The Heart as a Psychoneuroendocrine and Immunoregulatory Organ

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The heart as a multi-regulatory system. Artwork by Piet Michiels, Leuven, Belgium

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Abstract

The heart can be viewed not just as muscle pump but also as an important checkpoint for a complex network of nervous, endocrine, and immune signals. The heart is able to process neurological signals independently from the brain and to crosstalk with the endocrine and immune systems. The heart communicates with the psyche through the neuro-endocrine-immune system in a highly integrated way, in

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order to maintain the homeostasis of the whole body with peculiarities specific to males and females.

Keywords
Alarmin · Beta-blocker · Brain-heart axis · Cardiokine · Emotion · Heart-brain interaction · Mental stress · Psychic factors in heart disease · Psychosocial stress · Neuroendocrine regulation · Immunoregulatory function · Pattern recognition receptor · Toll-like receptor · Sex-specific analysis · Review

Introduction

As William Harvey wrote [1] in 1628, "every affection of the mind that is attended with either pain or pleasure, hope or fear, is the cause of an agitation whose influence extends to the heart." Following the research of Claude Bernard, also Charles Darwin in 1872 [2] described the relationship between the brain and the heart in a simple and clear way and in particular indicated that the heart, which has its own autonomous rhythm, is strongly influenced by bodily sensations and mental activity. The brain through the vagus nerve (called by Darwin "pneumogastric nerve" [3]) acts on the heart, which in turn retraces on the brain, outlining a network of reciprocal connections between the two most important organs of the human body. In addition to the nervous system, we will see that the heart is also at the center of a dense endocrine and immune network.

Chronic psychological stress leads to continuous mechanical stress and chronic overstraining of the heart muscle machinery [4–6] resulting in immune activation and, if repair mechanisms are not sufficient, in negative cardiac remodeling and heart failure [7].

Psycho-Neuro-Endocrine-Immunology (PNEI): The Crosstalk Between Psyche and Biological Systems

Life is based on the proper integration between the major biological systems: a physiological truth that is often obscured by the current scientific view that seeks to study, understand, and cure the human being with a purely mechanistic approach: as if man was only the sum of genetically determined components performing single independent functions. Already Aristotle warned us: "the whole is more than the sum of its parts."

Thanks to the research [8–10] of Ader, Cohen, Besedowsky, Pert, and Felten, started 40 years ago, we now know that the psyche communicates incessantly with the nervous, endocrine, and immune systems. All components reciprocally regulate their function, thus leading to a single large integrated system of adaptation to the environment [11]. In particular, in human physiology, the integration of nervous, endocrine, and immune systems includes psychic regulation. Mental processes affect immune activity (as well as neuroendocrine activity – as in the case of the "stress response" [12, 13]) and are in turn influenced by immune activity [14, 15] as well as mental activity which modifies brain morphology [16]. As described by F. Bottaccioli in the book *Integrative Cardiology,* p. 143 [17], "we can make this analogy: the software running on the brain machine modifies the machine itself. For this reason, the psyche-brain system cannot be compared with a computer system. In this latter case, if one changes the software, the hardware does not follow suit, whereas in the first case (the psyche-brain system) the software modifies the hardware."

Neurotransmitters, hormones, and cytokines are the coded words spoken by the nervous, endocrine, and immune systems. Indeed, these terms are somehow reductive nowadays, since the distinction between neurotransmitters and cytokines has become less clear, because nerves can

synthesize and release inflammatory substances such as histamine and cytokines such as interleukins (IL), i.e., IL-1 and IL-6 [9, 18]. On the other hand, immune cells can synthesize and release neurotransmitters and hormones, such as corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), endorphins, vasoactive intestinal peptides (VIPs), and others [9, 18]. In short, our body uses an "esperanto" type of "language" recognized by all its compartments [9, 18].

Sex differences in stress responses could be epigenetically inherited [19, 20] and can be found at all stages of life. These differences may relate to both the organizational and activational effects of gonadal hormones [21, 22] on brain structure, function [23], and neurochemistry (mainly serotonin (5-HT), corticotropin (CRF), and gamma-aminobutyric acid (GABA) signaling) and to genes on the sex chromosomes [24].

From puberty to menopause, adult women usually show lower hypothalamic-pituitary-adrenal axis (HPAA) and autonomic responses than men of the same age [25]. However, the HPAA response is higher in the luteal phase, when, for example, poststress-free cortisol levels approach those of men [26]. After menopause, there is an increase in sympathoadrenal responsiveness, which attenuates during oral hormone replacement therapy. Indeed the HPAA activity shows the same trends [25]. Interestingly, pregnancy is associated with an attenuated response of the sympathoadrenal and HPAA systems at least as assessed by biochemical stimulation [27]. Likely these sex differences in autonomic function are the result of estrogen exposure, which decreases sympathoadrenal responsiveness [28].

