JD, Jonsdottir MK, Kjartansson Ó, et al. Arterial stiffness, pressure and flow pulsatility and brain structure and function: the age, gene/environment susceptibility–Reykjavik study. Brain. 2011;134(Pt 11):3398–407.
47. Mitchell GF. Effects of central arterial aging on the structure and function of the peripheral vasculature: implications for end-organ damage. J Appl Physiol (1985). 2008;105(5):1652–60.
48. Hughes TM, Kuller LH, Barinas-Mitchell EJ, McDade EM, Klunk WE, Cohen AD, et al. Arterial stiffness and β-amyloid progression in nondemented elderly adults. JAMA Neurol. 2014;71(5):562–8.
49. Hughes TM, Wagenknecht LE, Craft S, Mintz A, Heiss G, Palta P, et al. Arterial stiffness and dementia pathology: Atherosclerosis Risk in Communities

(ARIC)-PET study. Neurology. 2018;90(14): e1248–e56.
50. Pase MP, Beiser A, Himali JJ, Tsao C, Satizabal CL, Vasan RS, et al. Aortic stiffness and the risk of incident mild cognitive impairment and dementia. Stroke. 2016;47(9):2256–61.
51. Charkoudian N, Rabbitts JA. Sympathetic neural mechanisms in human cardiovascular health and disease. Mayo Clin Proc. 2009;84(9):822–30.
52. Monahan KD. Effect of aging on baroreflex function in humans. Am J Physiol Regul Integr Comp Physiol. 2007;293(1):R3–R12.
53. Saint Martin M, Roche F, Thomas-Anterion C, Barthélémy JC, Sforza E, Group POcaces. Eight-year parallel change in baroreflex sensitivity and memory function in a sample of healthy older adults. J Am Geriatr Soc. 2015;63(2):270–5.
54. Meel-van den Abeelen AS, Lagro J, Gommer ED, Reulen JP, Claassen JA. Baroreflex function is reduced in Alzheimer's disease: a candidate biomarker? Neurobiol Aging. 2013;34(4):1170–6.
55. Zeki Al Hazzouri A, Elfassy T, Carnethon MR, Lloyd-Jones DM, Yaffe K. Heart rate variability and cognitive function in middle-age adults: the coronary artery risk development in young adults. Am J Hypertens. 2017;31(1):27–34.
56. Mahinrad S, Jukema JW, van Heemst D, Macfarlane PW, Clark EN, de Craen AJ, et al. 10-second heart rate variability and cognitive function in old age. Neurology. 2016;86(12):1120–7.
57. Ogliari G, Mahinrad S, Stott DJ, Jukema JW, Mooijaart SP, Macfarlane PW, et al. Resting heart rate, heart rate variability and functional decline in old age. CMAJ. 2015;187(15):E442–9.
58. Zulli R, Nicosia F, Borroni B, Agosti C, Prometti P, Donati P, et al. QT dispersion and heart rate variability abnormalities in Alzheimer's disease and in mild cognitive impairment. J Am Geriatr Soc. 2005;53(12): 2135–9.
59. Nonogaki Z, Umegaki H, Makino T, Suzuki Y, Kuzuya M. Relationship between cardiac autonomic function and cognitive function in Alzheimer's disease. Geriatr Gerontol Int. 2017;17(1):92–8.
60. Nagai M, Hoshide S, Kario K. The insular cortex and cardiovascular system: a new insight into the brain-heart axis. J Am Soc Hypertens. 2010;4(4):174–82.
61. Engelhardt E, Laks J. Alzheimer disease neuropathology: understanding autonomic dysfunction. Dement Neuropsychol. 2008;2(3):183–91.
62. Peters R, Anstey KJ, Booth A, Beckett N, Warwick J, Antikainen R, et al. Orthostatic hypotension and symptomatic subclinical orthostatic hypotension increase risk of cognitive impairment: an integrated evidence review and analysis of a large older adult hypertensive cohort. Eur Heart J. 2018;39:3135.
63. Rawlings AM, Juraschek SP, Heiss G, Hughes T, Meyer ML, Selvin E, et al. Association of orthostatic hypotension with incident dementia, stroke, and cognitive decline. Neurology. 2018;91:e759.
64. Wolters FJ, Mattace-Raso FU, Koudstaal PJ, Hofman A, Ikram MA, Group HBCCR. Orthostatic hypotension and the long-term risk of dementia: a population-based study. PLoS Med. 2016;13(10): e1002143.
65. Raz L, Knoefel J, Bhaskar K. The neuropathology and cerebrovascular mechanisms of dementia. J Cereb Blood Flow Metab. 2016;36(1):172–86.
66. Laosiripisan J, Tarumi T, Gonzales MM, Haley AP, Tanaka H. Association between cardiovagal baroreflex sensitivity and baseline cerebral perfusion of the hippocampus. Clin Auton Res. 2015;25(4): 213–8.
67. Xing CY, Tarumi T, Meijers RL, Turner M, Repshas J, Xiong L, et al. Arterial pressure, heart rate, and cerebral hemodynamics across the adult life span. Hypertension. 2017;69(4):712–20.
68. Parati G, Ochoa JE, Lombardi C, Bilo G. Assessment and management of blood-pressure variability. Nat Rev Cardiol. 2013;10(3):143–55.
69. Nagai M, Dote K, Kato M, Sasaki S, Oda N, Kagawa E, et al. Visit-to-visit blood pressure variability and Alzheimer's disease: links and risks. J Alzheimers Dis. 2017;59(2):515–26.
70. Nagai M, Dote K, Kato M, Sasaki S, Oda N, Kagawa E, et al. Visit-to-visit blood pressure variability, average BP level and carotid arterial stiffness in the elderly: a prospective study. J Hum Hypertens. 2017;31(4):292–8.
71. Monahan KD, Tanaka H, Dinenno FA, Seals DR. Central arterial compliance is associated with age- and habitual exercise-related differences in cardiovagal baroreflex sensitivity. Circulation. 2001;104(14):1627–32.
72. Ashor AW, Lara J, Siervo M, Celis-Morales C, Mathers JC. Effects of exercise modalities on arterial stiffness and wave reflection: a systematic review and meta-analysis of randomized controlled trials. PLoS One. 2014;9(10):e110034.
73. Tarumi T, Zhang R. Cerebral blood flow in normal aging adults: cardiovascular determinants, clinical implications, and aerobic fitness. J Neurochem. 2018;144(5):595–608.
74. Webb AJ, Fischer U, Mehta Z, Rothwell PM. Effects of antihypertensive-drug class on interindividual variation in blood pressure and risk of stroke: a systematic review and meta-analysis. Lancet. 2010;375(9718):906–15.
75. Kisler K, Nelson AR, Montagne A, Zlokovic BV. Cerebral blood flow regulation and neurovascular dysfunction in Alzheimer disease. Nat Rev Neurosci. 2017;18(7):419–34.
76. Iadecola C. Neurovascular regulation in the normal brain and in Alzheimer's disease. Nat Rev Neurosci. 2004;5(5):347–60.
77. Alosco ML, Gunstad J, Xu X, Clark US, Labbe DR, Riskin-Jones HH, et al. The impact of hypertension on cerebral perfusion and cortical thickness in older adults. J Am Soc Hypertens. 2014;8(8):561–70.

