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Preface

Organisms have rhythms, such as the rhythms of the cardiac and respiratory systems, endocrinological networks, brain circuits, awake–sleep rhythms, and so on. All these rhythms have a tendency to oscillate, increasing and decreasing depending on several factors. Such oscillations can give information on the state of the complex systems involved. Oscillations have been shown to be an integral part of the cardiorespiratory circle (Lotric and Stefanovska 2000), peripheral blood flow (Bracic and Stefanovska 1998a, b), renal functions (Constantinou and Yamaguchi 1981), the immunological system, cell metabolism (Selkov 1968), the extrapyramidal system (Brown 2003), and others. Several models have been developed to simulate systems or subsystems. It has been hypothesized that oscillations in dynamic coupled nonlinear environments serve as communication pathways for biological systems. Consequently, the uncoupling of oscillating organs would be the cause and not surrogate of organ dysfunction (Godin and Buchman 1996). Recognition of the dynamic nature of regulatory processes has challenged the traditional view of homeostasis (Lipsitz 2002), leading to the introduction of the term homeodynamics (Yates 1993).

During my training as an anesthesiologist at the Humboldt University in Berlin, Germany, I became acquainted with an older, experienced consultant at the medical intensive care unit. When he arrived before the morning round, he would simply check the monitors for changes in the heart rhythm of individual patients over the previous 24 h. I wondered what he was doing. He explained on one occasion that he looked at the ups and downs of heart rhythm. If they decreased, he would be concerned about the patient. He did not call this heart rate variability, but it was in fact exactly the concept I will discuss in this book. In most cases we can summarize it thus: variation is good and lack of variation is bad. This is probably true for many body rhythms, but there is already now substantial evidence that this is particularly true for the heart rhythm.

The cardiorespiratory circle is of special interest in many ways. Respiratory sinus arrhythmia (RSA) has been described in terms of a weak coupling between respiration and cardiac rhythms that are usually not phase locked (Lotric and Stefanovska 2000). The cardiorespiratory system has a high level of complexity

with different forms of self-organization, where oscillations show its complexity in a simple manifestation (Stefanovska 2002, Stefanovska et al 2002). The complexity of HRV decreases with increased age (Pikkujämsä et al. 1999; Acharya et al. 2004). Physiological explanations for HRV have been imbalances in sympathovagal activation and parasympathetic tone (Hughes 2000), changes in β-adrenergic receptor number and function, abnormal baroreflex function, central abnormalities of autonomic regulatory function, and, recently, changes in mediator levels (TNF) (Malave et al. 2003).

Increased interest developed as correlations between decreased heart rate variability and mortality, specially sudden heart death, was described early in landmark papers (Kleiger et al. 1987; Singer et al. 1988). Interest in this issue arose specially after the development of automated internal cardiac defibrillation devices as a therapeutic tool, when it became essential to identify risk patients who would benefit from an implantation. Today, some hospitals use HRV for this (or other purposes), others not at all. Karemaker concludes "The predictive value of (absence of) heart rate variations is now an acknowledged risk factor, strongly associated with long-term outcome of disease in cardiac patients" (Karemaker and Lie 2000, p. 435) and asks "one wonders why cardiac monitors in our hospitals only represent mean heart rate predominantly, but do not take heart rate variations into account" (Karemaker and Lie 2000, p. 436).

In the last years, hypotheses are emerging that discuss nonlinear properties not only as surrogate of a system but more as a property on its own. A diminished complexity of a system (a patient) is thus not a consequence of aging or disease but on the contrary, a more ordered system might be the cause of disease. Fractal dynamics is hence a fundamental feature of living or complex adaptive systems, and their disappearing is expected to have fatal consequences (Goldberger et al. 2002).

In this book I focus on heart rate variability in various ways. I decided in addition to discuss some algorithms that have either similar properties or also propose common mechanisms, such as heart rate turbulence. I discuss extensively the basic functional structures responsible for the generation of HRV. I summarize evidence for which structures are involved. In addition we regard it as essential to understand HRV under a systems biology perspective and present basic principles and mathematical models based on them.

In the clinical part, I am most interested in diseases or conditions for which relevant research has been done, like in the cardiologic field or intensive care. This is of course also corresponds to my interests. I am intensivist, working together with cardiologists and have special experience in pain treatment and palliative care. So it is not only by chance that I focus on different pain syndromes and cancer symptoms.

On the other hand, I am mostly interested in syndromes that are clearly defined. In some areas, particularly chronic fatigue, often synonymously called myalgic encephalomyelitis, several studies with HRV measures have been published. In difference to cancer fatigue or fatigue associated with former chemotherapeutic treatment, I feel that this patient group is still not optimally characterized and HRV research in heterogeneous groups seems to bring about confusion rather than clarity. This is also the case for irritable bowel syndrome (IBS), but I chose to discuss it due to some

evidence leading to the idea of IBS as specific visceral or autonomic neuropathic pain. I will discuss some of the problematic issues briefly in the last chapter.

It is important for the reader to keep in mind that things changed around 1996. Before 1996 – see also the first chapter on history – no standard for HRV existed. Results were not completely comparable, some measures were used that later disappeared (e.g., the so-called middle band in frequency domain), and the technical equipment was rather heterogeneous. Only after the publication of the report of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (1996) and similar excellent articles (e.g., Berntson et al. 1997), studies started to use common methods and to report on them exactly. Even though many studies do not use this standard (even when they claim to do so (Nunan et al. 2010)), it was a great breakthrough and diminished somewhat the value of studies conducted previously.

My intention with this book is to introduce an affordable diagnostic measure that provokes no adverse reactions and is feasible in hospitals and outpatient clinics as well as for general practitioners or rehabilitation units. At the same time I wish to make clear possibilities, but also some limitations. HRV is often used rather mechanically without deeper understanding of the background. I hope that my readers will regard this book as a contribution to their clinical and scientific work.

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Abbreviations

ACh	Acetylcholine
ACTH	Adrenocorticotropic hormone
AF	Atrial fibrillation
AFR	Atrial fibrillation rate
ANS	Autonomic nerve system
AP	Area postrema
ApEN	Approximate entropy
ASDNN	Average of the standard deviation of NN intervals
BP	Blood pressure
BRS	Baroreflex sensitivity
CABG	Coronary artery bypass grafting
cAMP	Cyclic adenosine monophosphate
CAN	Cardiac autonomic neuropathy
CHF	Congestive heart failure
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CRH	Corticotropin releasing hormone
CVD	Cardiovascular disease
CVRD	Cardiac volatility-related dysfunction
DAN	Diabetic autonomic neuropathy
DM	Diabetes mellitus
DMN	Dorsal motor nucleus of the vagus
DN	Diabetic neuropathy
DVC	Dorsal vagal complex
EPSP	Excitatory postsynaptic potentials
FFT	Fast Fourier transformation
HD	Hemodialysis
Holter monitoring	24 h Holter monitoring
HPA	Hypothalamic–pituitary axis
HRT	Heart rate turbulence
HRV	Heart rate variability

ICF	Instant center frequency
IPSP	Inhibitory postsynaptic potentials
LC	Locus coeruleus
LLE	Largest Lyapunov exponent
LVEF	Left ventricular ejection fraction
MI	Myocardial Infarction
MSNA	Muscle sympathetic nerve activity
NN50	Number of adjacent NN intervals which differ by at least 50 ms during a 24-h recording
NPY	Neuropeptide Y
NTS	Nucleus of the solitary tract
OVLT	Organum vasculosum lamina terminalis
PAF	Paroxysmal atrial fibrillation
pNN50	Percentage of adjacent NN intervals in a 24-h recording which differ by at least 50 ms
PTSD	Post-traumatic stress disorder
PVH	Paraventricular nucleus of the hypothalamus
PVN	Paraventricular nucleus
QoL	Quality of life
QST	Qualitative sensory testing
RMSSD	Root mean square of successive differences
RR	Relative risk
RVLM	Rostral ventrolateral medulla
RVMM	Rostral ventromedial medulla
SCD	Sudden cardiac death
SDANN	Standard deviation of average NN intervals
SDNN	Standard deviation of NN intervals
SFO	Subfornical organ
SNA	Sympathetic nerve activity
SNS	Sympathetic nervous system
SPWVT	Pseudo-Wigner–Ville transformation
SVES	Supraventricular extrasystole
VES	Ventricular extrasystole
VF	Ventricle fibrillation
VIP	Vasoactive intestinal peptide
VMA	Vanillylmandelic acid
VT	Ventricle tachycardia
WBC	White blood cell count

Contents

Part I
Theoretical and Pathophysiological Background

Chapter 1
History of Heart Rate Variability

The concept of heart rate variability is very old. Already early physicians observed variation in heart frequency, but only in the last 150 years more specific methods and ideas appeared. Rather than a comprehensive review, we offer here a sketch of the history of HRV. We mention names knowing that to relate a complex concept like HRV to single scientists is entirely wrong. In 1935, Ludwik Fleck was probably the first to describe scientific progress as collective work, arguing that to relate results to single scientists is not appropriate (Fleck 2012). We are convinced that his approach and interpretation could be easily used in the history of HRV. Thus, if we use specific names, this is not to highlight them at the expense of others who are similarly important. The authors are rather examples that stand for emerging concepts and discussions, while many more scientists and physicians also deserve credit. Therefore, we dedicate this chapter to the large historical community of clear-sighted and curious humans who have developed and are still developing the concept of heart rate variability in permanent collective interaction.

As Billman (2011) suggests, already early in their history, humans undoubtedly discovered pulsations at the thoracic wall and in peripheral arteria. The first written remark about heart rhythm is found in quotations of Herophilus (ca. 335–280 BC), who not only discovered arteries and veins (and their difference) but also described the arteries as pulsing rhythmically. As Billman argues, this suggests that Herophilus was probably the first person to measure heart rate. Herophilus was quoted by Galen who also quoted Archigenes describing eight different characteristics of the pulse. Galen of Pergamon focused on pulse and wrote not fewer than 18 books on it and at least eight treatises describing the use of pulse measurement for prognosis of illnesses (Billman 2011).

Western medical historians most often quote Galen regarding pulse, but pulse diagnosis was also used early in Indian and Chinese medicine. In China, pulse diagnosis was developed (depending on historical sources) between 800 and 200 BC. Bian Que (扁鹊, about 500 BC, also known as Qin Yueren, 秦越人) is on record as one of the first Chinese physicians who used and described pulse diagnosis. Bian Que, who lived about one generation before Hippocrates, was the first to describe

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Fig. 1.1 Bian Que (about 500 BC)

the "four diagnostic methods" of Traditional Chinese Medicine including pulse and tongue diagnostics (Fig.1.1).

The golden age of physiology started already in the eighteenth century. At this time, there was no distinction between physiologists and physicists, something that was reflected in both aims and methods. First observations of the permanent variation of pulse and arterial blood pressure were presented by Stephen Hales already in 1733. Hales also observed its relation to the respiratory cycle. Heartbeat interval fluctuations linked to spontaneous respiration were first described by Ludwig in 1847 (Ludwig 1847). This was eventually called respiratory sinus arrhythmia and is today regarded as part of the broad phenomenon of heart rate variability. He developed special instruments ("kymograph") to measure amplitude and frequency of the pulse wave in dogs. Another early observer of this property was one of the founders of experimental psychology, Wilhelm Wundt. Already in 1868 Donders described a respiration dependent activation of N. Vagus and discussed its relation to sinus arrhythmia. Later on, several studies observed the manipulation of the vagus nerve (Fig. 1.2).