Moreover, immunocompetent cells in the brain are responsive to steroid hormones, and their role in sex-specific brain development is an emerging field of interest. In fact, men and women seem to possess different number, morphology, and signaling profile of immune cells in their brain, playing a crucial role in early-life programming of sex differences in the brain and behavior [29].

The presence of an integrated network limits the concept of "hierarchy" between organs and suggests a revision of the past mechanistic and reductionist assumptions oversimplifying the human being. In the PNEI network, all organs work at the same level exchanging signals to maintain the integrity of the whole system in relation to the environment [30–32]. The heart is one of these knots. Herein we will discuss how the cardiovascular system communicates in the PNEI network (Fig. 15.1).

The Heart in the (Regulatory) Network

As described by Francisco Torrent-Guasp [34–39], and illustrated in Fig. 15.2, the heart can be viewed as a helical muscle tube that produces two simple loops that start at the pulmonary artery and end in the aorta: a spiral horizontal basal loop that surrounds the right and left ventricular cavities, and changes direction to cause a second spiral, produced by almost vertically oriented fibers, giving rise to the helical configuration of the ventricular myocardial band. These anatomic structures are subsequently activated by a sort of peristaltic wave, starting at the right ventricle (just below the pulmonary artery) and progressing toward the aorta to produce a sequence of:

1. Narrowing, caused by the basal loop contraction
2. Shortening (related predominantly to the descendant segment contraction)
3. Lengthening (produced by the ascendant segment contraction)
4. Widening, as a consequence of several factors that act during ventricular myocardial relaxation [34–39]

This sequential activation, which is still under investigation, leads to the mechanical events responsible for ejection to empty and subsequent suction to fill [34] the ventricles.

The heart, if adequately nourished, continues to beat alone [43], regardless of the brain. Moreover, from embryology we know that the heart begins to beat before the brain is formed. A transplanted heart is not connected to the host nervous system, but can immediately satisfy the

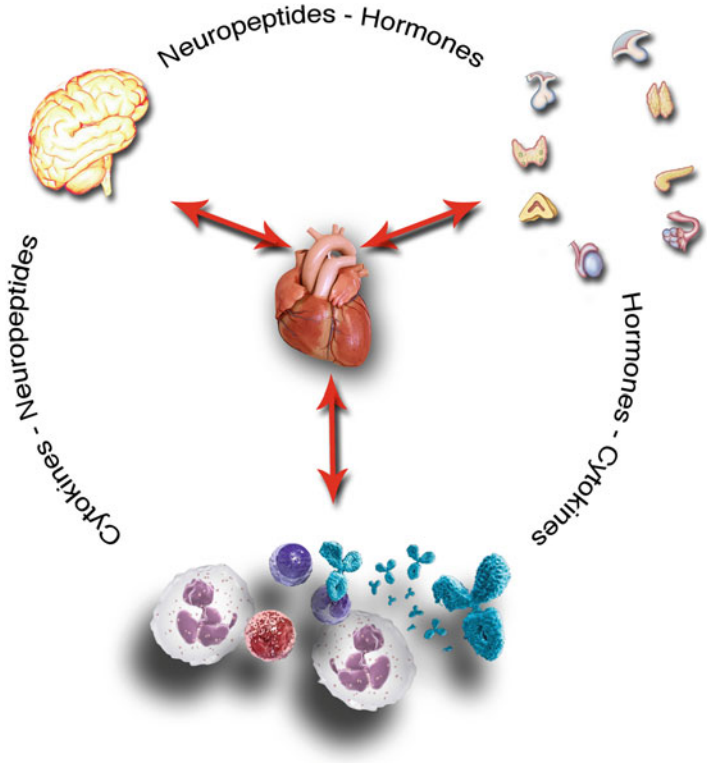

Fig. 15.1 The cardiovascular system in the psychoneurological, hormonal, and immune network: it receives and sends signals to the brain, to the immune, and to the endocrine system. (Modified from Dal Lin et al. [33])

physiological demands of its new host [44–46]. The heart rate is predominantly triggered by the rate of discharge of its dominating pacemaker (mainly the sinus atrial (SA) node and the atrium-ventricular (AV) node) whose action is fine-tuned in vivo from the balance between the sympathetic and parasympathetic nervous systems. A preserved heart rate variability is considered a sign of heart health [47–50], which highlights an important role of emotions in the cardiovascular equilibrium [51]. Indeed, the psyche-brain-heart connection is an important element that explains many otherwise unexplainable phenomena such as sudden deaths, coronary heart disease with normal cholesterol [52–54], and why women although more protected in terms of events than men have a higher mortality risk [55]. The brain-heart axis also explains why heart disorders affect brain functions (leading to stroke or cognitive dysfunction), and, on the contrary, psychoneurological pathologies (stroke, epilepsy, Parkinson's, Alzheimer's, depression, anxiety, psychosis) are accompanied by heart abnormalities [52–54, 56, 57].