78. Jefferson AL, Cambronero FE, Liu D, Moore EE, Neal JE, Terry JG, et al. Higher aortic stiffness is related to lower cerebral blood flow and preserved cerebrovascular reactivity in older adults. Circulation. 2018;138:1951.
79. Iadecola C. The pathobiology of vascular dementia. Neuron. 2013;80(4):844–66.
80. den Abeelen AS, Lagro J, van Beek AH, Claassen JA. Impaired cerebral autoregulation and vasomotor reactivity in sporadic Alzheimer's disease. Curr Alzheimer Res. 2014;11(1):11–7.
81. Hajjar I, Sorond F, Lipsitz LA. Apolipoprotein E, carbon dioxide vasoreactivity, and cognition in older adults: effect of hypertension. J Am Geriatr Soc. 2015;63(2):276–81.
82. van Opstal AM, van Rooden S, van Harten T, Ghariq E, Labadie G, Fotiadis P, et al. Cerebrovascular function in presymptomatic and symptomatic individuals with hereditary cerebral amyloid angiopathy: a case-control study. Lancet Neurol. 2017;16(2):115–22.
83. Wolters FJ, Zonneveld HI, Hofman A, van der Lugt A, Koudstaal PJ, Vernooij MW, et al. Cerebral perfusion and the risk of dementia: a population-based study. Circulation. 2017;136(8):719–28.
84. de Heus RAA, de Jong DLK, Sanders ML, van Spijker GJ, Oudegeest-Sander MH, Hopman MT, et al. Dynamic regulation of cerebral blood flow in patients with Alzheimer disease. Hypertension. 2018;72(1):139–50.
85. Ye J. Mechanisms of insulin resistance in obesity. Front Med. 2013;7(1):14–24.
86. Srikanthan P, Karlamangla AS. Relative muscle mass is inversely associated with insulin resistance and prediabetes. Findings from the third National Health and Nutrition Examination Survey. J Clin Endocrinol Metab. 2011;96(9):2898–903.
87. Lee CG, Boyko EJ, Strotmeyer ES, Lewis CE, Cawthon PM, Hoffman AR, et al. Association between insulin resistance and lean mass loss and fat mass gain in older men without diabetes mellitus. J Am Geriatr Soc. 2011;59(7):1217–24.
88. Mittal K, Katare DP. Shared links between type 2 diabetes mellitus and Alzheimer's disease: a review. Diabetes Metab Syndr. 2016;10(2 Suppl 1):S144–9.
89. Moloney AM, Griffin RJ, Timmons S, O'Connor R, Ravid R, O'Neill C. Defects in IGF-1 receptor, insulin receptor and IRS-1/2 in Alzheimer's disease indicate possible resistance to IGF-1 and insulin signalling. Neurobiol Aging. 2010;31(2):224–43.
90. Spielman LJ, Little JP, Klegeris A. Inflammation and insulin/IGF-1 resistance as the possible link between obesity and neurodegeneration. J Neuroimmunol. 2014;273(1–2):8–21.
91. Brosseron F, Krauthausen M, Kummer M, Heneka MT. Body fluid cytokine levels in mild cognitive impairment and Alzheimer's disease: a comparative overview. Mol Neurobiol. 2014;50(2):534–44.
92. Burns JM, Johnson DK, Watts A, Swerdlow RH, Brooks WM. Reduced lean mass in early Alzheimer disease and its association with brain atrophy. Arch Neurol. 2010;67(4):428–33.
93. Buchman AS, Yu L, Wilson RS, Schneider JA, Bennett DA. Association of brain pathology with the progression of frailty in older adults. Neurology. 2013;80(22):2055–61.
94. Ishii M, Wang G, Racchumi G, Dyke JP, Iadecola C. Transgenic mice overexpressing amyloid precursor protein exhibit early metabolic deficits and a pathologically low leptin state associated with hypothalamic dysfunction in arcuate neuropeptide Y neurons. J Neurosci. 2014;34(27):9096–106.
95. McGregor G, Harvey J. Food for thought: Leptin regulation of hippocampal function and its role in Alzheimer's disease. Neuropharmacology. 2018;136(Pt B):298–306.
96. Nation DA, Hong S, Jak AJ, Delano-Wood L, Mills PJ, Bondi MW, et al. Stress, exercise, and Alzheimer's disease: a neurovascular pathway. Med Hypotheses. 2011;76(6):847–54.
97. Forette F, Seux ML, Staessen JA, Thijs L, Babarskiene MR, Babeanu S, et al. The prevention of dementia with antihypertensive treatment: new evidence from the Systolic Hypertension in Europe (Syst-Eur) study. Arch Intern Med. 2002;162:2046–52.
98. Peters R, Beckett N, Forette F, Tuomilehto J, Clarke R, Ritchie C, et al. Incident dementia and blood pressure lowering in the Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG): a double-blind, placebo controlled trial. Lancet Neurol. 2008;7:683–9.
99. Li NC, Lee A, Whitmer RA, Kivipelto I, Lawler E, Kazis LE, et al. Use of angiotensin receptor blockers and risk of dementia in a predominantly male population: prospective cohort analysis. BMJ. 2010;340:b5465.
100. Zhuang S, Wang HF, Li J, Wang HY, Wang X, Xing CM. Renin-angiotensin system blockade use and risks of cognitive decline and dementia: a meta-analysis. Neurosci Lett. 2016;624:53–61.
101. Peters R, Booth A, Peters J. A systematic review of calcium channel blocker use and cognitive decline/dementia in the elderly. J Hypertens. 2014;32(10):1945–57; discussion 57–58.
102. Mossello E, Desideri G, Ungar A. Hypertension in the oldest old, beyond guidelines. In: Cardiac management in the frail elderly patient and the oldest old [Internet]. Cham: Springer Nature; 2017.
103. Li J, Wang YJ, Zhang M, Xu ZQ, Gao CY, Fang CQ, et al. Vascular risk factors promote conversion from mild cognitive impairment to Alzheimer disease. Neurology. 2011;76(17):1485–91.
104. Mossello E, Pieraccioli M, Nesti N, Bulgaresi M, Lorenzi C, Caleri V, et al. Effects of low blood pressure in cognitively impaired elderly patients treated with antihypertensive drugs. JAMA Intern Med. 2015;175(4):578–85.
105. Moonen JE, Foster-Dingley JC, de Ruijter W, van der Grond J, Bertens AS, van Buchem MA, et al. Effect of

discontinuation of antihypertensive treatment in elderly people on cognitive functioning-the DANTE study Leiden: a randomized clinical trial. JAMA Intern Med. 2015;175:1622.
106. Mossello E, Pieraccioli MC, Zanieri S, Fedeli A, Belladonna M, Nesti N, et al. Ambulatory blood pressure monitoring in older nursing home residents: diagnostic and prognostic role. J Am Med Dir Assoc. 2012;13(8):760.e1–5.
107. Seitz DP, Gill SS, Gruneir A, Austin PC, Anderson GM, Bell CM, et al. Effects of dementia on postoperative outcomes of older adults with hip fractures: a population-based study. J Am Med Dir Assoc. 2014;15(5):334–41.
108. Tinetti ME, Han L, Lee DS, McAvay GJ, Peduzzi P, Gross CP, et al. Antihypertensive medications and serious fall injuries in a nationally representative sample of older adults. JAMA Intern Med. 2014;174(4):588–95.
109. Naschitz JE. Blood pressure management in older people: balancing the risks. Postgrad Med J. 2018;94(1112):348–53.
110. Launer LJ, Miller ME, Williamson JD, Lazar RM, Gerstein HC, Murray AM, et al. Effects of intensive glucose lowering on brain structure and function in people with type 2 diabetes (ACCORD MIND): a randomised open-label substudy. Lancet Neurol. 2011;10(11):969–77.
111. Murray AM, Hsu FC, Williamson JD, Bryan RN, Gerstein HC, Sullivan MD, et al. ACCORDION MIND: results of the observational extension of the ACCORD MIND randomised trial. Diabetologia. 2017;60(1):69–80.
112. Tuligenga RH. Intensive glycaemic control and cognitive decline in patients with type 2 diabetes: a meta-analysis. Endocr Connect. 2015;4(2):R16–24.
113. Yaffe K, Falvey CM, Hamilton N, Harris TB, Simonsick EM, Strotmeyer ES, et al. Association between hypoglycemia and dementia in a biracial cohort of older adults with diabetes mellitus. JAMA Intern Med. 2013;173(14):1300–6.
114. Mossello E, Ceccofiglio A, Rafanelli M, Riccardi A, Mussi C, Bellelli G, et al. Differential diagnosis of unexplained falls in dementia: results of "Syncope & Dementia" registry. Eur J Intern Med. 2018;50:41–6.
115. Patrone C, Eriksson O, Lindholm D. Diabetes drugs and neurological disorders: new views and therapeutic possibilities. Lancet Diabetes Endocrinol. 2014;2(3):256–62.
116. Luchsinger JA, Perez T, Chang H, Mehta P, Steffener J, Pradabhan G, et al. Metformin in amnestic mild cognitive impairment: results of a pilot randomized placebo controlled clinical trial. J Alzheimers Dis. 2016;51(2):501–14.
117. Lu CH, Yang CY, Li CY, Hsieh CY, Ou HT. Lower risk of dementia with pioglitazone, compared with other second-line treatments, in metformin-based dual therapy: a population-based longitudinal study. Diabetologia. 2018;61(3):562–73.
118. Mossello E, Ballini E, Boncinelli M, Monami M, Lonetto G, Mello AM, et al. Glucagon-like peptide-1, diabetes, and cognitive decline: possible pathophysiological links and therapeutic opportunities. Exp Diabetes Res. 2011;2011:281674.
119. Gejl M, Gjedde A, Egefjord L, Møller A, Hansen SB, Vang K, et al. In Alzheimer's disease, 6-month treatment with GLP-1 analog prevents decline of brain glucose metabolism: randomized, placebo-controlled, double-blind clinical trial. Front Aging Neurosci. 2016;8:108.
120. Novak V, Milberg W, Hao Y, Munshi M, Novak P, Galica A, et al. Enhancement of vasoreactivity and cognition by intranasal insulin in type 2 diabetes. Diabetes Care. 2014;37(3):751–9.
121. Avgerinos KI, Kalaitzidis G, Malli A, Kalaitzoglou D, Myserlis PG, Lioutas VA. Intranasal insulin in Alzheimer's dementia or mild cognitive impairment: a systematic review. J Neurol. 2018;265(7):1497–510.
122. Colcombe SJ, Erickson KI, Scalf PE, Kim JS, Prakash R, McAuley E, et al. Aerobic exercise training increases brain volume in aging humans. J Gerontol A Biol Sci Med Sci. 2006;61(11):1166–70.
123. Erickson KI, Voss MW, Prakash RS, Basak C, Szabo A, Chaddock L, et al. Exercise training increases size of hippocampus and improves memory. Proc Natl Acad Sci U S A. 2011;108(7):3017–22.
124. Chapman SB, Aslan S, Spence JS, Defina LF, Keebler MW, Didehbani N, et al. Shorter term aerobic exercise improves brain, cognition, and cardiovascular fitness in aging. Front Aging Neurosci. 2013;5:75.
125. Sink KM, Espeland MA, Castro CM, Church T, Cohen R, Dodson JA, et al. Effect of a 24-month physical activity intervention vs health education on cognitive outcomes in sedentary older adults: the LIFE randomized trial. JAMA. 2015;314(8):781–90.
126. Ó Hartaigh B, Lovato LC, Pahor M, Buford TW, Dodson JA, Forman DE, et al. Effect of a long-term physical activity intervention on resting pulse rate in older persons: results from the lifestyle interventions and independence for elders study. J Am Geriatr Soc. 2016;64(12):2511–6.
127. Groot C, Hooghiemstra AM, Raijmakers PG, van Berckel BN, Scheltens P, Scherder EJ, et al. The effect of physical activity on cognitive function in patients with dementia: a meta-analysis of randomized control trials. Ageing Res Rev. 2016;25:13–23.
128. Zheng G, Xia R, Zhou W, Tao J, Chen L. Aerobic exercise ameliorates cognitive function in older adults with mild cognitive impairment: a systematic review and meta-analysis of randomised controlled trials. Br J Sports Med. 2016;50(23):1443–50.
129. Forbes D, Forbes SC, Blake CM, Thiessen EJ, Forbes S. Exercise programs for people with dementia. Cochrane Database Syst Rev. 2015;4:CD006489.
130. Chan WC, Yeung JW, Wong CS, Lam LC, Chung KF, Luk JK, et al. Efficacy of physical exercise in preventing falls in older adults with cognitive impairment: a systematic review and meta-analysis. J Am Med Dir Assoc. 2015;16(2):149–54.