Claude Bernard (12 July 1813–10 February 1878) was a French physiologist. He was the first to define the term "milieu intérieur" (now known as homeostasis, a term coined by Walter Bradford Cannon). His publications include "La fixité du milieu intérieur est la condition d'une vie libre et indépendante" ("The constancy of the internal environment is the condition for a free and independent life"). This is still the basic principle related to homeostasis today. He also argued that "The living body, though it has need of the surrounding environment, is nevertheless relatively

Fig. 1.2 Claude Bernard (*Source*: Académie nationale de medicine)

independent of it. This independence which the organism has of its external environment derives from the fact that in the living being, the tissues are in fact withdrawn from direct external influences and are protected by a veritable internal environment which is constituted, in particular, by the fluids circulating in the body."

Walter Bradford Cannon (1871–1945) was an American physiologist and professor and chairman of the Department of Physiology at Harvard Medical School. Cannon expanded on Claude Bernard's concept of homeostasis and developed four propositions around it. Of these, the last two claimed that the regulating system that determines the homeostatic state consists of a number of cooperating mechanisms that act simultaneously or successively and that homeostasis does not occur by chance but is the result of organized self-government. Dittmar proposed a vasomotor center in rostral ventrolateral medulla (Dittmar 1873).

The classical model of autonomic control describes a continuum with parasympathetic activation at one end and sympathetic activation at the other as Cannon proposed it (Cannon 1915). Langley divided the autonomic outflow to the cardiovascular and visceral tissues into sympathetic and parasympathetic components, based on their spinal origins (Langley 1921). He proposed that parasympathetic

efferents are more precise focused on target organs than sympathetic efferents. It were beyond others Eppinger and Hess, who focused on abnormalities of the regulations of autonomic functions. They asserted, that "clinical facts, such as respiratory arrhythmia, habitual bradycardia, etc. have furnished the means of drawing our attention to the variations in the tonus of the vagal system in man" (Eppinger and Hess 1915, p. 12, quoted after Berntson 1997). One report of early physiological research came from Bainbridge who tried to explain HRV in terms of alterations in baroreceptor and volume receptor responses associated with respiratoric alterations of intrathoracic pressure (Bainbridge 1920).

A step further to understand the autonomic nervous system was made by Adrian, who published the first recordings of sympathetic nervous system (SNS) activity in anesthetized cats and rabbits (Adrian et al. 1932). In the same period, Malzberg first described the association between major depression (then called "involution melancholia") and cardiac disease (Malzberg 1937), opening up a new area of research.

After the Second World War, HRV started to be a clinical issue when Hon and Lee observed in 1965 for the first time HRV fetal ECG. They noted that reduced beat-to-beat variation of the fetal heart was associated with distress before other detectable symptoms (Hon and Lee 1965), a principle still in use in every obstetric unit. In cardiology, Wolf was the first to draw attention to the relationship between heart rate variability and nervous system status (Wolf 1967), shortly after Valbona found HRV changes in patients with brain injury in 1965.

Explanations of respiratory sinus arrhythmia were developed when Green and Heffron described respiration-independent sympathetic rhythms in 1967. Katona observed the activity of cardiac efferents in anesthetized dogs and its consequences for hemodynamics in 1970. Shortly afterwards, a landmark study by Jose and Collison described the intrinsic heart rate after blocking both SNS and PNS with help of propranolol and atropine (Jose and Collison 1970).

A noninvasive approach to measure cardiac parasympathetic control in the anesthetized dog was introduced by Katona and Jih (1975), who suggested that changes in the magnitude of sinus arrhythmia indicated proportional changes in vagal tone. At this time, it was based on three assumptions: (a) the change of heart period is a linear function of vagal efferent activity, (b) during inspiration cardiac vagal efferent activity stops, and (c) the respiratory pattern and rate are constant (which at this time was guaranteed by the anesthesia used during the test).

Major breakthroughs were made in the 1980s. Axelrod and others started to analyze the frequency domain of HRV, and in connection to this they started to use short-term HRV of 10 min or less as well (Axelrod et al. 1987). Of particular importance was the increasing interest in nonlinear phenomena based on different lines of research. Especially Goldberger, the later founder of the important website PhysioNet, became increasingly interested in nonlinear algorithms (e.g., Goldberger et al. 1984, 1986; Goldberger and West 1987). An overview of his articles reveals the crucial influences, here he quotes significant European researchers like Hermann Haken, May's landmark paper about evolutionary models, and Shaw's article about chaos theory and strange attractors.

Probably the breakthrough of HRV in cardiology happened when Kleiger demonstrated a possible role of SDNN for predicting mortality after acute myocardial infarction (Kleiger et al. 1987). This was the starting point for several important cardiologic studies. Together with Bigger's introduction of short-term measures (Bigger et al. 1993), Kleiger's study sparked a crucial development in the more recent history of HRV – the joint Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (1996). The Task Force established minimal technical requirements, definitions, range of Power bands in frequency domain and recommendations on how to conduct clinical research and patient examinations with the help of HRV. This paper is probably the most frequently cited HRV paper. Literally no modern HRV study abstains from relating to this important standard, and no major revision has been necessary until today – because of the comprehensive presentation of currently accepted "linear measures" and because of still insufficiently consistent results with respect to a plethora of nonlinear algorithms.

Today, HRV is somewhere between. Astonishingly more than 10,000 papers have been published on it today, it is part of any more expensive pulse watch for sport enthusiasts, but its clinical use is very varied. We discuss the situation and future of HRV in the last chapter.

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Chapter 2
Linear, Nonlinear, and Complex Systems

Outline: In this chapter readers will be introduced to basic ideas and definitions of system theory, nonlinearity, nonlinear deterministic systems, and complexity. It will include examples and some hints to statistical and geometrical methods. This chapter is not essential for the clinical part of the book, but it is meant to offer a deeper understanding of the concepts of time series analysis, especially for nonlinear methods. We therefore recommended reading it.

Linear Systems

A linear system is simply something that can be defined completely by one or more linear equations. We have summarized some (mathematical) definitions around systems in Table 2.1. As an example consider a bucket into which water flows. If the amount of water per time unit is always the same, the amount of water in the bucket can be described with help of a linear equation. The equation can be solved analytically. It is possible to calculate the amount of water at any time if you know the beginning value (the amount of water in the bucket at $t=0$).

If you describe a system with the help of values taken at different intervals, you have a time series. Time series consist of a set of data and are necessarily discrete (not continuous). The linear numerical description of time series data consists of a first-power mathematical equation. This equation has therefore no exponents and describes a line in a Cartesian two-dimensional graphical system:

$$f(x) = a + bx. \tag{2.1}$$

A given amount of input stimulus x produces a proportional corresponding magnitude in output response y. The stimulus produces a response independent of initial conditions. To describe a linear system, statistics are appropriate, the stimuli being the independent, and response the dependent variable (Schumacher 2004).

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Table 2.1 Definitions

A *system* is a collection of variables interacting with each other to accomplish some purpose (McGillem and Cooper 1974).
A *dynamic system* is a system that evolves over time by accepting, then operating on, an original signal to produce a new set of signals (Strogatz 1994).
Signals represent the means by which energy is propagated through a system and may depict any variable within a system (McGillem and Cooper 1974).
A *time series data set* is a collection of observations (data points) made sequentially over time (Chatfield 1989).

The Eq. (2.1) is in fact the simplified form of a differential equation. A time series, however, can also be described by one or more difference equations. A difference equation describes a system stepwise. It returns value at time step 1, 2, 3, and so on. You obtain a numerical solution in a difference equation if you start with an initial value, calculate it according to the equation, reaching so the first result r_1. You put this result again into the equation, obtaining so the next result r_2. This process can be repeated infinitely and is called *iteration*.

$$f\left(x_{n+1}\right) = a + bx_n. \tag{2.2}$$

Difference equations were important for the discovery of mathematical chaotic systems, which will be explained later in this chapter.

Linear power spectrum techniques, which transform time series into frequency-domain data, are considered as linear signal analysis too. All power spectrum analysis techniques (like fast Fourier transformation or autoregressive modelling) transform a time series data set into its frequency components by decomposing the original signal into a series of sinusoidal waves analogous to a prism separating light into its corresponding colors.

Nonlinear Systems

A nonlinear system is mathematically defined as a 2nd- or higher-power system, that is, the independent variable in the mathematical equation contains an exponent. In a linear system, the variables produce an output response; whereas, in a nonlinear system the variables contribute to the output response. Although a linear system can be decomposed into its component parts, in a nonlinear system the parts interfere, cooperate, or compete with each other. A small change can alter the nonlinear system dramatically because the initial condition of all variables along with the input stimulus influences the output response (Strogatz 1994). Nonlinear dynamic systems theory allows for the mathematical reconstruction of an entire system from one known variable since the reconstructed dynamics are geometrically similar to the original dynamics.

Probably the simplest form of a nonlinear equation is

$$f(x) = x^2. \tag{2.3}$$

If you show a linear system in a graphical form, you see a (straight) line. Any nonlinear system will show a (more or less complicated) curve. A line has always the same slope at any point, a curve, however, has different slopes, maxima and minima.

These kinds of equations can in principle be solved analytically. We can calculate at any point the value of $f(x)$, but also the slope, global and local maxima and minima, or the position function. But in most cases, nonlinear systems cannot be solved analytically. Why are nonlinear systems so much harder to analyze than linear ones? The essential difference is that linear systems can be broken down into parts. Then each part can be solved separately and finally recombined to get the answer (Strogatz 1994). The problem here is that in the real world we do not find systems where variables act independently. It would be possible to describe the behavior of the heart rate over time if respiration would not have an effect on preload, blood pressure not on afterload, volume not on heart rate, and so on. In reality, most systems have parts that interact in one way or another, and this makes it necessary to describe such systems mathematically on a nonlinear way.

Chaos Theory

The misleading expression "chaos theory" describes the properties of nonlinear deterministic systems. It is a specialized sub-theory of nonlinear systems that describes the behavior of a system with few variables over time when the variables of the time step $n+1$ are dependent on the variables at time step n (compare Eq. (2.2)). The process of turning the result of one time step into the independent variable of the next time step is called iteration. In contradiction to the associations related with chaos, a chaotic system is directly dependent on its initial conditions, but the terminal state of the system after infinite time steps can vary considerably. With methods and algorithms of chaos theory it is possible to distinguish between stochasticity (real independent changes without any rule) and chaos (changes dependent on the conditions before). In fact, most biological time series are based on a combination of these two elements. The robustness of a chaotic system seems often to be dependent on stochasticity (also often called "noise"). This means that a physiological system, which is considerably deterministic, can possibly only be stable if some real random fluctuations are part of it.