Anatomical and Physiological Bases of the Brain-Heart Integration: Neurocardiology

Like the gastrointestinal system [58], the heart possesses a sufficiently extensive neuronal network to be characterized as its own "little brain" [59, 60]. The so-called intrinsic cardiac nervous system is connected to intrathoracic nervous ganglia, extrathoracic ganglions, spinal cord, and cortical nerve centers. Cardiac activity is not regulated only at the central level, but is predominantly established by beat-to-beat neurohormonal loops within autonomous intrathoracic nerve centers [61]. The anatomical and physiological details of the intrinsic cardiovascular system can be found in the book *Basic and Clinical Neurocardiology* by J.A. Armour and J.L. Ardell [61]. Below, a brief synthesis is presented to understand the deep connection between the heart and the brain.

In the heart there are three morphologic types of neurons (unipolar, bipolar, and multipolar, either intra- or inter-gangliar) with sensory and

Fig. 15.2 The architectural arrangement of the normal ventricle as described by Buckberg et al. [40, 41]: "the helical ventricular myocardial band model displays the fiber orientation of the detached circumferential fibers or the basal loop (upper right), whereby its predominantly horizontal fibers differ from the conical apical loop. The helical component which contains oblique right- and left-handed fibers. The descending and ascending segments are superimposed (top right image). The lower left and right images display finer orientation when these segments are separated. The lower left image displays the right-handed helix or descending segment. It is connected to the myocardial fold, as its oblique fibers course downward toward the apex. The lower right image shows the overlying left-handed helix or ascending segment. This segment is longer, and its oblique fibers course upward from the apex toward the aorta." Modified from Buckberg [42] reproduced with permission from John Wiley and Sons

afferent or efferent activity (sympathetic and parasympathetic) and interneurons of connection. These neurons can communicate through various molecules: acetylcholine, catecholamines and neuropeptides (somatostatin, neuropeptide Y, VIP, substance P, opioids such as dimorphins A and B, Leu-enkephalin, calcitonin gene-related peptide (CGRP)), serotonin, histamine, ATP, nitric oxide (NO), or amino acids (glutamate, aspartate). These molecules transduce the signal directly or bind to specific receptors (nicotinic, muscarinic type 1, 2, 3, 4, alpha- and beta-adrenergic (mainly expressed at the apex and in the mid-ventricular regions [62]), P2Y, P2X, H1, Ang II, AT1, mu1), influencing membrane ionic voltage channels, the action potential transmission, and ultimately the excitability of the heart cells. In vitro studies show that a functional unit exists between cardiac neurons and cardiomyocytes, which lose contractile activity if separated from the neurons to which they are intimately linked [63].

As described by Shaffer et al. [64], "while efferent (descending) regulation of the heart by the autonomic nervous system is well known (with parasympathetic nerves that exert their effects more rapidly (<1 s) than sympathetic nerves (>5 s) [65]), newer data have suggested a more complex modulation of heart function by the intrinsic cardiac nervous system [66]." These intracardiac neurons (sensory, interconnecting, afferent, and motor neurons) [67] integrate the sympathetic and parasympathetic impulses with the afferent signals occurring from the mechanosensory and chemosensory neurons within the heart. Interestingly, approximately 85–90% of fibers in the vagus nerve carry cardiovascular afferent signals to the brain, to a greater extent than by any other major organ [68].

Cardiovascular afferent activity manifests in complex patterns occurring across time scales from milliseconds to minutes [61] with both short-term and long-term memory functions that can influence heart rhythm, blood pressure, and hormonal release [64, 69].

Moreover, the cardiac afferent activity from pressure-sensitive neurons in the heart, carotid arteries, and the aortic arch [70] seems to primarily modulate cognitive functions (such as sensory-motor and perceptual performance) as revealed by the heart-brain interaction studies by John and Beatrice Lacey [71]. Their research focused on activity occurring within a single cardiac cycle, and they confirmed that the cardiovascular activity influences perception and cognitive performance [72].