Neural Effects on Cardiac Electrophysiology

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Interplay Between Beta-Adrenergic Receptors and Ion Channels

Elisabetta Cerbai, Raffaele Coppini, Laura Sartiani, and Alessandro Mugelli

Contents

Abstract

The interaction between brain and heart involves many actors, among which the sympathetic nervous system plays a major role.

Since the first description of adrenoceptors by Raymond Ahlquist in 1948 and the use of beta-blockers by Sir James W. Black in patients with angina pectoris 10 years later, molecular cardiology has been investigating the intimate mechanisms enabling cardiac muscle to adapt (or maladapt) to emotional stress or physical demand. This continuous effort, exploiting state-of-the-art technologies to date, led to an impressive progress in our understanding of

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*,
https://doi.org/10.1007/978-3-030-28008-6_7

the machinery nearby the beta-adrenergic receptor and underneath, much more complex than imagined by pioneering studies of neural-brain axis. This review examines the features of these receptors – subtypes, localization, pathways, and effectors – mediating electrophysiological response of cardiomyocytes, with particular emphasis to control of excitation contraction coupling mechanisms and implications for arrhythmogenesis and cardiomyopathies.

Keywords

Beta-adrenergic receptors · Cardiac arrhythmias · Cardiomyocytes · Excitation-contraction coupling · Ion channels

Introduction

"...τό μ' ἦ μὰν
καρδίαν ἐν στήθεσιν ἐπτόαισεν"
(Sappho, fragment 31 – Lesbos, 630–570 BC)

For many of us, remnants of Sappho's poem "*seems to me to be equal to the gods*" come to the memory together with the powerful impression of the poet's *heart fluttering in her breast* while listening and looking at her beloved. This is one of the first and most evocative descriptions of the effects of sensory perceptions on cardiac electrophysiology whose molecular and biophysical basis would have been – yet incompletely – explained 2500 years later.

The mechanisms underlying the interplay between nervous system and cardiac function involve neuronal pathways, mainly parasympathetic and sympathetic innervation (the so-called extrinsic cardiac nerves) and intrinsic nervous system (a network of intrinsic cardiac ganglia), but also endocrine hormones (adrenaline, endorphins) and autacoids (prostaglandins, serotonin, histamine, adenosine) can modulate neuron discharge or input. Readers are referred to specialized book chapters for a comprehensive description of neural control of cardiac electrical activity. Here, we will focus on the effect of sympathetic stimulation via β-adrenergic receptor (β-AR) signaling on cardiac excitation in physiological and diseased conditions and insights into arrhythmogenesis.

β-Adrenergic Receptors in the Heart

Subtypes, Localization, and Signaling

β-ARs belong to the wide family of G-protein-coupled receptors, At least three different receptor subtypes have been identified (β_1-, β_2, and β_3-ARs), whose density and subcellular localization vary depending on site (nodal vs. atrial or ventricular cardiomyocytes), disease (e.g., heart failure), or developmental state (fetal vs. adult). β_1-ARs, the prominent β-adrenergic subtype (around 70%), couple to G-proteins (Gs). The second messenger involved in the majority of β_1-AR-mediated effects is the cyclic adenosine 3′,5′-monophosphate (cAMP), which regulates key physiological processes such as cardiac contractility and relaxation. As illustrated in Fig. 1, cAMP is synthetized by adenylyl cyclase (AC) via stimulatory Gs proteins coupled to β-ARs. The balance between AC-mediated production and degradation by phosphodiesterases (PDEs) tightly controls the intracellular concentration of cAMP. This is a heterogeneous superfamily of enzymes, including seven families which catalyze the hydrolysis of cAMP to 5′-AMP [1]. Each family exhibits specificity in terms of intracellular distribution and rate of cAMP degradation, thus regulating the amplitude and duration of cAMP transient, its spreading in intracellular compartments, and downstream activation of effectors. Compartmentalization of β-AR mediated signaling is granted by subcellular distribution of receptor subtypes (see later) but, mostly, by the presence of scaffolding proteins that chain AC, cAMP targets, and PDEs in macromolecular complexes, thus confining the signal (and downstream action) into "self-limiting intracellular pools": A-kinase anchoring proteins (AKAPs). For example, a complex is found in t-tubules where the AKAP150 protein links the AC5/6 isoform, the cAMP-dependent protein kinase (PKA), calcineurin (protein phosphatase type 2), the

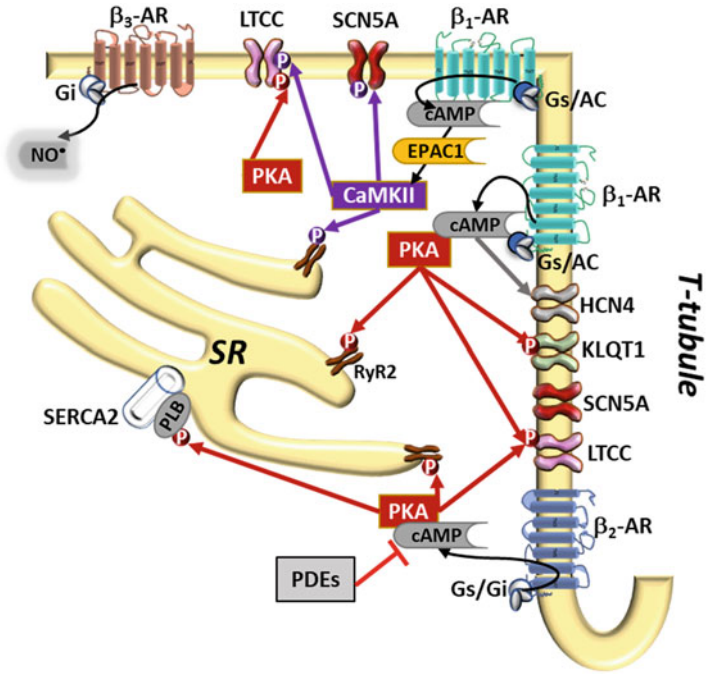

Fig. 1 Schematic representation of β-AR and ion channels crosstalk in cardiomyocytes. β_{1-3}-AR, β-adrenergic receptor subtypes; Gs, Gi, stimulatory or inhibitory G proteins; AC, adenylyl cyclase; EPAC1, exchange proteins directly activated by cAMP type 1; CaMKII, Ca2+/calmodulin-dependent protein kinase II; PKA, protein kinase A; PDEs, phosphodiesterases; PLB, phospholamban; RyR2, ryanodine receptor; SERCA2, sarcoplasmic/endoplasmic reticulum calcium ATPase 2; SR, sarcoplasmic reticulum. NO•, nitric oxide; SCN5A, cardiac sodium channel; LTCC, L-type calcium channel; HCN4, hyperpolarization-activated cyclic nucleotide-gated channel; KLQT1, delayed rectifier potassium channel

membrane protein caveolin-3, and the cardiac calcium channel Cav1.2.