Among many investigators and pioneers who paved the way of modern mathematical chaos theory was the meteorologist E. Lorenz and the ethologist R. May. Lorenz modelled atmospheric convection in terms of three differential equations and described their extreme sensitivity to the starting values used for their calculations. May showed that even simple systems (in this case interacting populations)

could display very "complicated and disordered" behavior. Among other pioneers in the field were D. Ruelle and F. Takens. They related the still mysterious turbulence of fluids to chaos and were the first to use the name "strange attractor." Soon thereafter M. Feigenbaum revealed patterns in chaotic behavior by showing how the quadratic map switches from one state to another via period doubling. The term "chaos" had been already introduced by T.- Y. Li and J. Yorke during their analysis of the same map. Several Russian mathematicians like A. Kolmogorov and Y.G. Sinai have also contributed to the characterization of chaos, its relation to probabilistic laws, and information theory (Faure and Korn 2001).

There is no simple powerful and comprehensive theory of chaotic phenomena, but rather a cluster of theoretical models, mathematical tools, and experimental techniques. Chaos theory is a specialized application of dynamic system theory. Nonlinear terms in the equations of these systems can involve algebraic or more complicated functions and variables and these terms may have a physical counterpart, such as forces of inertia that damp oscillations of a pendulum, viscosity of a fluid, nonlinear electronic circuits, or the limits of growth of biological populations, to name a few. Since this nonlinearity renders a closed form of the equations impossible, investigations of chaotic phenomena try to find qualitative and quantitative accounts of the behavior of nonlinear differentiable dynamical systems. Qualitative approaches include the use of state spaces or phase spaces to characterize the behavior of systems on the long run, or to describe fractals as pattern of self-similarity.

Phase space is a mathematical and abstract construct with orthogonal coordinate directions representing each of the variables needed to specify the instantaneous state of a system, such as velocity and position (of ,e.g., a pendulum) or pressure and volume changes (e.g., of a lung connected to a respirator). Common for variables is that they are time dependent. Time itself is not represented as coordinate, but on the phase space curve itself. Typically, a phase space starts at a certain point and the system goes through a finite (or infinite) time length. The system might be end at a certain point, which is often called an attractor or a limit point. A limit point for instance is the point where a pendulum finally ends. In the absence of friction, however, the pendulum moves on the same way for infinite time, which leads to a limit circle that describes a stable oscillation. A normal attractor shows a kind of equilibrium, either with or without movement of the system. A system can possibly never reach equilibrium. But beyond attractors or limit cycles, chaotic systems can also reach a kind of equilibrium without moving on the same track again. This is described by the term "strange attractor" that is shown by curves in state space that never repeat but are similar to each other. Limit points are in addition distinguished with regards to local stability. An attractor is regarded as locally stable when perturbations are damped over time, whereas they are seen as unstable if small perturbations increase over time. Locally unstable attractors are also called repellors. A third class of equilibrium points is saddle points that are attractors from some regions, but repellors for other regions.

A physical system can undergo transitions if some of the parameters are disturbed. Perturbations can cause the system to oscillate until it finally returns and ends at the same end point. Consider a stress response of the body. Systemic-released adrenaline and synaptically released noradrenaline results in an increased

heart rate. The system will eventually adapt, catecholamines will be eliminated, and (if the stress becomes chronic) receptors will be internalized. At the end, the system will return to a kind of equilibrium.

The amount of perturbations a system is able to tolerate without coming into transition to another state correlates with its robustness. Most systems tend to be robust to most perturbations. The cardiac system can be perturbed in many ways. The blood volume can be increased or decreased, the concentrations of electrolytes can change with some consequences for frequency and rhythm patterns, the rhythm itself can be perturbed by the vegetative nervous system, but in most cases the heart rhythm as signal returns eventually to its basic values, the system is robust. But some quite small perturbations can change the system dramatically. This can lead to a transition to, for instance, atrial fibrillation or asystole. It is typical for systems to be generally robust but sensitive to some probably small perturbations.

Transitions can be showed in logistic maps. These usually two-dimensional maps show a final value of a measured or observed parameter after finite (or infinite) iterations (nothing other than the attractor) dependent on a control parameter (the independent value). The classical logistic map is derived from the already named population studies. The logistic equation is a first order difference equation of the form:

$$x_{n+1} = kx_n\left(1 - x_n\right) \tag{2.4}$$

where x is the dependent value of the system and k is the independent factor. In population biology, x was a relative value between 0 and 1, where 1 represents the maximal possible population in an area and 0 extinction. k represents the growth factor: the higher k is, the faster the population grows. It turns out that for low values of k, the initial population settles down to a stable size that will reproduce itself each year. As k increases, the first unstable fix point appears. The successive value of the population x oscillates in a 2-year circle between two alternate numbers. For increasing values of k, a cycle repeats every 4 years, 8 years, and so on. This is called a period doubling or cascade. Finally, the behavior becomes chaotic; at this stage wild fluctuations hide very effectively the simplicity of the underlying rule (Fig. 2.1).

The cardiac cycle represents a deterministic system in which the RR-distance depends partially on the RR-distances of the last heartbeats. But there are only few mere deterministic systems. Usually, as stated earlier, systems have both deterministic and stochastic elements. Stochastic elements again represent either other complex systems that might be partially deterministic in nature (pseudostochasticity) or might represent gradually real stochastic systems (consequences of quantum fluctuations). This stochastic element is often called “noise” and is often of high importance. It has been repeatedly shown that noise is essential for the stability of artificial and real neural networks. Reducing the “noise” leads to a breakdown of the system, whereas a certain amount of stochasticity leads to stability and rhythmicity. Noise in neuronal communication increases the efficacy of the signal recognition.[1]

[1] For a larger discussion, see (Rieke et al. 1999).

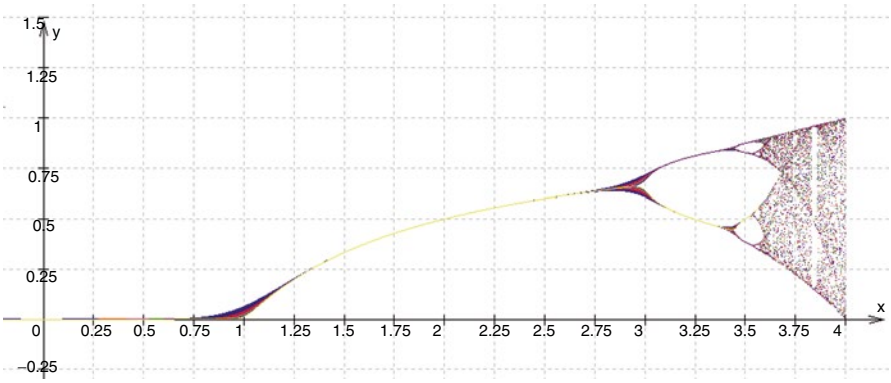

Fig. 2.1 Logistic map of the equation $x_{n+1} = kx_n(1 - x_n)$ (also called bifurcation diagram)

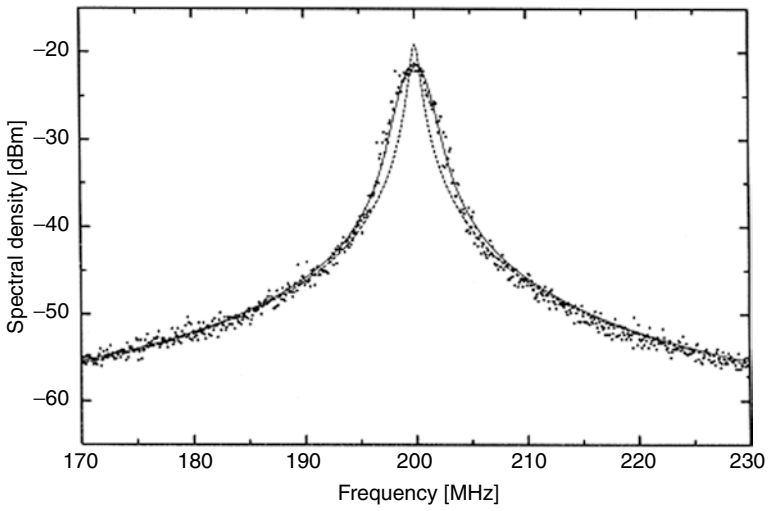

Fig. 2.2 White noise

Noise (stochasticity) is differentiated in white, brown, and pink noise. White noise is a random signal with a flat power spectral density. In other words, the signal's power spectral density has equal power in any frequency band, having a given bandwidth. White noise is considered analogous to white light, which contains all frequencies. Brown noise,[2] also called red noise, is the kind of noise produced by random Brownian motion. Its spectral density is $1/f^2$ denoting more energy at lower frequencies. Pink noise is defined as a signal with a frequency spectrum proportional to the reciprocal of the frequency. It is called pink noise for being intermediate between white noise and brown noise (Figs. 2.2, 2.3, and 2.4).

[2] It is not called after the color but in honor of Robert Brown, the discoverer of Brownian motion.

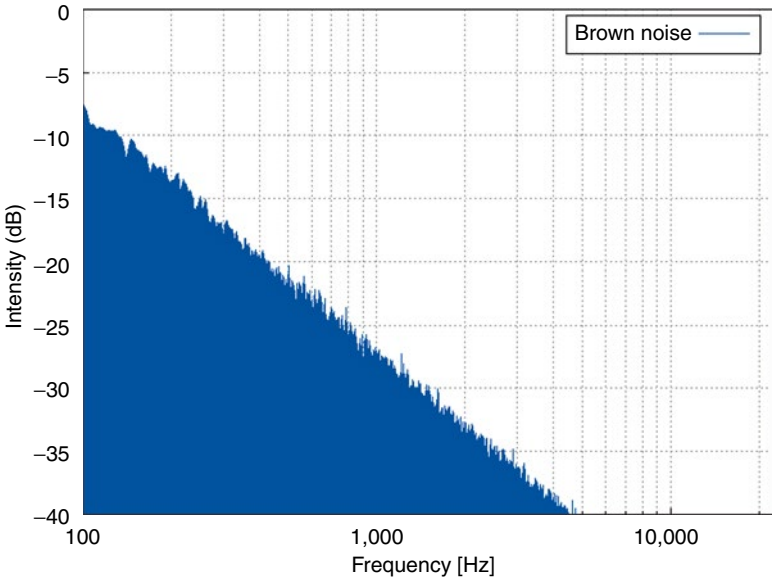

Fig. 2.3 Brown (red) noise

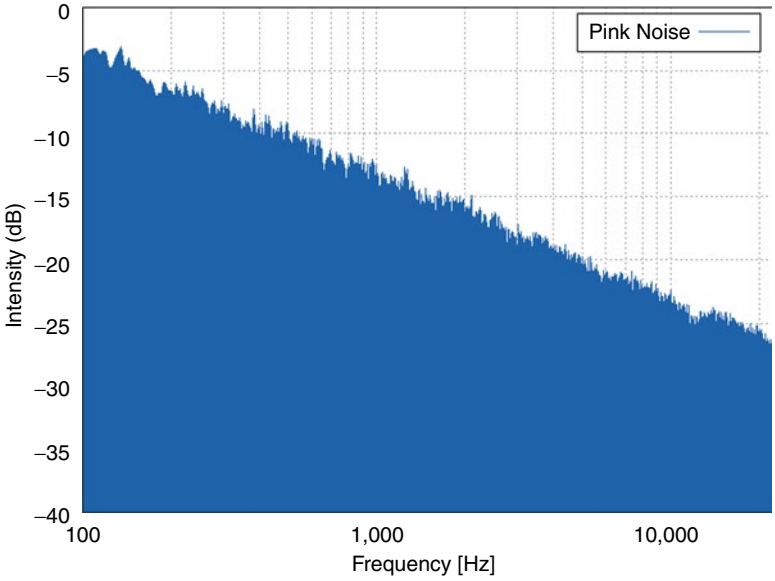

Fig. 2.4 Pink noise

An older linear tool for examining time series is Fourier analysis, specifically *FFT* (fast Fourier transform). FFT transforms the time domain into a frequency domain and examines the series for periodicity. The analysis produces a *power*

spectrum, the degree to which each frequency contributes to the series. If the series is periodic, then the resulting power spectrum reveals peak power at the driving frequency. Plotting log power versus log frequency:

- *White noise* (and many chaotic systems) has zero slope.
- *Brown noise* has slope equal to −2.
- *1/f (Pink) noise* has a slope of −1.