Velden and Wölk described that cognitive performance fluctuates at a rhythm around 10 Hz, demonstrating that afferent inputs from the heart synchronize cortical activity projecting on the neurons in the thalamus [73]. An important aspect of their work was the finding that "it is the 'pattern and stability' (the rhythm) of the heart's afferent inputs, rather than the number of neural bursts within the cardiac cycle, that are important

in modulating thalamic activity, which in turn has global effects on brain function" [73].

Starting from this evidence, a growing body of research indicates that the afferent information processed by the intrinsic cardiac nervous system [60] can influence activity in the fronto-cortical areas [74–76] and motor cortex [77–79], affecting psychological factors, such as attention level, motivation [80], perceptual sensitivity [81], and emotional processing [82, 83]. Figure 15.3 describes the connections between the intrinsic cardiac neurons, the brainstem, the hypothalamus, the thalamus, the amygdala, and the cerebral cortex [66, 90].

Finally, according to the model of neurovisceral integration [74, 90–96], the information shared by the heart with the brain may also be coded by rhythmic [97] and electromagnetic patterns [98–100] which may represent the basis of intuitive-emotional processes [76, 84, 101, 102], awareness and feelings [103–105], and a rational, detached and "less egocentric" reasoning [106].

A disease arises when a disorganization occurs in this network of connections (intracardiac nervous system-intrathoracic nervous system-central nervous system): in fact, peculiar remodeling patterns accompany and often precede ischemic pathology, arrhythmias [107], heart failure, and arterial hypertension [61].

The Heart as an Endocrine Station

The heart serves and operates as a (loop) center to process and encode information [61] as it is also an endocrine gland producing its own hormones and neurotransmitters.

Since the early 1980s [108, 109], studies on the "endocrine heart" appeared. In addition to the well-known atrial natriuretic peptides (ANPs), cerebral natriuretic peptide (BNP) and C-type natriuretic peptide (CNP), many substances are produced and secreted into the blood by myocardial cells, fibroblasts, and endothelial and heart immune cells. All these molecules (called "cardiokines") maintain heart homeostasis and interact in cardiac remodeling in the context of acute or chronic cardiovascular affections [110], among others, the tumor necrosis factor alpha (TNF-alpha), beta-transforming growth factor beta (TGF-beta), GDF-15 (growth differentiation factor-15), activin-A, myostatin, adrenomedullin, and endocannabinoids [52].

Natriuretic Peptides

ANP (produced at the atrial level), BNP (produced at the atrial and ventricular level), and CNP (secreted by neurons and by the heart endothelium) have systemic action as they present brain, kidney, adrenal, adipose tissue, muscles, bones, pancreas, liver, immunitary cells, and platelets' receptors [111]. In addition to their antihypertensive activity, natriuretic peptides play an important metabolic role to ensure adequate energy reserves to the heart, affecting lipolysis processes and improving the glucose cellular uptake [112]. They also intervene in thermogenesis processes, converting white fat into brown fat [113].

The Heart as an Immune Organ

Inside the heart are usually present macrophages, dendritic cells, mast cells, and a small number of B and T lymphocytes [114]. Although essential for protecting the heart tissue from bacterial infections, they are activated in the event of tissue damage (such as myocardial infarction or myocarditis) and produce inflammation, whose excessive intensity and duration can lead to ventricular dilatation and heart failure [115].

Resident cardiac immune cells are triggered by two distinct orders of "alarmins" [116]: pathogen-derived (PAMPs) and damage-derived (DAMPs) molecules, which are released by dying, injured, or dysfunctional cells (with mitochondrial impairment [117, 118]) and recognized by specific pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs).

It is interesting to note that physical and mental stress, through sympathetic mediated