Our comprehension of cAMP targets and effectors has grown significantly in recent years. Most of β-AR-mediated cardiac effects have been attributed classically to activation of PKA, a tetrameric enzyme with two cAMP binding regulatory subunits and two catalytic subunits which phosphorylates multiple substrates (including channels and pumps). cAMP also binds and activates cyclic nucleotide-gated ion channels, such as HCN (see Hyperpolarization-Activated Cyclic Nucleotide-Gated (HCN) Channels) and Popeye domain-containing (POPDC) proteins. Recently, a family of proteins directly activated by cAMP, named EPAC (exchange proteins directly activated by cAMP), was discovered as an important new mechanism for cAMP-mediated signaling [2]. The family consists of two proteins, independent from PKA, EPAC1 and 2, the former being the most abundant one in mouse and human hearts in the adulthood. Binding of cAMP to the specific domain causes a conformational change, exposes both the catalytic and targeting domains of EPAC which exchange GDP for GTP, and promote the activation of a small G protein, Rap.

PKA phosphorylates several substrates involved in key steps of excitation contraction coupling in atrial and ventricular cardiomyocytes. Target proteins of PKA are located on the sarcolemma (e.g., L-type calcium channels, ultra-rapid and slow delayed potassium currents), in the sarcoplasmic reticulum (phospholamban, ryanodine receptors), or in the contractile machinery (cardiac troponin I, cardiac myosin-binding protein C). In physiological conditions, all these effects increase and speed up intracellular calcium transient and contractility (inotropic and lusitropic effect). A similar signaling mechanism results from stimulation of β_2-ARs accounting for the remaining

30% of receptor subtypes; however, they also couple to inhibitory G-proteins (Gi) with opposite effect on adenylate cyclase activity and downstream signaling pathways. It is worth to recall briefly that inhibitory G proteins (Gi) in cardiomyocytes have been traditionally associated to vagal stimulation, via type-2 muscarinic receptors (M_2R). These receptors are largely distributed on the sarcolemma, and their stimulation leads to inhibition of adenylyl cyclase, decrease of intracellular cAMP, and direct (i.e., cAMP-independent) activation of potassium channels, $I_{K,ACh}$. The opposite effect of β_2-AR and M_2R stimulation has been considered a sort of dogma for many years, and still holds true: the positive chronotropic an inotropic effect of catecholamines (↑cAMP) is blunted by the negative ones by acetylcholine (↓cAMP). Thus, the demonstration of a dual signaling pathway downstream β-AR stimulation dispelled a sort of dogma [3].

In nodal cells and in the conduction system (His-Purkinje fibers), cAMP directly modulates the hyperpolarization-activated, cyclic nucleotide-gated channels (HCN), causing a gain of function of the funny current (I_f), which contributes to the steepness of diastolic depolarization. This mechanism is of utmost importance in setting heart rate and atrio-ventricular conduction; the molecular and pharmacological properties of HCN channel family have been recently reviewed [4].

β-AR Subtypes Link to Different Signaling Pathways

The balance between opposite effects initiated by β_1-AR and β_2-AR stimulation resides in several differences that have been partially elucidated only in recent years. First, the relative proportion, which is in favor of the β_1-AR subtype, although the percentage of β_2-AR increases in heart failure also due to downregulation of the first one at the mRNA and protein level. Second, compartmentalization: β_1-AR are located both the transverse t-tubular system (TATS) and crest regions of the sarcolemma, while β_2-AR are located mainly in TATS [5] and co-assemble with the scaffold protein caveolin-3. L-type calcium channels and HCN4 also locate and co-assemble with caveolin-3 proteins [6]. In addition, diverse distribution of phosphodiesterases (PDE) subtypes accounts for the presence of intracellular nanodomains due to fast and specific cAMP degradation [7], being β_2-AR stimulation overall more restrained than the β_1-AR. The compartmentalization of β-AR and PDE isoforms within the cardiomyocyte underlies differences in response to β_1- or β_2-AR stimulation. While cAMP elevation in response to β_1-AR activation is diffuse and extends to the whole cytosol regardless of the stimulation site, cAMP signals in response to β_2-AR activation are always confined to the subcellular region surrounding the activated receptor cluster. It is therefore supposed that β_1-ARs mediate the long-term global response to sympathetic activation, while β_2-ARs control cardiomyocyte function on a beat-to-beat basis.

The β_3-AR subtype represents a case apart. These receptors mainly couple to Gi proteins activating nitric oxide synthase [8]. Although barely expressed in human and rodent cardiomyocytes, β_3-ARs undergo upregulation and gain of function in heart failure where they may contribute to negative inotropic effect [9]. Recently, we observed specific upregulation of β_3-AR during commitment and differentiation of embryonic stem cells toward cardiomyocytes, which appears to modulate expression and function of HCN channels [10].

The Neuro-Cardiac Junction: Cardiac Sympathetic Synapses

Novel evidence suggests that signal transmission between sympathetic neurons and the heart operates in a quasi-synaptic fashion rather than as a slow endocrine response, underlying a quick physiological regulation of cardiac function on a beat-to-beat basis [11]. Using optogenetics to activate selectively single sympathetic neurons, the group of Mongillo demonstrated that the response in terms of cAMP elevation occurs only in the cardiomyocytes that are directly contacted by the neuron's terminations and within a very short timeframe of a few milliseconds. This fast

synapse-like behavior is the result of the direct coupling between neuronal sites releasing neurotransmitters and responsive cardiomyocyte membranes: these neuro-cardiac junctions are specialized extracellular signaling domains with an elevated concentration of norepinephrine. The junctional domain on the cardiomyocyte membrane features a high density of β-ARs and complexes of the cAMP/PKA pathway [11]. Interestingly, optogenetic activation of sympathetic neurons innervating the sino-atrial node led to an instantaneous chronotropic effect with single-beat precision. Whether and how the structure and function of the neuro-cardiac junction change in heart failure and other cardiac diseases remains to be assessed. Heart failure is associated with a reduced myocardial response to sympathetic nerves activation; a derangement of neuro-cardiac junction organization, with increased distance between neuronal terminations and cardiomyocyte membranes, may explain such observation.

β-ARs Modulate Ion Channels and Pumps in the Sarcolemma

Calcium Channels

In the working myocardium, the predominant isoform of L-type calcium channels (LTCC) is CaV1.2; most of these channels (75%) localize in transverse t-tubules, deep invaginations of the sarcolemmal membrane, in close proximity with proteins involved in β-AR signaling such as adenylate cyclase and PKA. Both CaV1.2 and CaV1.3 coexist in nodal cells: they contribute to the so-called "calcium clock" in the sinoatrial node (SAN), i.e., rhythmic release of intracellular calcium. Together with the pacemaker current I_f, calcium kinetics sets sinus rhythm and conduction velocity in the atrioventricular node (AVN) (see Zamponi et al. [12] for a review). The alpha subunit (forming the pore of the channel) is the main site of PKA-mediated phosphorylation at the C-terminal possibly via the interaction between the CaVβ subunit and a protein called Ahnak1. Catecholamines modulate LTCC also via a PKA-independent mechanism: the calcium-calmodulin kinase type 2 (CaMKII): β_1-AR (but not β_2-AR) stimulation promotes the interaction among CaMKII and the regulatory proteins β-arrestin and Epac1, forming a stable complex with the receptor. In turn, CaMKII-mediated phosphorylation increases open probability of LTCC; interestingly, recent data suggest that this signal occurs mainly on calcium channels located in the sarcolemma outside t-tubules and has been associated with abnormalities occurring in cardiac hypertrophy and failure [6].