1/*f* noise is interesting because it is ubiquitous in nature, and it is a sort of *temporal fractal*. In the way a fractal has self-similarity in space, 1/*f* noise has self-similarity in time. Pink noise is also a major player in the area of *complexity*.

Several attempts have been made to quantify chaos (this means to describe the amount of deterministic behavior if there is something that might resemble a strange attractor). Some of them are based on the assumption that strange attractors fulfill the condition satisfying the "ergodic" hypothesis, which proposes that trajectories spend comparable amounts of time visiting the same regions near the attractor.

The *Lyapunov exponent* is used frequently. It is a measure of exponential divergence of nearby trajectories in the state space. Otherwise stated, it depends on the difference between a trajectory and the path it would have followed in the absence of perturbation. Assuming two points x_1 and x_2 initially separated from each other by a small distance δ_0, and at time t by distance δ_t, then the Lyapunov exponent λ is determined by the relation

$$\delta_{x(t)} = \delta_{x(0)} e^{\lambda t} \tag{2.5}$$

where λ is positive if the motion is chaotic and equal to zero if the two trajectories are separated by a constant amount as, for example, if they are periodic (a limit cycle).

Entropy is a quantity that comes originally from thermodynamics. It describes the amount of disorder in a given system (this is a rather simplified description. A probably better verbal approach is to term it as the number of degrees of freedom of a system). A chaotic system can be considered as a source of information. It makes prediction uncertain due to the sensitive dependence on initial conditions. Any imprecision in our knowledge of the state is magnified as time goes by. A measurement made at a later time provides additional information about the initial state. From a macroscopic point of view, the second law of thermodynamics tells us that a system tends to evolve toward the set of conditions that has the largest number of accessible states compatible with the macroscopic conditions. In a phase space, the entropy of a system can be written as

$$H = -\sum_{i=1}^{n} p(i) \log\ p(i) \tag{2.6}$$

where p is the probability that the system is in state i. In practice one has to divide the region containing the attractor in n cells and calculate the relative frequency (or probability p) with which the system visits each cell. Entropy has a special significance in time series and we shall revisit the methodology in the Chap. 4. The

prototype is the Kolmogorov–Sinai entropy or Shannon entropy. In heart rate variation approximate entropy and more recently sample entropy are used.

Where Lyapunov exponent and entropy focus on the dynamic of trajectories in the phase space, *dimension* emphasizes the geometric features of attractors. Traditionally, dimension is understood in the classic Cartesian way. A dimension is a parameter (or measurement) required to define the characteristic of an object. In mathematics generally, dimensions are the parameters required to describe the position and relevant characteristics of any object within a conceptual space – where the number of dimensions of a space are the total number of different parameters used for all possible objects considered in the model. An even more abstract perspective generalizes the idea of dimensions in the terms of scaling laws. The so-called Hausdorff dimension is an extended nonnegative real number associated to metric space. To define the Hausdorff dimension for a given space X, we first consider the number $N(r)$ of circles of radius r which are required to cover X completely. Clearly, as r gets smaller, $N(r)$ gets larger. Roughly, if $N(r)$ grows the same way as $1/r^d$ as r is squeezed down to zero, then we say X has the dimension d. Related methods include the box-counting dimension, also called Minkowski–Bouligand dimension.

Fractals are irregular geometric objects. An important (defining) property of a fractal is *self-similarity*, which refers to an infinite nesting of structure on all scales. Strict self-similarity refers to a characteristic of a form exhibited when a substructure resembles a superstructure in the same form. Heart rate on the frequency domain (see time-domain analysis) is fractal in nature and measures of fractality have been used to characterize the amount of nonlinearity (see fractal analysis).

Nonlinear statistic tools have been introduced in the last decades. Return maps, also called Poincaré plots, have been used to distinguish between stochastic systems or deterministic systems (Clayton 1997). Briefly, return maps plot a point in a Cartesian system where x is the current value of the time series and y is the next point of the time series. This is repeated for the next pair of values. Stochastic time series show a distribution like in Figs. 2.1 and 2.5.

If we look at a time series produced with the already known logistic equation $x_{n+1} = kx_n(1 - x_n)$ with a k of 3.99, this time series looks graphically highly stochastic (Fig. 2.6).

A return map, however, reveals the deterministic properties of this time series (Fig. 2.7).

Complexity

Complex systems are sometimes positioned between simple systems and stochastic systems. One approach uses the idea of predictability. A system may be predictable (we know how it will develop over a certain time range) or may not be predictable (we know definitely that we don't know how the system will develop over a certain time range). Highly predictable and highly unpredictable systems are *simple*, since the method of forecasting is so straightforward (Crutchfield 2002). But most interesting systems are between those extremes. Interest in them arose because complex

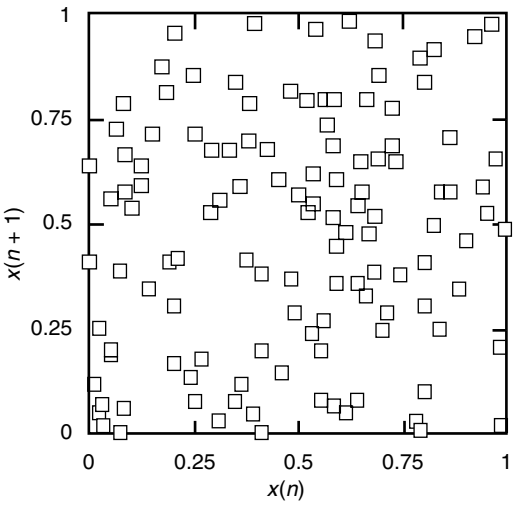

Fig. 2.5 Return map of a stochastic time series (From Clayton (1997))

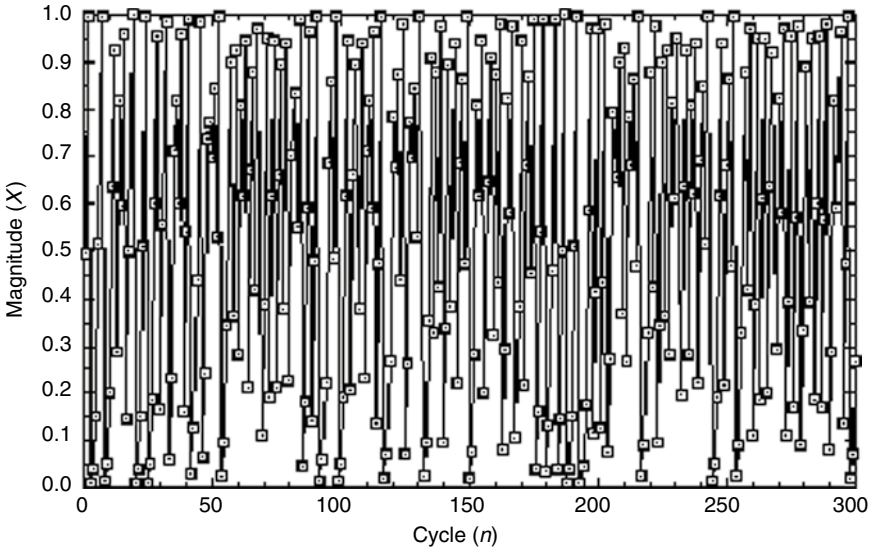

Fig. 2.6 Time series of $x_{n+1} = 3.99\, x_n(1 - x_n)$ (From Clayton (1997))

systems seem to be sensitive to some small perturbations, but at the same time complex systems can be quite resistant to other perturbations, which makes them robust and adaptable (Holt 2004).

There exist several different definitions of complex systems. At the present time, the notion of complex system is not precisely delineated yet. The idea is somewhat fuzzy and it differs from author to author. Main approaches include:

- The number of components in the system (the system's *dimension*)
- The degree of *connectivity* between the components

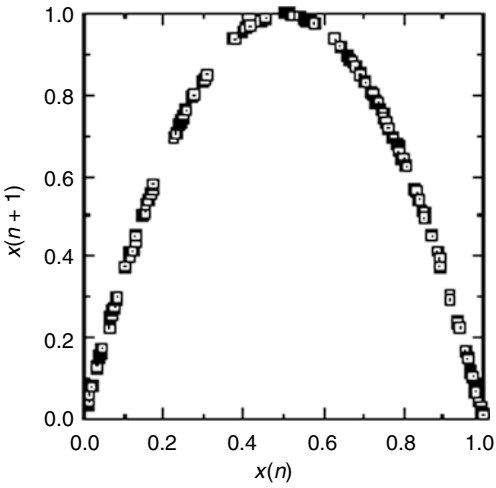

Fig. 2.7 Return map of $x_{n+1} = 3.99\, x_n(1 - x_n)$ (From Clayton (1997))

- The dynamic properties and *regularity* of the system's behavior
- The information content and *compressibility* of data generated by the system (Holt 2004)

But there is fairly complete agreement that the "ideal" complex systems, those that we would like most to understand, are the biological ones and especially the systems having to do with people: our bodies, our groupings, our society, and our culture. Lacking a precise definition, it is possible to convey the meaning of complexity by enumerating what seem to be the most typical properties. Some of these properties are shared by many non-biological systems as well.

Complex Systems Contain Many Constituents Interacting Nonlinearly

Nonlinearity is a necessary condition for complexity, and almost all nonlinear systems whose phase space has three or more dimensions are chaotic in at least part of that phase space. This does not mean that all chaotic systems are complex. For one thing, chaoticity does happen with very few constituents; complexity does not.

The Constituents of a Complex System Are Interdependent

Here is an example of interdependence. Consider first a non-complex system with many constituents, say a gas in a container. Take away 10 % of its constituents, which are its molecules. Nothing very dramatic happens. The pressure changes a little or the volume or the temperature or all of them. But on the whole, the final gas

looks and behaves much like the original gas. Now, do the same experiment with a complex system. Take a human body and take away 10 %, let's just cut out a leg! The result will be rather more spectacular than for the gas.

A Complex System Possesses a Structure Spanning Several Scales

Take the example of the human body again. Scale 1: head, trunk, limbs, and the macroscopic scale; Scale 2: blood vessels, nerves, and tissue level; Scale 3: cells and communications between individual cells; Scale 4: intracellular, genome, proteonome, and translational processes; Scale 5: biological chemistry, enzymatic processes, and physical chemistry. At every scale we find a structure. Different scales influence each other. This is an essential and radically new aspect of a complex system, and it leads to the fourth property.