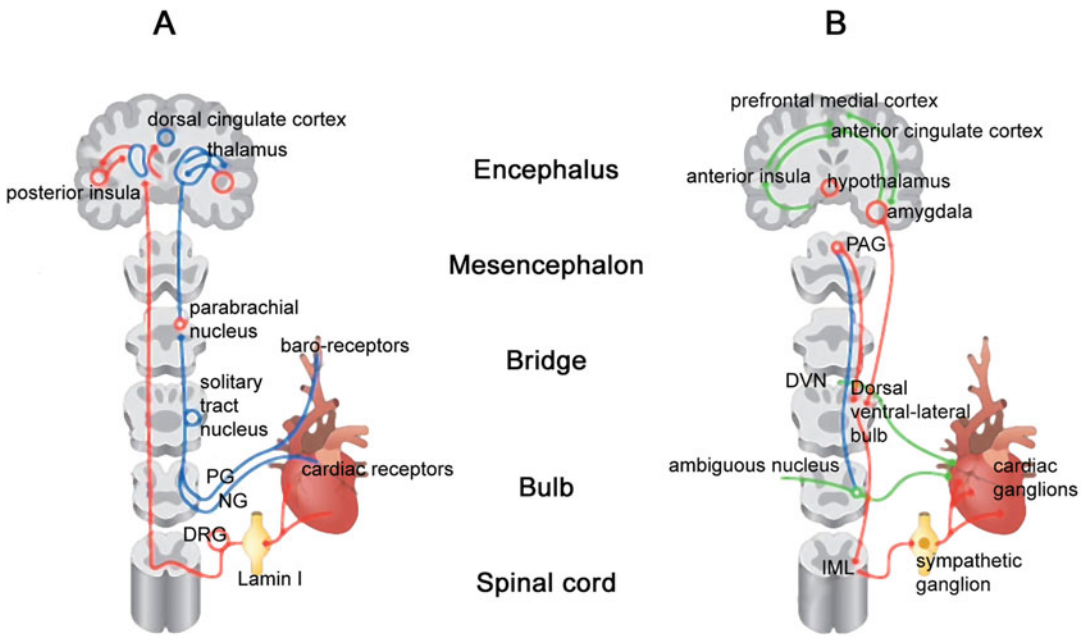

Fig. 15.3 (**a**) Schematic neural communication pathways interacting between the heart and the brain. The intrinsic cardiac nervous system integrates information from the extrinsic nervous system and from the sensory neurites within the heart. The heart sends afferents to the brain through the glossopharyngeal nerve (IX) and vagus nerve (X) (which connect to the petrosal (PG) and nodose (NG) ganglia) and through the nerves associated with the dorsal root ganglia (DRG) and lamin I of the spinal cord sensitive roots. Signals arrive to the brain at the back of the insula, in the middle cingulate cortex, in the hypothalamus, and in the locus coeruleus. Thus, cardiovascular afferents have connections to a number of brain centers involved in emotion and stress perception including thalamus, hypothalamus, and amygdala. Broad evidence implicates anger along with other emotions and mental stress in playing a significant role in myocardial ischemia, arrhythmias, and sudden death [52]. Indeed, these brain areas are connected with visual and acoustic cerebral areas, and this explains how visual [84–87] or acoustic stressors [88] may alter heart function for bad and for good [89]. (**b**) The pathways from the central nervous system (prefrontal medial cortex, anterior cingulate cortex, anterior insula, amygdala, and hypothalamus) reach the heart: the sympathetic way (red) descends into the spinal cord's intermediate mid-column to connect to the "star-shaped" ganglion, which connects to the intrinsic cardiovascular system. An increase in sympathetic activity is the principal method used to increase heart rate (HR) above the intrinsic level generated by the SA node. Following the onset of sympathetic stimulation, there is a delay of up to 5 s before the stimulation induces a progressive increase in HR, which reaches a steady level in 20–30 s if the stimulus is continuous [64]. The slowness of the response to sympathetic stimulation is in direct contrast to vagal stimulation, which is almost instantaneous. However, the effect on HR lasts longer, and even a short stimulus can affect HR for 5–10 s. Efferent sympathetic nerves target the SA node and AV node via the intrinsic cardiac nervous system and the bulk of the myocardium (heart muscle). Action potentials conducted by these motor neurons trigger norepinephrine and epinephrine release and binding to beta-adrenergic (β1) receptors located on cardiac muscle fibers. This speeds up spontaneous depolarization in the SA and AV nodes, increases HR, and strengthens the contractility of the atria and ventricles. The parasympathetic path (in green and blue) descends from the dorsal motor nucleus of the vagus nerve, from the solitary tract nucleus and the ambiguous nucleus and connects to the heart ganglia. The most obvious effect of vagal activity is to slow or even stop the heart. The vagus nerves are the primary nerves for the parasympathetic system and innervate the intrinsic cardiac nervous system and project to the SA node, AV node, and atrial cardiac muscle. Increased efferent activity in these nerves triggers acetylcholine release and binding to muscarinic (mainly M2) receptors. This decreases the rate of spontaneous depolarization in the SA and AV nodes, slowing HR. Because there is sparse vagal innervation of the ventricles, vagal activity minimally affects ventricular contractility. The response time of the sinus node is very short, and the effect of a single efferent vagal impulse depends on the phase of the cardiac cycle at which it is received. Thus, vagal stimulation results in an immediate response that typically occurs within the cardiac cycle in which it occurs and affects only one or two heartbeats after its onset. After cessation of vagal stimulation, HR rapidly returns to its previous level. An increase in HR can also be achieved by reduced vagal activity or vagal block. Thus, sudden changes in HR (up or down) between one beat and the next are parasympathetically mediated [64]. Modified from 81 reproduced with permission from Wolters Kluwer Health Inc. Abbreviations: DVN, dorsal motor nucleus of the vagus nerve; PAG, periaqueductal gray substance; IML spinal cord intermediate lateral column

neurohormonal mechanisms [52–54], can trigger an acute coronary syndrome (ACS) by promoting the secretion of inflammatory substances and inducing cardiac mast cells to release degradative and procoagulant enzymes [119].