Sodium Channels

β-AR-activated kinases play an utmost role in post-translational modifications of the sodium channels. PKA-mediated phosphorylation increases sodium current (I_{Na}) amplitude and action potential upstroke velocity; however, from a physiological point of view, the consequences are less defined and largely dependent from the effect of PKA-mediated phosphorylation also on other conductances. For example, the effect on calcium (see above) and potassium channels leads to opposite effects on action potential duration (APD), generally resulting in acceleration of repolarization and shorter effective refractory period in cardiomyocytes from large mammals (including humans) [13], thus allowing for faster recovery of sodium channels from inactivation. At the same time, increased heart rate shortens the diastolic interval and hence reduces I_{Na} recovery from inactivation. In general, at least in physiological conditions and in healthy cardiac tissue, these effects (shortening of APD and diastolic interval) combine to maximize I_{Na} conductance at high heart rate and – joint to the phosphorylation of the gap junction protein connexin 43 – accelerate conduction velocity [14]. A different scenario exists in cardiac disease. Dysregulated phosphorylation due to persistent β-AR stimulation or oxidative stress (which activates CaMKII) has been shown to slow sodium channel inactivation, giving rise to the so-called *late* sodium current ($I_{Na,L}$). At the intracellular level, persistent sodium entry causes calcium

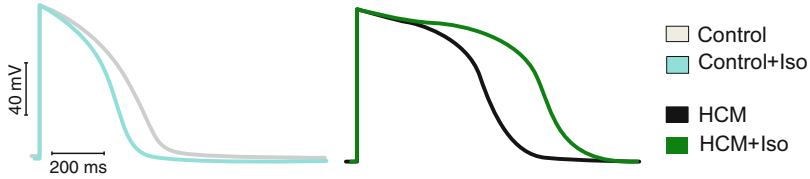

Fig. 2 Effects of β-AR stimulation of action potential from control and diseased human cardiomyocytes. (Modified from Ferrantini et al. [19])
Representative superimposed action potentials elicited at 0.5 Hz in control (left) and HCM (right) cardiomyocytes, in the absence and presence of isoprenaline; Left: gray trace is baseline, light-blue trace is with isoprenaline; Right: black trace is baseline, green trace is with isoprenaline

overload by impairing calcium extrusion via the sodium/calcium exchanger. A prominent $I_{Na,L}$ has been described in cardiomyocytes from animal models of cardiomyopathies [15], as well as in human hypertrophic cardiomyopathy [16]. Some of these aspects will be treated more extensively in the next sections.

Potassium Channels

These channels represent the largest and most heterogeneous family of channels; knowledge of their structure and properties is constantly changing and classification consequently updated. Limiting our attention to voltage-gated potassium channels, delayed rectifier potassium channels are the most relevant in terms of β-AR modulation. The slow and rapid components (I_{Kr} and *IKs*, also termed Kv11.1 and Kv7.1) are ubiquitously expressed in the human myocardium, while the ultrarapid component (I_{Kur}, Kv1.5) is restricted to the human atrial tissue. Noradrenaline, acting via both α_1- and β-ARs through different pathways, negatively modulates I_{Kr} [17]. Conversely, it is generally accepted that PKA-dependent phosphorylation following β_1 or β_2-AR stimulation increases I_{Ks}, while β_3-AR decreases it [18]. However, the consequence in terms of action potential repolarization cannot be easily predicted. In human cardiomyocytes from donor hearts, I_{Kr} is the predominant player in basal conditions, while the contribution of I_{Ks} is amplified under β-AR stimulation. Indeed, we observed a reduction of action potential/duration (APD) in healthy human cardiomyocytes challenged with isoprenaline (Fig. 2, left panel). It is intuitive to speculate that conditions associated with loss of function of either component (e.g., Long QT syndrome) or both (e.g., heart failure, hypertrophy, drugs) may lead to opposite effects of catecholamines, such as APD prolongation and appearance of arrhythmogenic mechanisms at single cell (Fig. 2, right panel) [19] and multicellular level [20].

Hyperpolarization-Activated Cyclic Nucleotide-Gated (HCN) Channels

HCN channels – conducting both Na^+ and K^+ ions – activate upon hyperpolarization and are modulated by intracellular cAMP (see Sartiani et al. [4] for a comprehensive review). Of the four isoforms identified so far, HCN2 and HCN4 are the most sensitive to intracellular cAMP levels, sympathetic (via β-AR) and parasympathetic (via M_2 muscarinic receptors) stimulation having opposite effects. The highest HCN expression occurs in nodal cells, SAN and AVN, followed by His-Purkinje cells, and its amplitude finely adjusts the slope of diastolic depolarization depending on the autonomic balance. Besides its canonical expression in primary or subsidiary pacemaker cells, I_f is constitutively present in the human atria, modulated by catecholamines but also by autacoids (serotonin, adenosine) and natriuretic peptides (reviewed in Sartiani et al. [4]). An ectopic I_f also occurs in diseased human and rodent ventricular cardiomyocytes, its amplitude being linearly related to the severity of cardiac

hypertrophy [21, 22]. This overexpression has been interpreted as the consequence of remodeling toward a fetal phenotype [23]. An example of the effect of β-ARs on I_f expressed in ventricular cardiomyocytes from failing human hearts is shown in Fig. 3: selective β_1 or β_2-AR stimulation causes a positive shift of I_f activation curve while β_3-AR stimulation has an opposite effect, as a consequence of the aforementioned differences in downstream signaling pathways and mediators (see Fig. 1). These differences are emphasized when inhibitory G proteins are irreversibly activated by PTX (Fig. 3), which does not modify β_1-mediated response on HCN channels, but strongly amplifies the effect of β_2-ARs (associated to both Gs and Gi) and abolishes β_3-mediated negative shift of I_f.

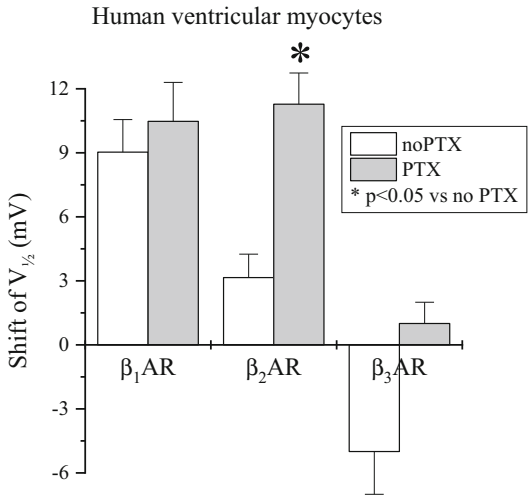

Fig. 3 Effect of stimulation of β-AR subtypes on I_f activation in human failing cardiomyocytes
β_1-AR stimulation with 1 μM noradrenaline (NA) caused a positive shift of midpoint activation (V_H) of I_f (8.9 ± 1.3 mV, $n = 5$) significantly larger than that caused by β_2-AR stimulation obtained with 1 μM isoprenaline plus the selective β_1-AR antagonist CGP 20712A (0.1 μM) (4.5 ± 1.1 mV, $n = 4$). The positive shift of V_H induced by β_2-AR was significantly increased (11.3 ± 1.4 mV, $n = 5$) by preincubation of human ventricular myocytes (HuVM) with pertussis toxin (PTX, 0.5 μg/ml) ($p < 0.05$ vs. untreated cells), thus suggesting that also in HuVM, β_2-AR are coupled to both stimulatory and inhibitory G proteins. β_1-AR stimulation was practically unaffected by PTX-treatment (shift: 10.5 ± 1.8 mV, $n = 3$). On the contrary, β_3-AR stimulation with the selective agonist SR58611A (1 μM) consistently caused a negative shift of I_f activation (−5 mV, $n = 4$), abolished by PTX treatment

Sarcoplasmic Reticulum Receptors and Pumps

An extensive description of cardiac excitation contraction coupling (ECC) mechanisms is beyond the scope of this chapter and the reader is referred to dedicated reviews. Here, it is sufficient to recall that ECC relays upon the proximity (≈15 nm) between clusters of CaV1.2, located in transverse t-tubules, and clusters of type 2 ryanodine receptors (RyR2) located in the junctional sarcoplasmic reticulum (Fig. 1). These structures form the so-called cardiac dyad that – together with proteins responsible for calcium upload, buffering, binding, and extrusion – modulates the amplitude and duration of calcium transient and, hence, contraction/relaxation. The RyR2 channel is part of a macromolecular complex, which tightly modulates channel activity (open/close state); however, post-translational modifications such as phosphorylation (by PKA and CaMKII), dephosphorylation (by phosphatases), and S-nitrosylation are responsible for physiological adaption to cardiac rhythm or disease-induced maladaptation and arrhythmias. The sarcoplasmic reticulum (SR) calcium pump (SERCA2) plays an utmost role in controlling intracellular calcium homeostasis, by removing about 90% of cytosolic calcium ions released from SR during systole. Modulation of SERCA2 by β-AR stimulation mainly occurs via PKA-mediated phosphorylation of phospholamban (PLB), which inhibits SERCA2 in its de-phosphorylated state. Increased calcium entry through LTCC, faster Ca^{2+} uptake via SERCA2 (loading SR), and PKA (or CaMKII)-mediated phosphorylation of RyR2s (lowering the threshold for Ca^{2+} release): all these mechanisms concur to enhance the propensity to spontaneous calcium release from the SR into the cytosol and to trigger the spontaneous cellular Ca^{2+} waves and arrhythmia upon β-AR stimulation. However, recent data suggest that intracellular cAMP also stabilizes the threshold for SR Ca^{2+} release by activating SERCA2 directly, via PKA-

mediated phosphorylation, a sort of negative feedback mechanism able to attenuate the arrhythmogenic propensity [24]. To add further complexity to the general picture, it is worth to mention the emerging role of Epac1 and downstream signaling in β-AR mediated effects on SR function. CaMKII-mediated phosphorylation of PLB (at Thr17) and RyR2 (at Ser2814) have been observed following exposure to the Epac activator 8-CPT in mice, although the two targets appear to be preferentially phosphorylated at low (PLB) or high (RyR2) extracellular calcium [25]. In conclusion, β-ARs exert a fine-tuning modulation of intracellular calcium homeostasis by acting on multiple targets and via differential signaling pathways.