A Complex System Is Capable of Emerging Behavior

Emergence happens when you switch the focus of attention from one scale to the coarser scale above it. A certain behavior, observed at a certain scale, is said to be emergent if it cannot be understood when you study, separately and one by one, every constituent of this scale, each of which may also be a complex system made up of finer scales. Thus, the emerging behavior is a new phenomenon special to the scale considered, and it results from global interactions between the scale's constituents. The combination of structure and emergence leads to *self-organization*, which is what happens when an emerging behavior has the effect of changing the structure or creating a new structure. There is a special category of complex systems that was especially created to accommodate living beings. They are the *complex adaptive systems*. As their name indicates, they are capable of changing themselves to adapt to a changing environment. They can also change the environment to suit themselves. Among these, even narrower categories are *self-reproducing*: they know birth, growth, and death. Needless to say, we know very little that is general about such systems considered as theoretical abstractions. We know a lot about biology. But we don't know much, if anything, about other kinds of life, or life in general.

Let us return now to the relationship between complexity and chaos. They are not at all the same thing. When you look at an elementary mathematical fractal, it may seem to you very "complex", but this is not the same meaning of complex as when saying "complex systems." The simple fractal is chaotic; it is not complex. Another example would be the simple gas mentioned earlier: it is highly chaotic, but it is not complex in the present sense. We already saw that complexity and chaos have in common the property of nonlinearity. Since practically every nonlinear system is chaotic some of the time, this means that complexity implies the presence of chaos.

But the reverse is not true. Chaos is a very big subject. There are many technical papers. Many theorems have been proved. But complexity is much, much bigger. It contains lots of ideas that have nothing to do with chaos. Chaos is basically pure mathematics, and by now it is fairly well known. Complexity is still almost totally unknown. It is not really mathematics, but more like theoretical physics. The field of chaos is a very small subfield of the field of complexity. Perhaps the most striking difference between the two is the following. A complex system always has several scales. While chaos may reign on scale n, the coarser scale above it (scale $n-1$) may be self-organizing, which in a sense is the opposite of chaos. Therefore, let us add a fifth item to the list of the properties of complex systems.

Complexity Involves Interplay Between Chaos and Non-chaos

Many people have suggested that complexity occurs "at the edge of chaos" (Kauffman 2002), but this is not entirely clear. Presumably it means something like the following: imagine that the equations of motion contain some "control" parameter that can be changed depending on the environment (e.g., temperature, concentration, intensity of some external factor like sunlight). We know that most nonlinear systems are not 100 % chaotic: they are chaotic for some values of the control parameter and not chaotic for others. Then there is the edge of chaos, i.e., the precise value of the control for which the nature of the dynamics switches. It is like a critical point in phase transitions. It is the point where the long-range correlations are most important. Perhaps complex systems, such as biological systems, manage to modify their environment so as to operate as much as possible at this edge of chaos place, which would also be the place where self-organization is most likely to occur. It makes sense to expect self-organization to happen when there are strong long-range correlations. Finally, there is one more property of complex systems that concerns all of us very closely, which makes it especially interesting. Actually, it concerns all social systems, all collections of organisms subject to the laws of evolution. Examples could be plant populations, animal populations, other ecological groupings, our own immune system, and human groups of various sizes such as families, tribes, city states, social or economic classes, sports teams, Silicon Valley dotcoms, and of course modern nations and supranational corporations. In order to evolve and stay alive, in order to remain complex, all of the above need to obey the following rule.

Complexity Involves Interplay Between Cooperation and Competition

Once again this is interplay between scales. The usual situation is that competition on scale n is nourished by cooperation on the scale below it (scale $n+1$). Insect colonies like ants, bees, or termites provide a spectacular demonstration of this. For

a sociological example, consider the bourgeois families of the nineteenth century of the kind described by Jane Austen or Honoré de Balzac. They competed with each other toward economic success and toward procuring the most desirable spouses for their young people. And they succeeded better in this if they had the unequivocal devotion of all their members, and also if all their members had a chance to take part in the decisions. Then of course there is war between nations and the underlying patriotism that supports it. Once we understand this competition–cooperation dichotomy, we are a long way from the old cliché of "the survival of the fittest," which has caused so much damage to the popular understanding of evolution (Baranger).

Monitoring, Predicting, and Managing Complex Systems

The wish to monitor complex systems can have several reasons. The conditions of complex systems might reflect their robustness or fragility. This can mirror robustness against perturbations from outside the system, but also robustness against internal oscillations. As described, complex systems can move to a point where a transition occurs. Several forms of transitions have been described in theoretical models and also partially observed in real-world systems (Scheffer et al. 2009). Monitoring complex systems has to be done over time. Changes of surrogate parameters might describe that the system approach a possible threshold – a so-called tipping point – where the systems shifts abruptly from one stage to the next.

It is well known that it is not possible to predict the state of any iterative system beyond certain iterations. At the same time it is known that any system has a finite number of states of equilibrium or quasi-equilibrium that it can reach. This is not necessarily contradictory. The non-predictability of a system regards first the impossibility to predict certain variables. It was originally recognized in meteorology – that even the best computer using the best model is not able to forecast the weather more than some days in advance. But on the other hand, rhythmicity leads to predictability. We know that usually winter is cooler than summer, rain falls in springtime even if we are not able to predict exactly a day's temperature or the days when it will rain. The predictability in complex systems can mean that the number of possible states is known, but in the beginning, the attractor the system will be going toward is not yet known.

Illness interpreted within a complex systems paradigm can be described as a system being in equilibrium (an attractor state that means health) that is perturbed by an external or internal event. This perturbation is big enough to cast the system out of equilibrium. Then eventually it moves back to the same basin of attraction (equilibrium in health) or to another basin of attraction (chronic illness or death). The direction of the system (and the velocity of changes) might be more interesting as the state of the system itself at a certain point of time. A systems dynamic approach can be to monitor the system and in particular the system changes (using special variables that represent a system state) and to react fast according to these

changes. Part of this theory is that early reactions in beginning changes might require less measures or even minimal measures in difference to a system which is already far in the direction of another basin of attraction.

In nonlinear systems, big perturbations might only have small effects, but in the right moment, a small perturbation may be enough to cause a system change (Scheffer et al. 2009). If we assume that the latter situation can be defined, it should be possible either to perturb the system in an adequate manner, pushing it over the tipping point, or conversely to avoid a transition by using countermeasures when the system is evolving near transition points. It is important to recognize, however, that there is not only one kind of transition. In models, critical thresholds for transitions correspond to bifurcations (Kuznetsov 1995). Particularly relevant are catastrophic bifurcations that occur after passing a critical threshold when a positive feedback propels the system through a phase of directional change toward a contrasting state (Scheffer et al. 2009). Other classes of bifurcations occur when one kind of attractor is exchanged with another, e.g., a terminal cycle against a strange (chaotic) attractor.

With help of models it is possible to identify clues that may be associated with a system near a transition point. One of the most important clues has been discussed as a "critical slowing down" phenomenon (Wissel 1984). "Critical slowing down" has been observed in very distinct phenomena, as in cell-signaling pathways (Bagowski and Frrell 2001), ecosystems (Scheffer et al. 2009), and climate (Lenton et al. 2008). Close to the bifurcation points, the exchange rates of the system around the equilibrium become zero. This implies that as the system approaches such critical points, it becomes increasingly slow in recovering from small perturbations (Scheffer et al. 2009). This slowing can begin already far from the tipping point and increases as the tipping point is approached (Van Nes and Scheffer 2007). In real systems this phenomenon could be tested by inducing small perturbations that are not sufficient to drive the system over the transition point and then by measuring the rates of change. Otherwise it can be possible to observe the effects of usually always existing natural perturbations on the exchange rates.

Slowing down can lead to an increase in autocorrelation in fluctuation patterns. This can be shown mathematically (Scheffer et al. 2009). The reason is that in case of a reduced exchange rate, the system at point b is more and more similar to the system at one point a in the past, the system has a memory of itself, so to say. This autocorrelation phenomenon can be measured with help of the frequency spectrum of the system (Livina and Lenton 2007). Another consequence can be increased variance – as eigenvalue approaches zero, the impacts of shock do not decay and their accumulating effects increase the variance of the state variable (Scheffer et al. 2009). Another possibility is to look at the asymmetry of fluctuations (Guttal and Jayaprakash 2008). This is not necessarily a result of critical slowing down. It has rather something to with an approaching unstable attractor from one side in the state space. Also flickering can occur, if the system is near a system shift, being alternately attracted by two basins of attraction. This has been discussed as an alarming sign before phase transitions, e.g., in models of lake eutrophication (Carpenter and Brock 2006).

In conclusion, in the last years several interesting approaches to predict system transitions have been proposed. However, sophisticated ideas to manage complex systems are either lacking or only theoretical. Regarding complex social systems, scientists are rather skeptical about managing theories (Willke 1999).

Summary

- Linear systems are only a special condition. Most systems are only linear if they are simplified. Most biological systems are nonlinear in nature.
- In principle, systems consist of stochastic and deterministic elements. It is possible, but not always easy to analyze systems in order to quantify the fraction of determinism. Determinism means simply that the behavior of a system over time is dependent on its history.
- Nonlinear deterministic ("chaotic") systems show robustness, which is partially dependent on stochastic noise. This robustness is with respect to some kinds of perturbation. On the other hand, nonlinear deterministic systems can be highly sensitive to certain other perturbations, leading to fast disintegration of the system
- Complex systems are nonlinear systems, where their parts interact nonlinear and where there exist different interacting scales. Complex system show emergent behavior, they can change from a disordered to an ordered state and vice versa.

Further Readings

Many excellent introductions to nonlinear and complex systems have been published in the last years. Important ideas and materials of this chapter were obtained from Strogatz (1994), Clayton (1997), Faure and Korn (2001), Kauffman (2002), and Baranger.

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Chapter 3
The Autonomic Nervous System

Outline: In this chapter we introduce the autonomic nervous system. Principles and newer views from neuroscience are presented and discussed. It has a special focus on effects and interactions of the autonomic nervous system and the cardiovascular and respiratory systems, which are important for the understanding of the physiology and pathophysiology of heart rate variations.

Introduction

The autonomic nervous system (or vegetative nervous system) controls the heart, smooth muscles, endocrine, and exocrine glands and has an afferent (sensory) and an efferent part. It is distinct from the somatic nervous system in several ways. The central control of the vegetative nervous system is allocated in the hypothalamus but several other brain regions including the amygdala, the prefrontal cortex, and the association areas of the limbic cortex exert influence on the hypothalamus itself. The efferent nervous activity of the ANS is largely regulated by autonomic reflexes; in many of them sensory information is first transmitted to homoeostatic control centers to be processed there with a specific reaction. The autonomic nervous system has its specific transmitter substances and receptors and a particular form of connections that can be divided in preganglionic and postganglionic fibers.