In particular, mast cells in the heart have a high inflammatory potential represented by the mixture of substances present in their cytoplasmatic vesicles [120]. Autoptic studies revealed the presence of an important number of cardiac mast cells within the coronary arteries in subjects affected by hypertension, dilated cardiomyopathy, and mitral valve defects [121]. These highly - pro-inflammatory cells are susceptible to external environmental stimuli (e.g., PM 10 and PM 2.5 thin dust pollutants) [18, 122] but also to the "internal environment," such as to stress mediators (in particular CRH) and other urocortins, cardiac neurons neuropetides such as neurotensin and substance P, and IL-1 and IL-6 [123]. The inflammatory cascade triggered by cardiac mast cells during mental stress may produce an ACS with coronary spasm and thrombosis [119]. Finally, there is strong evidence that premenopausal female cardioprotection may at least partly be due to gender differences in cardiac mast cells [123]. A possible explanation for the differences between male and female cardiac mast cells may be that estrogen prevents the release of mast cell proteases or other products such as TNF-alpha [124].

A Neuro-Endocrine-Immune Symphony Plays on Coronary Endothelium

We recently reviewed [33, 52–54] the neuroendocrine and immune influences that act on the coronary endothelium, influencing its function and that can be studied through the evaluation of the coronary microvascular function [125]. In summary, as reported [52], "on endothelial cells acts a real neuro-endocrine-immune symphony in which the melody is played by the vitamin D [126], parathyroid hormone (PTH) [127], renin-angiotensin-aldosterone system (RAAS) axis [56, 128] in concert with thyroid and thyroid stimulating (TSH) hormones [129], growth hormone (GH) and insulin-like growth factor 1 (IGF-1) [130, 131], cortisol and ACTH [132], sex hormones [133, 134], insulin and glucagon-like protein-1 (GLP-1) [135], adipokines [56], oxytocin, vasopressin, and prolactin [136], melatonin [137, 138], bilirubin, heme catabolic pathway, and gamma-glutamyltransferase [139, 140]. Rounding out the orchestra is the immune system [141], with the familiar example of inflammation as a key process involved in the pathogenesis of atherosclerosis [47], the already discussed action of platelets and the autonomic balance, where the predominance of the sympathetic system on the parasympathetic, is a determining factor for endothelial dysfunction [56]."

In Addition to Cholesterol, Nutrition, and Sedentary Lifestyle, There Is a Psychological Risk at the Heart of Many Cardiac Disorders

Every year in the United States, about 450,000 people die of sudden cardiac death [142]. The causes can be multiple: congenital valve or coronary anomalies, hypertrophic cardiomyopathy, and, of course, coronary atherosclerosis. But despite the underlying coronary atherosclerosis, the main cause of sudden death is the alteration of heart rhythm due to a massive sympathetic stimulation of the heart [143]. In fact, at least 12% of myocardial infarctions and sudden deaths can also arise with healthy coronary vessels and even with an "antiatherosclerotic" lipid profile [143]. They happen mainly in females, with psychological disorders and high levels of emotional stress [143].

This evidence recalls what occurs in Takotsubo syndrome or stress-related heart disease. In this scenario, patients as a consequence of either positive or negative emotional events exhibit very high levels of catecholamines that cause left ventricular akinesia and its typical ballooning [144], as classic example, a woman who manifests a Takotsubo within a few hours of her husband's sudden death [145] or after joyful events such as becoming a grandmother,

grandchildren visiting from abroad, etc. [146, 147].

Emotional stress and myocardial ischemia seem to be more of a female feature [148].

Mental Stress Myocardial Ischemia

There is sufficient evidence that psychosocial stress plays a paramount role in the onset of a cardiovascular disease [149], especially coronary artery disease and all its risk factors [150, 151]. Even adverse early life events, in particular during childhood and adolescence, predispose individuals to a greater rate of inflammatory-based diseases including cardiovascular ones through epigenetic signatures [152]. Nowadays it's well known that depression, anxiety, and post-traumatic stress disorder lead to cardiovascular disorders [153] and myocardial ischemia through neuroendocrine and immune mediators [154].