Alterations in Receptor-Channel Interplay in Cardiac Disease and Arrhythmogenesis

The Broken Heart Syndrome

In the complex and yet unexplained mutual relationship between heart and brain, it is worth to start from the most striking evidence of what emotion, fear, or strong emotional stress can cause to the heart. Anecdotally, unexplained chest pain and death under psychological stress have been reported since centuries in any culture. In the 1990s, Sato and co-workers reported a transient dysfunction of the left ventricle and termed it *takotsubo* syndrome because the heart's shape recalled a Japanese trap for octopus [26]. Takotsubo syndrome affects mainly women, but it has been described also in men as a consequence of psychotropic drug abuse. Although its origin is certainly multifactorial, with hormonal and genetic factors playing a relevant role, the combination of stress and – occasionally – amphetamines strongly advocates for the involvement of sympathetic stimulation. Indeed, epinephrine and norepinephrine levels were found higher during the acute phase of *takotsubo* cardiomyopathy, usually 2–3 times higher than those found in patients with acute myocardial infarction [27]. Catecholamine-mediated stunning of myocardium occurs via a number of mechanisms, including mid-ventricular obstruction, epicardial vasospasm, microvascular dysfunction, and deleterious effects on cardiomyocytes. Excessive β_2-AR activity (i.e., in presence of exceptionally high circulating epinephrine levels) has been postulated as the main determinant of this disease, as it leads to cardiac dysfunction and myocyte injury through calcium leakage due to hyperphosphorylation of the ryanodine receptor [28]. Predominant apical involvement has been explained by a denser concentration of adrenoceptors (and in particular β_2-ARs) in the apex as compared with the basis, as ascertained by experiments in animal models of the disease. In a rat model, high-dosage bolus of intravenous epinephrine, but not norepinephrine, produced the characteristic reversible apical depression of myocardial contraction coupled with basal hypercontractility, typical of *takotsubo* cardiomyopathy [29]. Interestingly, this effect was prevented via G_i inactivation by pertussis toxin pretreatment. High-dose epinephrine was in fact able to induce direct cardiomyocyte cardio-depression via the alternative signaling pathway associated with the β_2-AR receptor, i.e., the G_i-dependent pathway. At very high concentrations, epinephrine selectively favors the activation of the G_i pathway of the β_2 receptor, while it preferably activates the β_2-AR-G_s excitatory pathway at lower concentrations; this epinephrine-specific β_2-AR-G_i signaling may have evolved as a cardioprotective strategy to limit catecholamine-induced myocardial toxicity during acute stress. The organization of cardiomyocyte signaling subdomains (described in previous sections) also appears to be involved in the pathogenesis of *takotsubo* cardiomyopathy, as shown in a recent paper by Gorelik's lab [7]. Using an elegant approach, they showed a different sensitivity to catecholamines in the apical versus basal ventricular cardiomyocytes, the first being more prone to "stunning" under stressful conditions. Interestingly, in this model of takotsubo, the susceptibility of the ventricular apex to a catecholamine storm was not due to receptor or channel number, but to their sublocalization: basal cardiomyocytes have higher density of t-tubules, where diffusion of cAMP to calcium channels and ryanodine receptors is more strictly controlled by PDEs. Indeed, inhibiting type 4 PDE or disrupting

the tubular nanodomains, which constrain β_2-AR, caveolin-3, and calcium channels and/or their downstream signals, switch from basal into apical features.

Interplay Between β-ARs and Calcium Channels in Heart Failure

The role of the t-tubular network in maintaining the appropriate crosstalk between β-AR and calcium handling has been recently elucidated. Disorganization of TATS has been described in cardiomyopathies of different etiology, such as heart failure and hypertrophic cardiomyopathy in humans [15] as well as in animal models [16], along with spatial alteration of proteins involved in excitation contraction coupling, β-AR and CaV1.2. Recently, exploiting ultrafast random-access multi-photon microscopy allowed some of us to simultaneously record action potential and calcium release at a subcellular resolution, nearby tubular and crestal sarcolemma [30, 31]. In these experimental conditions, the β-AR signaling on ryanodine receptors (RyR2) was preserved in cells from failing hearts; however, major changes occur in the density and regularity of the t-tubular network and also in the functioning of apparently preserved t-tubules [32]. Overall, both the lack of t-tubules and the failure of action potential propagation in defective ones may contribute to blunt the effect of the β-adrenergic signaling on calcium transients, impairing especially the physiological acceleration of calcium rise. In particular, the effects of β-AR stimulation on the frequency of Ca^{2+} sparks, decay, and variability of Ca^{2+} transients were similar in cardiomyocytes from control or failing rat hearts. However, differences emerged related to compartmentalization of β-AR signaling: in HF cells, upon exposure to isoproterenol, the rate of Ca^{2+} rise accelerated only in the proximity of t-tubules that regularly conducted the action potential, not at t-tubules that failed to conduct action potentials. These findings can be interpreted in light of different distribution of cAMP pools and targets in the cardiomyocyte, as previously discussed.

β-AR Signaling in Heart Failure: The Role of PDEs

A hallmark of heart failure is the hyperactivation of sympathetic system, leading to high plasma levels of noradrenaline and blunted β-AR signaling as a consequence of hyperstimulation and decreased receptor number and function [33]. However, attempt to circumvent β-AR down-regulation by increasing intracellular cAMP levels with the PDE inhibitor milrinone revealed effectiveness in short term, but led to premature death in HF patients, thus precluding its long-term use. During the last decades, seminal studies contributed to elucidate the mechanisms underlying the fine regulation of cAMP levels and the compartmentalization PDE isoforms in cardiomyocytes [34]. Recent studies, however, resumed PDEs as drug targets in HF by exploiting inhibition of PDE1, an isoform thought to be absent in cardiomyocytes up to the demonstration of the functional presence of PDE1A and 1C 10 years ago. More recently, thanks to the availability of inhibitors, two independent studies focused on PDE1C in different models of heart failure. PDE1C inhibition protected mouse cardiomyocytes against angiotensin II- or doxorubicin-induced cell death and, interestingly, did it via enhancement of the cAMP production due to stimulation of type-2 adenosine receptors (A_2R) which co-localize with PDE1C [35]. The second study, a positive inotropic and lusitropic action, was observed in mammal hearts following PDE1C inhibition by IT-214, additive to those of β-AR stimulation and similarly linked to A_2R [36]. Ongoing clinical trials with the PDE1C inhibitor ITI-214 may lead to novel therapeutic opportunities for patients with heart failure.

β-AR, AMPK, and Cardiac Arrhythmias

A major consequence of β-AR stimulation of the heart is the increased workload and basal energy demand requiring beat-to-beat adjustment of energetic homeostasis. A hallmark response to β-AR stimulation in cardiac and extra-cardiac tissues is the activation of AMP-activated protein kinase (AMPK), a central mediator in adaptive functions

aimed to cope with enhanced energy requirements. AMPK is a ubiquitous heterotrimeric kinase composed of a catalytic α-subunit and regulatory β and γ subunits [37]. α1 and α2 isoforms are expressed in the cardiac tissue, where the function is increasingly documented in both physiological and pathological conditions. AMPK acts as specific sensor of tissue energetic state and accomplishes different functions holding elevate value in cardio-protection.

AMPK targets several substrates in cardiac tissue, mainly metabolic enzymes, which are stimulated or inhibited to accomplish two main specific functions: upregulating energy sources by increasing ATP-generating catabolism and downregulating energy-consuming processes by reducing energy-consuming pathways. A strong body of evidence indicates a protective role of AMPK against disease progression and inherent propensity to develop arrhythmic activities in clinically relevant settings, such as cardiac hypertrophy, failure, and atrial fibrillation [38]. However, AMPK activity may also promote arrhythmogenic mechanisms acting directly on properties of cardiac ion channels. One of them is the incomplete sodium channel inactivation in cardiac myocytes caused by AMPK activity; this modification leads to prolonged sodium entrance into the cardiac myocyte, which enhances the likelihood of arrhythmic events (see below).

Although evidence is not conclusive yet, also cardiac potassium channels may contribute to the direct arrhythmogenic effects of AMPK activation. In particular, there are data supporting a downregulation of cardiac inward rectifier (I_{K1}) and slow delayed rectifier (I_{Ks}) channels, which both enhance arrhythmogenic prolongation of action potential.