The main role of the autonomic nervous system is to maintain balance in the body under varying conditions. The hypothalamus is able to control three different systems. Apart from the ANS the hypothalamus controls the endocrine system and an ill-defined neural system concerned with motivation (Saper et al. 2000). The autonomic system is a visceral sensory *and* motor system based on reflexes. These visceral reflexes are (almost) not under voluntary control. It has three major divisions: sympathetic, parasympathetic, and enteral (the latter is often underestimated). In principle, a real autonomic system (e.g., the enteric system) is sparsely connected with other parts of the nervous system and is largely self-contained.

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In a traditional view, the sympathetic and the parasympathetic systems are opposed to each other, the former responsible for stress reactions and the latter for relaxing. Virtually all visceral reflexes are mediated by local circuits in the brainstem and spinal cord (Iversen et al. 2000). However, recently this view has been challenged. We discuss more recent views discussed at the end of this chapter. A more modern characterization is that the sympathetic nervous system is a "quick response mobilizing system" and the parasympathetic is a "more slowly activated dampening system."

It has been proposed that there exist individual patterns in stress response that are highly reliable, such as primarily vagal cardiac withdrawal, primarily sympathetic cardiac activation, or both cardiac withdrawal and sympathetic activation. Correlations between high-frequency power (often related to the parasympathetic system) and sympathetic indices did not consistently covary across individuals and the median correlation was low (Cacioppo 1994). We discuss the proposed relations between ANS and HRV in particular in Chap. 5.

Anatomical Structures

Supraspinal Autonomic Network

The autonomic nervous system can be divided into sympathetic, parasympathetic, and enteric parts. In addition it can be divided into a central nervous and a peripheral part. The central nervous part is rather a network, a highly interconnected set of structures in forebrain and brain stem. One of the most important components is the nucleus of the solitary tract (NTS), which receives extensive sensory inputs (through, among others, cranial nerves VII, IX, and X and N vagus). The nucleus itself projects to supraspinal and spinal circuits that control autonomic responses. Ascending projections from the NTS reach the forebrain sites including hypothalamic nuclei, amygdala, and insular cortex. This includes the carotid sinus reflex, the gag reflex, the cough reflex, the baroreceptor and chemoreceptor reflexes, several respiratory reflexes, the aortic reflex, and reflexes within the gastrointestinal system regulating secretion and motility. The other important part of the NTS regards integration of autonomic functions with a wider range of responses like from the endocrine and behavioral systems. Together with NTS, the hypothalamus plays a major role here. The projections from MTS to forebrain are partially processed in the parabrachial nucleus (important for behavioral responses). This again has projections to the periaqueductal gray, amygdala, visceral thalamus, hypothalamus, and cortex.

Synaptic contacts exist also between the neurons in the NTS and C1 neurons in the rostral ventrolateral medulla (RVM), which have an important role in the control of cardiovascular homoeostasis. The RVM neurons in turn project to the locus coeruleus (LC), which is the main source of noradrenergic innervations of higher brain sites including the hypothalamus and PVN. Projections arise from the RVM and LC

to sympathetic preganglionic neurons in the spinal cord. There are also descending pathways from the PVN to the RVM and NTS.

The periaqueductal gray coordinates vegetative reaction (e.g., in stress). Amygdala and prefrontal cortex regions have an important role in conditioned behavioral responses but also in the connection between visceral input, output, and emotional states. A typical clinical conditioning happens in cancer patients who get nausea already when they see the cancer clinic or cancer nurses. Repeated treatments with emetogene cytostatics lead to an association between the view of the clinic and nausea, which is partially processed in the amygdala and forwarded to the hypothalamus and brain stem structures.

The connection between the parabrachial nucleus and thalamus is relayed to the anterior insular cortex where the internal organs are represented topically. This part of the visceral sensory cortex interacts with parts of the cingulate cortex (the infralimbic area), which represents the motoric part of the system and can cause blood pressure changes or gastric contractions.

The hypothalamus is a small, complex brain region. In case of the ANS, it has an integrative function by regulating five basic physiological needs:

- Blood pressure and electrolyte composition control by a set of regulatory mechanisms (control of drinking, salt appetite, maintenance of blood osmolality, vasomotor tone, and others)
- Regulation of body temperature (control of metabolic increase of temperature, behavioral)
- Energy metabolism control (regulating eating, digestion, metabolic rate)
- Reproduction control (by hormonal regulation of pregnancy, lactation, and breastfeeding)
- Control of emergency functions and reactions to stress (muscle blood flow and tissue blood flow regulation, release of adrenal stress hormones) (Iversen et al. 2000)

The hypothalamus is able to regulate this based on indirect and direct projections reporting internal states; own internal sensory neurons measuring changes in local temperature, osmolality, glucose, and sodium; and neurons responsive to circulating hormones like leptin and angiotensin II through circumventricular organs. Integrated in hypothalamic circuits are set points. For instance, the hypothalamus acts like a thermostat. A temperature is set (normally around 37 °C). In case of differences between the set temperature and the measured temperature, the hypothalamus activates cooling (e.g., sweating) or heating (e.g., shivering) mechanisms to reach the set temperature. In case of fever, the set temperature is increased (due to circulating interleukins, among other factors), which induces the typical shivering reaction in beginning infections. To accomplish this control function, the hypothalamus contains a complex structure of interlinked nuclei, whose description is beyond the aim of this chapter.

One of the hypothalamic nuclei receiving input from the NTS is the paraventricular nucleus (PVN). The PVN is associated with the synthesis and release of corticotropin-releasing hormone (CRH), an important substance in the HPA axis.

This ascending link between the NTS and PVN provides a pathway that can modulate neurohormonal anti-inflammatory responses. The role of the medial prefrontal cortex has been emphasized; it has a critical role in the regulation and harmonization of behavioral and physiological responses (Thayer 2006).

In a network-like structure like the brain, it is in fact not easy to designate brain regions that do not influence HRV. In ongoing research it is important to distinguish between the orders of magnitude of influences. The structures mentioned are major players, but they are not the only ones: the whole system consists of several interlinked subnetworks connected to each other. In fact, this reflects the significance of HRV as a possible surrogate index of this supraspinal networks (Thayer et al. 2012).

Spinal and Peripheral Autonomic Nervous System

In the somatic motor system the motor neurons are part of the central nervous system. They are located in the spinal cord and the brain stem and project directly to skeletal muscle. In contrast to this, the motor neurons of the sympathetic and parasympathetic motor systems are located outside the spinal cord in autonomic ganglia. The autonomic motor neurons, also called postganglionic neurons, are innervated by central neurons (also called preganglionic neurons). Thus, there is one synapse between the central control and the target tissue. The sympathetic and parasympathetic system has sensory elements that project to the vegetative centers in the brain stem. Some branches project also directly to the autonomic ganglia as part of a local reflex circuit.

Differently from somatic motor neurons, autonomic motor neurons have no specialized postsynaptic regions, but have their effects through nerve endings with several swellings (varicosities) where vesicles containing transmitter substances accumulate. Synaptic transmission occurs thus at multiple sides of the highly branched axon terminals of autonomic nerves. The neurotransmitter diffuses through the interstitial fluid to wherever its receptors are located in the tissue. Control is therefore not exact, goal orientated, but more diffuse. On the other hand, a few autonomic nerves are able to control large areas of smooth muscle or other target tissues. This is due to gap junctions that allow the spread of electrical activity from cell to cell. As a result, the discharge of few autonomic nerve fibers to an effector tissue might alter the activity of the whole area.

The ANS is composed of two anatomically and functionally different divisions called the sympathetic and the parasympathetic system (SNS, PNS, respectively). Their function is at all times tonical that means that it has every time some activity in form of action potentials, which can increase or decrease. Most though not all target tissues are innervated by both divisions, often with opposing effects. In general, SNS dominates in stress situations, whereas PNS is idle. In addition, the PNS in particular is involved in basic body functions like digestion and urination.

Sympathetic preganglionic fibers form a column in the intermediolateral horn of the spinal cord extending from the first thoracic spinal segment to rostral lumbar segments

(Iversen et al. 2000). They leave the spinal cord and form synapses in the ganglia of the sympathetic chains, which lie along each side of the spinal cord. Preganglionic fibers are thin but myelinated and are relatively slow conducting. Postganglionic fibers in contrast are not myelinated. There exists a preganglionic/postganglionic fiber ratio of 1:10–1:20. A few preganglionic fibers control many postganglionic fibers by having synapses with them in often more than one ganglion. Apart from the postganglionic nerves in the head, postganglionic fibers represent about 9 % of the spinal nerve. The fibers that innervate the heart, lung, and vessels are probably most relevant for the physiology of heart rate variability. In addition, the adrenal medulla consists of preganglionic SNS neurons synapsing directly with glandular tissue. The cells of the medulla do not have endocrinological origin, but came during the embryological development from neuronal lines. The medulla can so be seen as an aggregation of postganglionic SNS neurons that send their transmitter substances through the whole body with the help of blood circulation. A particular feature of SNS is to innervate blood vessels, primarily arterioles and veins, most of them only receiving SNS, not PNS fibers. Therefore vascular tone (and sweating) is regulated by SNS only.

Cardiovascular sympathetic efferents can be broadly classified into three groups according to their dominant characteristic: thermosensitivity, glucosensitivity, and barosensitivity (Lohmeier 2001). The *thermosensitive* cardiovascular efferents consist mainly of cutaneous vasoconstrictors, which are activated by hypothermia, emotional stimuli, and hyperventilation. The *glucosensitive* group controls adrenalin release from the adrenal medulla and is activated by hypoglycemia and physical exercise. The *barosensitive group* is the largest of the three. Regardless of organ or tissue being innervated, these neurons show ongoing activity in rest (sympathetic tone) and they discharge in bursts that are highly synchronized with the arterial pulse and respiration (Dempsey et al. 2002; Jänig and Habler 2003). Barosensitive sympathetic efferents control the heart and the kidneys as well as the release of noradrenalin from a subset of adrenal chromaffin cells. They also constrict resistance arterioles with the exception of those in the skin (Jänig and Habler 2003). Barosensitive efferents are subject to numerous reflex regulations that operate as either feedback or feedforward mechanisms. For example, whereas ventilation (afferents of the lung) and arterial pressure (carotid and aortic receptors) inhibit activity, muscle receptors during exercise, nociceptors in the heart and skin, or central and peripheral chemoreceptors (activated by hypoxia or hypercapnia) increase the discharge. Barosensitive receptors are usually activated in all organs simultaneously, with the exception of the selective inhibition of real sympathetic nerves by atrial stretch or volume expansion (Figs. 3.1 and 3.2) (Coote 2005).

Barosensitive efferents seem to be regulated mainly by the rostral ventrolateral medulla (RVLM) and the cutaneous circulation by the rostral ventromedial medulla (RVMM). The central control of adrenalin secretion is not completely understood. It is not under baroreceptor control, but well regulated by the RVLM. One group of adrenaline-producing cells is the C1-cells located in the RVLM. Their discharge is similar to the barosensitive fibers. In addition, most RVLM cells release glutamate. Some C1-cells are connected with the hypothalamus, probably involved in sodium and water balance.