In order to assess the effects of stress on cardiac function, it is possible to use the mental stress-induced myocardial ischemia (MSIMI) test. This is a provocative test alternative to exercise and pharmacological stress-induced myocardial ischemia that uses psychological stimulations (mental arithmetic, simulated public speaking, problem-solving tasks, cognitive and psychomotor challenges and tasks involving the recall of negative emotions) rather than physical exercise [155]. Interestingly, stress-related ischemic alterations seen after the MSIMI have not been described during exercise/pharmacological stress [156]. MSIMI is frequent among patients with coronary arteriosclerosis. This ischemia is often asymptomatic, occurs at lower workload and oxygen demand than exercise-induced ischemia [157], has a negative prognostic impact (being not directly related to the severity of coronary stenosis) [158], and may not be affected by the action of beta-blockers [159]. MSIMI leads to coronary microvascular constriction [160, 161] and cardiac electrical instability [158].

Finally, mental stress, activating the sympathetic-adrenal-medullary axis, eliciting the release of catecholamines, determines the release of DAMPs and the activation of cardiac mast cells [119]. In turn, DAMPs can activate the innate immune response leading to sterile inflammation [162, 163], which can result in myocarditis and cardiomyopathy [115], as well as atherosclerosis [150], even in animal models [164].

The Woman's Heart

Traditionally, heart attacks have always been considered a male issue. This view is no longer the case today: in the United States and in many European countries, female mortality (even before menopause) for cardiovascular disease is even higher than male mortality [165]. This is very intriguing because in female, cholesterol and arteriosclerosis do not fully explain this evidence and contrast the established idea of a cardioprotective role of estrogens (just thinking to the increased risk of heart attack when taking birth control pills [166, 167]). Up to one third of women with cardiac ischemia have no coronary occlusion [168]. In particular, coronary spasms, plaque erosion (not angiographically critical), and arrhythmias play a greater role in cardiac events affecting women under the age of 60 [168]. From a clinical point of view, women have a milder symptomatology than men, which can easily lead to a delay in diagnosis and therapy [169]. In the medical history of these patients, often there are socioeconomic problems [18], strong conjugal stress, or episodes of violence and sexual abuses [170].

In Fig. 15.4 are depicted the traditional and nontraditional cardiovascular risk factors along with those specific for females.

As recently described [171], a woman's heart looks stiffer than the male's one. When heart failure occurs in women, left ventricular remodeling is oriented toward concentric hypertrophy. As a result, heart failure occurs in most cases with preserved ejection fraction (HFpEF). This is in contrast with heart failure in men, where the prevailing phenotype is heart failure with reduced ejection fraction (HFrEF). The renin-angiotensin system would appear to be less activated. Consequently, fibrosis is less important