Acquired/Congenital Channelopathies and Catecholamine-Induced Arrhythmias

Cardiac channels are suited to respond to autonomic input, even to abrupt changes; however, lethal arrhythmogenic mechanisms may occur due to genetic defects or transcriptional–post-translational alterations in channel properties or number. Activation kinetics of HCN channels quickly adapts to $\beta_{1/2}$-AR stimulation in SAN cells. A gain-of-function mutation (R524Q) in cardiac HCN4 channel has been demonstrated in subjects with inappropriate sinus tachycardia. These channels display a higher sensitivity to cAMP (hence to $\beta_{1/2}$-AR stimulation), giving rise to a steeper diastolic depolarization and faster spontaneous firing in SAN cells, hence enhanced cardiac rate [39]. Also endurance training athletes, as well as aged people, eventually experience sinus bradycardia although causes are not genetic in this case [40], rather associated to modifications of SAN and atria functional and structural properties that may predispose also to atrial tachyarrhythmias.

In human atrial cardiomyocytes, in fact, HCN current is constitutively present and modulated by several neurotransmitters and endogenous factors. Some signals have been implicated in the pathogenesis of atrial fibrillation, such as catecholamines, serotonin, atrial natriuretic peptide (ANP). Catecholamines enhance I_f via Gs-coupled β_1- and β_2-ARs, as previously discussed; a similar effect occurs with serotonin acting on subtype-4 5-HT receptors [41, 42]. Both serotonin and catecholamines amplify HCN current shifting the activation voltage to positive values. Interestingly, ANP exerts a similar effect via its NP receptors (type A and B), which stimulate a guanylyl-cyclase activity. However, in this case, the cyclic nucleotide does not act on HCN channels directly; rather, intracellular cGMP inhibits a PDE causing a consequent increase of intracellular cAMP [43]. All these mediators may promote the function of HCN channels at physiological potentials enhancing the propensity to atrial arrhythmias.

In the ventricle, upregulation of HCN2 and HCN4 channels in failing human hearts is a hallmark of cardiac maladaptive remodeling [22]. This "ectopic" I_f exhibits a typical sensitivity to autonomic transmitters, similar to that described in the SAN cells, with a positive shift of voltage dependence upon $\beta_{1/2}$-AR stimulation. As reviewed in Sartiani et al. [4], I_f is larger and

activates at more positive potentials in human ventricular myocytes from explanted failing hearts than in cells from donor hearts and is more prominent in ischemic than in dilated cardiomyopathy. Functional alterations go hand-in-hand with increased levels of HCN4 and HCN2 proteins and transcripts [22, 44]. Similar changes have been widely confirmed in animal models of cardiac hypertrophy and failure. Recently, in a mouse model of dilated cardiomyopathy, enhanced HCN current – due to ventricular up-regulation of HCN2 and HCN4 proteins – was proved to cause ventricular tachycardia, premature ventricular contractions, and sudden cardiac death [45]. In isolated cells from the same mice, β-AR stimulation caused the appearance of arrhythmogenic mechanisms such as early afterdepolarizations and spontaneous action potentials.

Patients with long QT syndrome are at high risk of sudden cardiac death triggered by exercise or emotion. Especially in LQT1 associated to I_{Ks} loss of function, lack of APD adaption to increased β-AR stimulation can lead to repolarization de-synchrony and transmural dispersion. A similar condition may occur due to congenital (LQT3) or acquired abnormalities in sodium channel inactivation leading to sustained sodium entry ($I_{Na,L}$). As shown in Fig. 2, in septal cardiomyocytes from patients with hypertrophic cardiomyopathy, β-AR prolongs, rather than shortening, APD [19]. This is the consequence of a complex remodeling of electrophysiological properties involving CaMKII-mediated phosphorylation of sodium channel (which delays inactivation), reduced potassium currents, and increased calcium and sodium/calcium exchanger currents [15]. As detailed above, β-adrenergic simulation increases both I_{Ks} potassium current and $I_{Ca,L}$ that have opposite effects on AP duration. In the healthy human cardiomyocyte, the net effect is a shortening of APD, as the increase of repolarizing K^+-currents prevails over the augmentation of the depolarizing Ca^{2+}-current. In hypertrophic cardiomyopathy however, the expression of all K^+ channels is severely decreased, including I_{Ks}, while the density of $I_{Ca,L}$ is unchanged: therefore, upon β-AR stimulation, the increase of $I_{Ca,L}$ prevails over the augmentation of I_K, ultimately leading to APD prolongation [19]. This abnormal response may be relevant for the pathogenesis of stress-induced arrhythmias in hypertrophic cardiomyopathy: indeed, prolongation of APD is paralleled by an increase of intracellular diastolic calcium and sodium concentrations, as well as a higher frequency of early and delayed afterdepolarizations (EADs and DADs). Interestingly, the frequency of EADs and the degree of APD prolongation were significantly higher in cells from patients exhibiting a higher rate of documented nonsustained ventricular tachycardia at 24-h ECG [15].

Mutations in RyR2 underlie deadly arrhythmias named catecholaminergic polymorphic ventricular tachycardia (CPVT) [46]. Although pathogenic mechanisms remain controversial, it is largely agreed that defective RyR2 increases calcium leak from sarcoplasmic reticulum exacerbated by β-AR stimulation, impairs atrial and ventricular contractility [47], and causes the appearance of DADs and triggered activity, resulting in ventricular tachycardia and fibrillation.

Conclusion

Modulation of ion channels by β-adrenergic stimulation is a crucial modulator of cardiac function in physiological settings. The fast coupling between sympathetic nerves and cardiomyocyte membranes expressing β-ARs, combined with the compartmentalization and the rapid activation/inactivation cycle of the cAMP/PKA cascade, allows for a fine-tuned modulation of cardiac electrical and mechanical function on a beat-to-beat basis. The majority of the molecular structures responsible for adrenergic modulation of cardiac function, from the nerves down to the target ion channels and transporters, are altered in cardiac diseases such as heart failure, and may therefore be responsible for the abnormal responsiveness of diseased hearts to sympathetic activation, with severe implications for mechanical dysfunction and stress-induced arrhythmias.