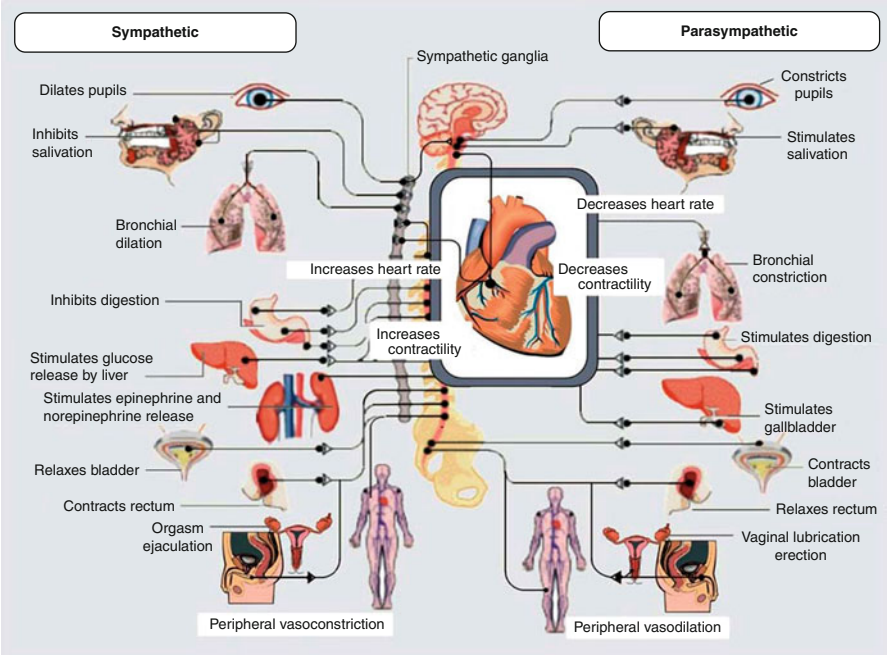

Fig. 3.1 A diagrammatic illustrations of the role of the two arms of the autonomic nervous system (with permission of the Vinik 2012)

The sympathetic baroreflex is a feedback loop. The afferent loop involves mechanoreceptors that are activated by distension of the arterial wall. Increase in blood pressure activates baroreceptors and cause inhibition of cardiac, real, and vasomotor sympathetic efferents, which, in turn, leads to restoration of blood pressure. This reflex effects in dampening short-term blood pressure fluctuations (Dempsey et al. 2002) and can be modulated in case of need without decreasing reflex sensitivity that involves both neural and humeral elements (see Fig. 3.3). The mechanisms include activating C1 neurons in the RVLM by glutamate release induced by, for example, pain or exercise and simultaneous activation of GABAergic pathways that inhibit efferent parts of the reflex circuit, blocking partially the baroreceptor reflexes. Angiotensin II's effects on vessel endothelium involving production of nitrite oxide can increase this effect (Fig. 3.3).

In contradiction to the sympathetic part, parasympathetic preganglionic nerves are located in several brain stem nuclei (beyond others, nucleus ambiguous, the dorsal vagal nucleus, and the Edinger-Westphal nucleus) and in parts of the sacral spinal cord. Preganglionic parasympathetic nerves innervating targets in thorax and abdomen leave the brain stem mainly through the vagal nerve (nerve X). The preganglionic to postganglionic fiber ratio in the parasympathetic system is 1:3. Differently than sympathetic ganglia, parasympathetic ganglia are often localized near their target organs, making axons of the preganglionic neurons often quite long compared to those of SNS. Terminal ganglia are frequently near their target organs.

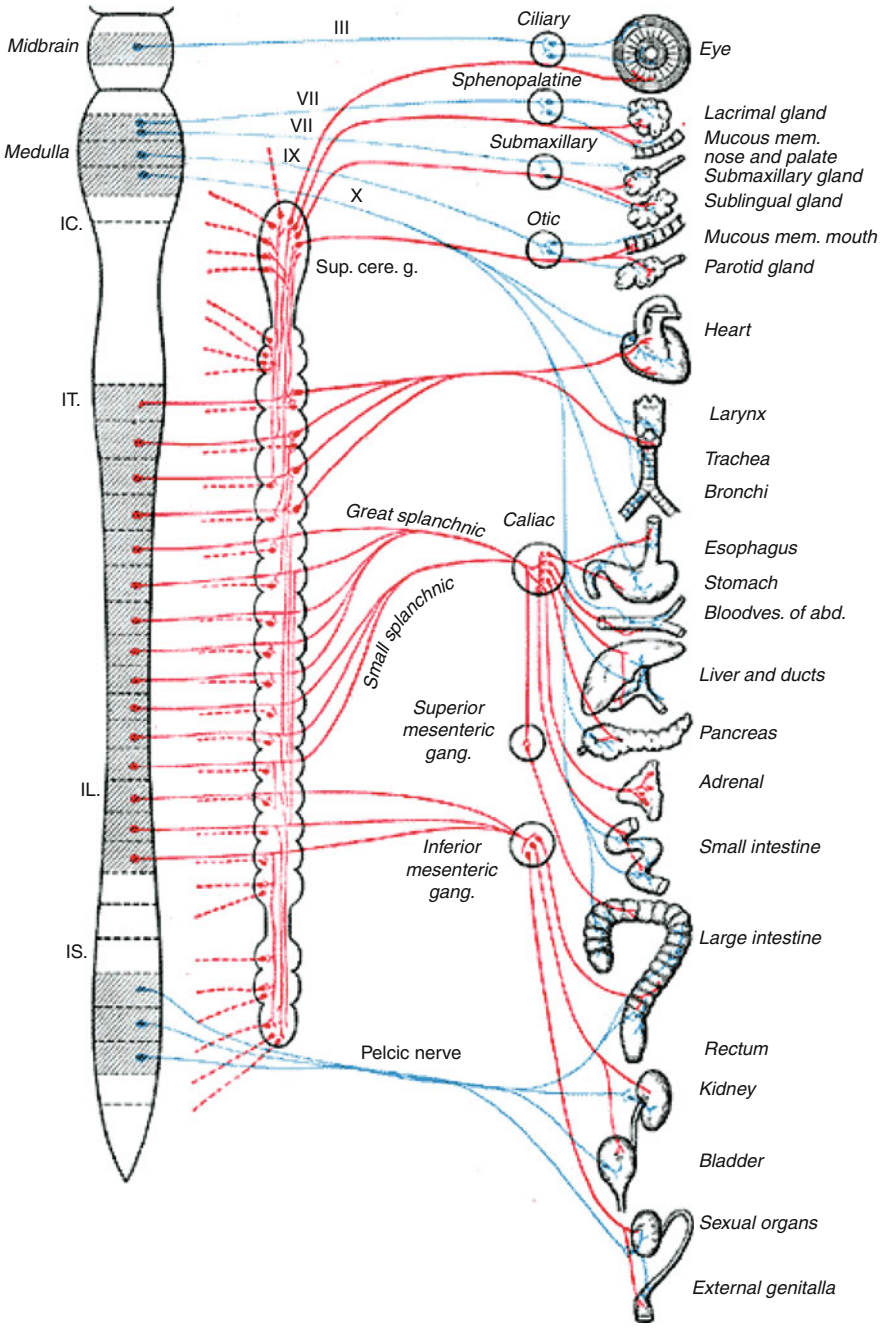

Fig. 3.2 Classical graphical view of the sympathetic and parasympathetic system (Grays 1918)

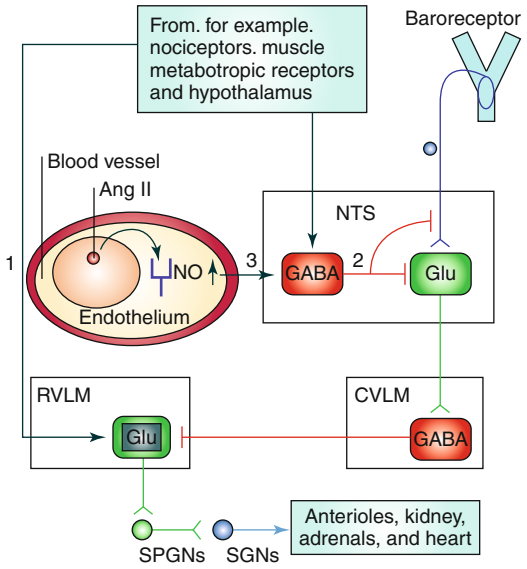

Fig. 3.3 Neural and humoral control of the baroreflex (Guyenet (2006), with friendly permission of Nature Publishing Group)

Several preganglionic neurons exit the CNS through cranial nerves, in particular nerve III (oculomotorius, innervates the eyes), nerve VII (facial nerve, innervates the lacrimal gland, the salivary glands, and the mucus membranes of the nasal cavity), nerve IX (pharyngeal nerve, innervates the saliva glands), and, most importantly, nerve X (vagal nerve, innervates visceral thoracal and most visceral abdominal organs). The vagal nerve is at the same time the main source for information about the internal state of thoracic and abdominal organs. Visceral vagus afferent fibers, residing in the nodose ganglion, terminate primarily within the dorsal vagal complex (DVC) of the medulla oblongata. The DVC consists of the already mentioned nucleus tractus solitarius (NTS), the dorsal motor nucleus of the vagus (DMN), and the area postrema (AP) (Berthoud and Neuhuber 2000). The DMN is the major origin of preganglionic vagus efferent fibers; cardiovascular vagal efferents originate also within the medullar nucleus ambiguous. The AP, which lacks a blood–brain barrier, is an important circumventricular organ and the site for humoral immune-to-brain communication, as described below. The main portion of vagal sensory input is received by neurons in the NTS that coordinate autonomic function and interaction with the endocrine system (Iversen et al. 2000).

Ascending and descending vagal connections provide a neuronal substrate for interaction between HPA axis and SNS as an immunomodulatory mechanism. The transmission of cytokine signals to the brain through the vagal sensory neurons depends on the magnitude of the immune challenge. It is likely that the vagal afferent neural pathway plays a dominant role in mild to moderate peripheral inflammatory responses, whereas, acute, robust inflammatory responses signal the brain primarily via humoral mechanisms (Pavlov et al. 2003). The role of the vagal afferent pathway has been underlined by experimental studies where manipulation of the pathway resulted in changed system reactions after exposure to endotoxins.

Transmitter Substances

The main neurotransmitters of the vegetative nervous system are well known. Acetylcholine (ACh) and noradrenalin (NA, also called norepinephrine) have been discovered in relation to research targeted on the ANS. Preganglionic neurons of the ANS use ACh as neurotransmitter. Postganglionic sympathetic neurons use noradrenalin and postganglionic parasympathetic neurons use ACh. Nerve fibers releasing ACh are also termed cholinergic fibers. Nerve fibers releasing noradrenalin are also termed adrenergic. ACh is rapidly inactivated by acetylcholinesterase (to its components choline and acetate). Acetylcholinesterase is one of the fastest enzymes in the body, needing less than 1 ms to remove ACh from the synaptic gap. Noradrenalin is taken up presynaptically where it is reused or metabolized by monoamine oxidase (MAO) transforming it to 3-methoxy-4-hydroxymandelic acid (vanillyl mandelic acid; VMA) that can be found in the urine. By contrast, circulating noradrenalin and adrenalin are inactivated by catechol-O-methyltransferase (COMT) in the liver. Catecholamines are often described as metabolized at sites distant from their sites of synthesis and release after their entry into the extracellular fluid or even the blood stream. But there is overwhelming evidence suggesting that most noradrenalin is eliminated in presynaptic cells (Eisenhofer et al. 2004). In a first step, catecholamines are transformed to 3-methoxy-4-hydroxyphenylglycol. Most VMA is produced by oxidation of circulating MHPG by alcohol dehydrogenase located mainly in the liver.