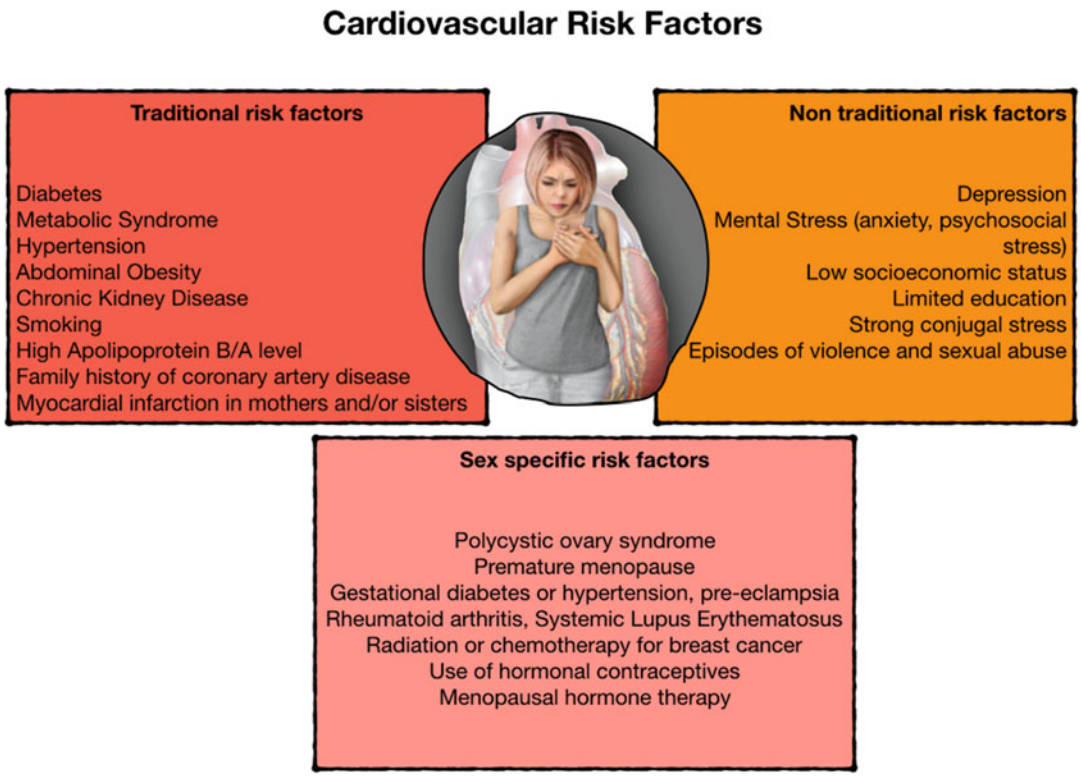

Fig. 15.4 Traditional and nontraditional cardiovascular risk factors and more women-specific risk factors. (Image modified from Gebhard C. Eur Heart J. 2017;38:1066–1068. Reproduced with permission from MediDesign Frank Geisler)

at a myocardial level, although there is a general stiffening of the circulatory system with an increase in the effective afterload. The reason for the preferential concentric hypertrophy and HFpEF instead of left ventricular dilation and HFrEF is still unknown. Some authors suggest that in normal conditions, in women the myocyte diameter is reduced with respect to men, and it may therefore be possible to increase the amount of contractile proteins without stretching the sarcomere [171].

Finally, the female heart seems to be stiffer: left ventricular diastolic elastance is higher for women than for men at comparable levels of filling pressure as shown in Fig. 15.5 [172].

Conclusions

The study of the heart and its connections with the psycho-neuro-endocrine-immune system leads at least to two types of conclusions, one theoretical and one practical.

As George Engel said about 40 years ago in *Science* [173], the reduction of complex phenomena in simple determinations (reductionism), the separation between "biological" and "psychological" phenomena (mind and body dichotomy), and the interpretation of life exclusively in physical or chemical terms (physicalism) are obstacles to the study of the human being and its physiopathology: obstacles that are causing very heavy consequences in terms of the effectiveness, costs [174], and credibility [175–180] of our care systems. Thanks to the PNEI, we have the tools for a scientific investigation of complex phenomena which, on different scales, determine the balance between health and illness and to study and rediscover therapeutic solutions that go beyond the current pharmacological vision. For example, as we have extensively documented in a recent book [17], the treatment of dyslipidemia can be

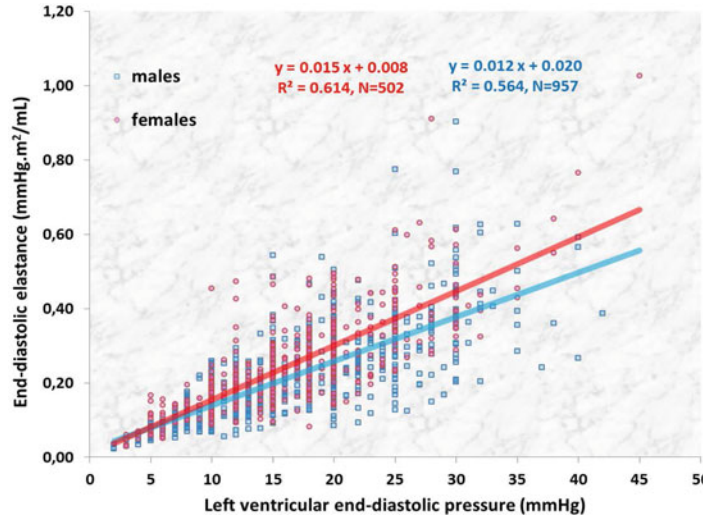

Fig. 15.5 Left ventricular diastolic elastance is higher in women compared to men. For women (N = 502) mean end-diastolic elastance is 0.2459 mmHg. m^2/mL (95% CI 0.2349–0.2570) and higher ($P < .0001$) compared to men ($N = 957$), showing an average of 0.2114 (95% CI 0.2046–0.2182). (From [172], with permission). *LV diastolic stiffness is higher for women than for men at comparable levels of filling pressure (EDP)*

effectively achieved by an integrated approach that includes, in addition to nutrition and physical activity, a range of phytotherapic products and proper management of mental stress, given that excessive cholesterol lowering increases the risk of heart attacks and general mortality [181, 182].

From a practical point of view, we count on very high standard of care in acute setting, while in the chronic and preventive context, we need to reconsider the management of patients with heart disease by investing more time and resources in terms of proper nutrition [183], physical activity, and stress management [54, 184, 185].

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