References

1. Musheshe N, Schmidt M, Zaccolo M. cAMP: from long-range second messenger to nanodomain signalling. Trends Pharmacol Sci. 2018;39(2):209–22.
2. Laudette M, Zuo H, Lezoualc'h F, Schmidt M. Epac function and cAMP scaffolds in the heart and lung. J Cardiovasc Dev Dis. 2018;5(1):9.
3. Xiao RP, Ji X, Lakatta EG. Functional coupling of the beta 2-adrenoceptor to a pertussis toxin-sensitive G protein in cardiac myocytes. Mol Pharmacol. 1995; 47(2):322–9.
4. Sartiani L, Mannaioni G, Masi A, Romanelli MN, Cerbai E. The hyperpolarization-activated cyclic nucleotide–gated channels: from biophysics to pharmacology of a unique family of ion channels. Pharmacol Rev. 2017;69(4):354–95.
5. Nikolaev VO, Moshkov A, Lyon AR, Miragoli M, Novak P, Paur H, et al. Beta2-adrenergic receptor redistribution in heart failure changes cAMP compartmentation. Science. 2010;327(5973):1653–7.
6. Sanchez-Alonso JL, Bhargava A, O'Hara T, Glukhov AV, Schobesberger S, Bhogal N, et al. Microdomain-specific modulation of L-type calcium channels leads to triggered ventricular arrhythmia in heart failure. Circ Res. 2016;119(8):944–55.
7. Wright PT, Bhogal NK, Diakonov I, Pannell LMK, Perera RK, Bork NI, et al. Cardiomyocyte membrane structure and cAMP Compartmentation produce anatomical variation in beta2AR-cAMP responsiveness in murine hearts. Cell Rep. 2018;23(2):459–69.
8. Gauthier C, Leblais V, Kobzik L, Trochu JN, Khandoudi N, Bril A, et al. The negative inotropic effect of beta3-adrenoceptor stimulation is mediated by activation of a nitric oxide synthase pathway in human ventricle. J Clin Invest. 1998;102(7):1377–84.
9. Gauthier C, Tavernier G, Charpentier F, Langin D, Le Marec H. Functional beta3-adrenoceptor in the human heart. J Clin Invest. 1996;98(2):556–62.
10. Spinelli V, Sartiani L, Mugelli A, Romanelli MN, Cerbai E. Hyperpolarization-activated cyclic-nucleotide-gated channels: pathophysiological, developmental, and pharmacological insights into their function in cellular excitability. Can J Physiol Pharmacol. 2018;96 (10):977–84.
11. Prando V, Da Broi F, Franzoso M, Plazzo AP, Pianca N, Francolini M, et al. Dynamics of neuroeffector coupling at cardiac sympathetic synapses. J Physiol. 2018;596(11):2055–75.
12. Zamponi GW, Striessnig J, Koschak A, Dolphin AC. The physiology, pathology, and pharmacology of voltage-gated calcium channels and their future therapeutic potential. Pharmacol Rev. 2015;67(4):821–70.
13. Jost N, Virág L, Bitay M, Takács J, Lengyel C, Biliczki P, et al. Restricting excessive cardiac action potential and QT prolongation. Circulation. 2005;112: 1392–9.
14. Campbell AS, Johnstone SR, Baillie GS, Smith G. Beta-adrenergic modulation of myocardial conduction velocity: connexins vs. sodium current. J Mol Cell Cardiol. 2014;77:147–54.
15. Coppini R, Ferrantini C, Yao L, Fan P, Del Lungo M, Stillitano F, et al. Late sodium current inhibition reverses electromechanical dysfunction in human hypertrophic cardiomyopathy. Circulation. 2013; 127(5):575–84.
16. Coppini R, Mazzoni L, Ferrantini C, Gentile F, Pioner JM, Laurino A, et al. Ranolazine prevents phenotype development in a mouse model of hypertrophic cardiomyopathy. Circ Heart Fail. 2017;0(3). pii: e003565.
17. Zankov DP, Yoshida H, Tsuji K, Toyoda F, Ding WG, Matsuura H, et al. Adrenergic regulation of the rapid component of delayed rectifier K+ current: implications for arrhythmogenesis in LQT2 patients. Heart Rhythm. 2009;6(7):1038–46.
18. Bosch RF, Schneck AC, Kiehn J, Zhang W, Hambrock A, Eigenberger BW, et al. beta3-adrenergic regulation of an ion channel in the heart-inhibition of the slow delayed rectifier potassium current I(Ks) in guinea pig ventricular myocytes. Cardiovasc Res. 2002;56 (3):393–403.
19. Ferrantini C, Pioner JM, Mazzoni L, Gentile F, Tosi B, Rossi A, et al. Late sodium current inhibitors to treat exercise-induced obstruction in hypertrophic cardiomyopathy: an in vitro study in human myocardium. Br J Pharmacol. 2018;175(13):2635–52.
20. Kang C, Badiceanu A, Brennan JA, Gloschat C, Qiao Y, Trayanova NA, et al. Beta-adrenergic stimulation augments transmural dispersion of repolarization via modulation of delayed rectifier currents IKs and IKr in the human ventricle. Sci Rep. 2017;7(1):15922.
21. Cerbai E, Barbieri M, Mugelli A. Occurrence and properties of the hyperpolarization-activated current if in ventricular myocytes from normotensive and hypertensive rats during aging. Circulation. 1996; 94(7):1674–81.
22. Stillitano F, Lonardo G, Zicha S, Varro A, Cerbai E, Mugelli A, et al. Molecular basis of funny current (I(f)) in normal and failing human heart. J Mol Cell Cardiol. 2008;45(2):289–99.
23. Cerbai E, Pino R, Sartiani L, Mugelli A. Influence of postnatal-development on I(f) occurrence and properties in neonatal rat ventricular myocytes. Cardiovasc Res. 1999;42(2):416–23.
24. Fernandez-Tenorio M, Niggli E. Stabilization of Ca(2+) signaling in cardiac muscle by stimulation of SERCA. J Mol Cell Cardiol. 2018;119:87–95.
25. Lezcano N, Mariangelo JIE, Vittone L, Wehrens XHT, Said M, Mundina-Weilenmann C. Early effects of Epac depend on the fine-tuning of the sarcoplasmic reticulum Ca(2+) handling in cardiomyocytes. J Mol Cell Cardiol. 2018;114:1–9.
26. Dote K, Sato H, Tateishi H, Uchida T, Ishihara M. Myocardial stunning due to simultaneous multivessel coronary spasms: a review of 5 cases. J Cardiol. 1991;21(2):203–14.
27. Wittstein IS, Thiemann DR, Lima JA, Baughman KL, Schulman SP, Gerstenblith G, et al. Neurohumoral

features of myocardial stunning due to sudden emotional stress. N Engl J Med. 2005;352(6):539–48.
28. Ellison GM, Torella D, Karakikes I, Purushothaman S, Curcio A, Gasparri C, et al. Acute beta-adrenergic overload produces myocyte damage through calcium leakage from the ryanodine receptor 2 but spares cardiac stem cells. J Biol Chem. 2007;282(15):11397–409.
29. Paur H, Wright PT, Sikkel MB, Tranter MH, Mansfield C, O'Gara P, et al. High levels of circulating epinephrine trigger apical cardiodepression in a beta2-adrenergic receptor/Gi-dependent manner: a new model of Takotsubo cardiomyopathy. Circulation. 2012;126 (6):697–706.
30. Crocini C, Coppini R, Ferrantini C, Yan P, Loew LM, Poggesi C, et al. T-tubular electrical defects contribute to blunted beta-adrenergic response in heart failure. Int J Mol Sci. 2016;17(9). pii: E1471.
31. Crocini C, Coppini R, Ferrantini C, Yan P, Loew LM, Tesi C, et al. Defects in T-tubular electrical activity underlie local alterations of calcium release in heart failure. Proc Natl Acad Sci U S A. 2014;111(42):15196–201.
32. Ferrantini C, Crocini C, Coppini R, Vanzi F, Tesi C, Cerbai E, et al. The transverse-axial tubular system of cardiomyocytes. Cell Mol Life Sci. 2013; 70(24):4695–710.
33. Lefkimmiatis K, Zaccolo M. cAMP signaling in subcellular compartments. Pharmacol Ther. 2014; 143(3):295–304.
34. Leroy J, Abi-Gerges A, Nikolaev VO, Richter W, Lechene P, Mazet JL, et al. Spatiotemporal dynamics of beta-adrenergic cAMP signals and L-type Ca2+ channel regulation in adult rat ventricular myocytes: role of phosphodiesterases. Circ Res. 2008;102(9):1091–100.
35. Zhang Y, Knight W, Chen S, Mohan A, Yan C. Multiprotein complex with TRPC (transient receptor potential-canonical) channel, PDE1C (phosphodiesterase 1C), and A2R (adenosine A2 receptor) plays a critical role in regulating cardiomyocyte cAMP and survival. Circulation. 2018;138(18):1988–2002.
36. Hashimoto T, Kim GE, Tunin RS, Adesiyun T, Hsu S, Nakagawa R, et al. Acute enhancement of cardiac function by phosphodiesterase type 1 inhibition. Circulation. 2018;138(18):1974–87.
37. Carling D. The AMP-activated protein kinase cascade – a unifying system for energy control. Trends Biochem Sci. 2004;29(1):18–24.
38. Harada M, Nattel SN, Nattel S. AMP-activated protein kinase: potential role in cardiac electrophysiology and arrhythmias. Circ Arrhythm Electrophysiol. 2012; 5(4):860–7.
39. Baruscotti M, Bianco E, Bucchi A, DiFrancesco D. Current understanding of the pathophysiological mechanisms responsible for inappropriate sinus tachycardia: role of the if "funny" current. J Interv Card Electrophysiol. 2016;46(1):19–28.
40. D'Souza A, Bucchi A, Johnsen AB, Logantha SJ, Monfredi O, Yanni J, et al. Exercise training reduces resting heart rate via downregulation of the funny channel HCN4. Nat Commun. 2014;5:3775.
41. Lonardo G, Cerbai E, Casini S, Giunti G, Bonacchi M, Battaglia F, et al. Pharmacological modulation of the hyperpolarization- activated current (I-f) in human atrial myocytes: focus on G protein-coupled receptors. J Mol Cell Cardiol. 2005;38(3):453–60.
42. Pino R, Cerbai E, Calamai G, Alajmo F, Borgioli A, Braconi L, et al. Effect of 5-HT4 receptor stimulation on the pacemaker current I(f) in human isolated atrial myocytes. Cardiovasc Res. 1998;40(3):516–22.
43. Lonardo G, Cerbai E, Casini S, Giunti G, Bonacchi M, Battaglia F, et al. Atrial natriuretic peptide modulates the hyperpolarization-activated current (I-f) in human atrial myocytes. Cardiovasc Res. 2004;63(3): 528–36.
44. Suffredini S, Stillitano F, Comini L, Bouly M, Brogioni S, Ceconi C, et al. Long-term treatment with ivabradine in post-myocardial infarcted rats counteracts f-channel overexpression. Br J Pharmacol. 2012;165(5): 1457–66.
45. Kuwabara Y, Kuwahara K, Takano M, Kinoshita H, Arai Y, Yasuno S, et al. Increased expression of HCN channels in the ventricular myocardium contributes to enhanced arrhythmicity in mouse failing hearts. J Am Heart Assoc. 2013;2(3):e000150.
46. Priori SG, Napolitano C, Tiso N, Memmi M, Vignati G, Bloise R, et al. Mutations in the cardiac ryanodine receptor gene (hRyR2) underlie catecholaminergic polymorphic ventricular tachycardia. Circulation. 2001;103(2):196–200.
47. Ferrantini C, Coppini R, Scellini B, Ferrara C, Pioner JM, Mazzoni L, et al. R4496C RyR2 mutation impairs atrial and ventricular contractility. J Gen Physiol. 2016;147(1):39–52.

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S. Govoni et al. (eds.), *Brain and Heart Dynamics*,
https://doi.org/10.1007/978-3-030-28008-6