Not only noradrenaline but probably adrenaline as well plays a role in sympathetic nerves as co-transmitter, being incorporated in postganglionic sympathetic nerves and released with noradrenaline up to 24 h after its uptake (Majewski et al. 1981; Quinn et al. 1984). Furthermore, infusion of pharmacologic doses of adrenaline has been shown to promote noradrenergic transmission, probably by stimulating prejunctional β_2 receptors (Majewski et al. 1982). More recent studies showed evidence for cardiac adrenaline release also in chronic heart failure patients under baseline conditions possibly released by cardiac sympathetic nerve cells. There has also evidence for uptake both in heart and kidney neurons (Johansson et al. 1997). As mentioned above, adrenaline is co-released in the RVLM central barosensitive pathways together with glutamate. Normally the influence of glutamate is substantially low; in dehydration or abnormal blood gas conditions, however, it makes a greater contribution (Guyenet 2000; Brooks et al. 2004). Autonomic ganglia also receive afferent fibers containing neurokinins (SP, CGRP).

Adenosine triphosphate (ATP) is an important co-transmitter together with noradrenaline in many postganglionic sympathetic neurons. By acting on ATP-gated ion channels (P_2 purinergic receptors), they are responsible for some of the fast reactions of the target tissues (for example smooth muscles). Adenosine is formed by the hydrolysis of ATP and acts on the P_1 purinergic receptor located both pre- and postsynaptically. It possibly plays an important role in sympathetic transmission. Adenosine may dampen sympathetic function after intense sympathetic activation by activating receptors on sympathetic nerve endings that inhibit further noradrenaline and ATP release. Adenosine has also inhibitory actions in cardiac and smooth muscle

that tend to oppose the excitatory effect of noradrenaline, which generates an intraganglionic reflex loop with a mainly negative feedback effect. Another transmitter substance in sympathetic nerve endings is neuropeptide Y (in as many as 90 % of neurons). Neuropeptide Y potentiates both adrenergic and purinergic effects postsynaptically (in tissues with less dense sympathetic innervation) or presynaptically inhibiting release of noradrenaline and ATP (in areas with dense sympathetic innervation). Galanin and dynorphin are often co-localized with neuropeptide Y.

In some preganglionic nerve terminals, acetylcholine is co-localized with a luteinizing hormone-releasing hormone (LHRH)-like peptide. High-frequency stimulation causes release of this peptide resulting in a slow, long-lasting EPSP in all postganglionic neurons. To obtain this effect, the peptide diffuses beyond the synaptic gap. This slow peptidergic EPSP like the slow cholinergic EPSP result from the closure of M type channels and the opening of Na^+ and CA^{++} channels. The peptidergic excitatory potential alters the excitability of autonomic ganglion cells over long periods after intense activation of preganglionic inputs. This generates an intra-ganglionic reflex loop that has mainly a negative feedback effect. Other neuropeptides co-localized with ACh-containing fibers include enkephalins, neurotensin, somatostatin and substance P, postganglionic neurons in addition CGRP and vasoactive intestinal polypeptide (VIP) (Iversen et al. 2000).

Both ANS neurotransmitters and circulating catecholamines bind to specific receptors on cell membranes. Adrenergic and muscarinergic receptors are G protein coupled. Activation of them leads to triggering of a second messenger system in the cell. Therefore the same catecholamine on the same receptor can cause different reaction in different cells, depending of the second messenger system coupled to the receptor. Muscarinergic receptors in postsynaptic nerve cells can be excitatory or inhibitory. In contrast to this, nicotinergic ACh receptors cause fast influx of sodium and calcium into the postsynaptic cell, leading to depolarization and excitation of the postganglionic neurons.

Adrenergic receptors can be divided into α and β receptors, which again can be divided into α_1 and α_2 and β_1 and β_2, respectively. α_1 receptors are most widely distributed leading to an increase of intracellular calcium. Stimulated α_2 receptor cause a decrease in cAMP and have an inhibitory effect. α_2 receptor have an important role as presynaptic receptors causing inhibition. Their function is a negative feedback cycle that stops profuse release of noradrenalin. Stimulation of β receptors leads to an increase of cAMP, but this can lead to activating or inhibitory effects. β_1 activation in the heart leads to increased frequency, whereas β_2 activation leads to relaxation of smooth muscles, e.g., in the airway. There exist also β_3 receptors, predominantly in adipose tissue, that provoke lipolysis when activated (Table 3.1).

Basal Sympathetic Tone

The network responsible for the basal sympathetic tone is located in the rostral ventrolateral medulla (RVLM), the spinal cord, the hypothalamus, and the nucleus of the solitary tract (NTS). Limbic, cortical, and midbrain structures are mainly responsible

Table 3.1 Effects of autonomic nerve activity on some effector tissues

Tissue	Sympathetic receptor	Sympathetic stimulation	Parasympathetic stimulation
Heart	β1, β2	Heart rate ↑	Heart rate ↓
		Force of contraction ↑	Rate of conduction ↓
		Rate of conduction ↑	
Arterioles			
Skin	α1	Strong constriction	–
Abdominal viscera	α1	Strong constriction	–
Kidney	α1	Strong constriction	–
Skeletal muscle	α1, β2	Weak constriction	–
Lungs			
Airways	β2	Bronchodilation	Bronchoconstriction
Glands	α1, β2	Secretion ↓	Secretion ↑
Liver	α1, β2	Glycogenolysis	–
		Gluconeogenesis	–
Sweat glands	Muscarinic;	Generalized sweating	–
	α1	Localized sweating	–
Adrenal medullae	Nicotinic	Secretion of adrenalin ↑	–
		Noradrenalin	
Stomach			
Motility	α1, β2	Decreased	Increased
Sphincters	α1	Contraction	Relaxation
Secretion			Stimulation
Intestine			
Motility	α1, β2	Decreased	Increased
Sphincters	α1	Contraction	Relaxation
Secretion			Stimulation
Gallbladder	β2	Relaxation	Contraction
Kidney	β1	Renin secretion ↑	–
Eye			
Radial muscle of iris	α1	Contraction (dilation of pupil; mydriasis)	–
Sphincter muscle of iris		–	Contraction (constriction of pupil; miosis)
Ciliary muscle	β2	Relaxation for far vision	Contraction for near vision

Modified after McCorry (2007)

for rapid behavior-related adjustments, but are probably not involved in the long-term regulation of BP (with exception of stress-related hypertension). The score of sympathetic network is regulated by many classes of sensory afferents that project either to the NTS or to the spinal cord. The central portion of this network is also regulated at multiple levels by circulating hormones and blood-borne factors. Peptide hormones (e.g., angiotensin II) and cytokines (e.g., interleukin 1) influence this network via circumventricular organs (subfornical organ SFO, organum vasculosum lamina terminalis OVLT, and area postrema AP) or through endothelial receptors

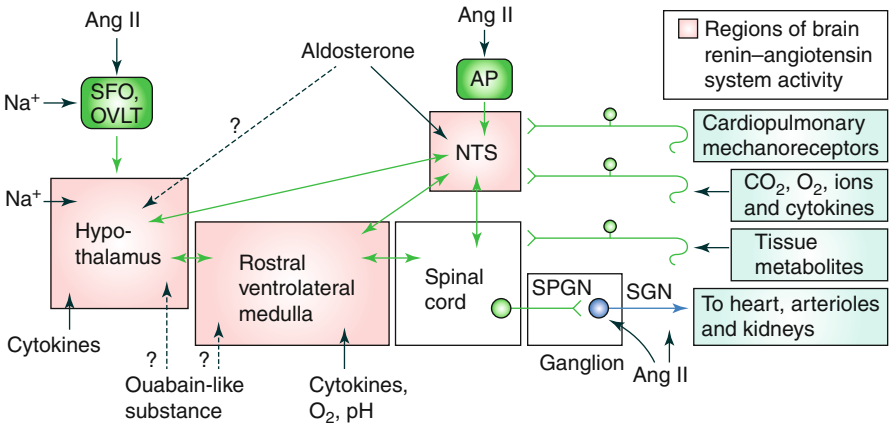

Fig. 3.4 CNS network that regulates the basal sympathetic tone (Guyenet (2006), with friendly permission of Nature Publishing Group)

triggering the release of mediators that subsequently cross the blood–brain barrier (e.g., nitric oxide and prostaglandins) (Ericsson et al. 1997). These transendothelial mechanisms operate in the hypothalamus, the RVLM, and the NTS. Freely diffusible hormones (e.g., ouabain-like substance and aldosterone) act also on this network, but their sites of action in the brain are not conclusively known (Geerling et al. 2006; Huang and Leenen 2005). This central network responds also to changes in sodium and osmolality, detected at multiple hypothalamic sites, to changes of CO_2 via brain stem chemoreceptors and is able to detect hypoxia directly in the brain stem. Moreover, virtually every component of the central network is influenced by the brain renin–angiotensin system through increased production of radical oxygen species and possibly other mechanisms (Morimoto et al. 2001; Zimmerman and Davisson 2004). Finally, hormones such as angiotensin II also influence the sympathetic ganglia. Transmitter release by sympathetic ganglionic neurons is regulated presynaptically by angiotensin II and catecholamines (Fig. 3.4) (Guyenet 2006).

There has been discussion of an organotopy theory that maintains that separate groups of RVLM barosensitive neurons control different organs or areas like skeletal muscle arteries, splanchnic arteries, the heart, or the kidneys. Some physiological evidence for this exists, but it is not conclusive (Guyenet 2006). In case of elevated blood pressure, both a general elevated sympathetic tone, but also selective elevated SNA in the kidneys, have been discussed.

Oscillations in the Sympathetic Nervous System

Oscillations in the human body can be found in every system investigated. Therefore it is not surprising when oscillations of the SNS can be recorded in various ways. Sympathetic rhythms were observed early in association with respiration.

Respiration-independent rhythms were observed about 50 years ago (Green and Heffron 1968), but their significance and role is still under debate. Rhythms are both observed in preganglionic and postganglionic nerves, especially regulating heart and blood vessels (but also in muscle sympathetic nerve activity, see below). They are not always based on rhythms measured in single nerve fibers, frequently it can be an emergent property of several hundred nerves measured simultaneously and show increasing and decreasing amplitude of the signal. Principally, two kind of rhythms can be distinguished, oscillations at a frequency between 2 and 6 Hz and oscillations around 10 Hz.

Oscillations between 2 and 6 Hz have been related to the cardiac cycle. Earlier, the main interpretation for this was that the cardiac-related rhythm reflects pulse-synchronous baroreceptor-mediated inhibition of randomly generated activity (Barman and Gebber 2000). Recent ideas discuss this rhythm pattern as a result of a nonlinear oscillator that is forced to the frequency of the heartbeat by weakly coupling to pulse-synchronous baroreceptor nerve activity. This can be shown by phase walk (a property of weakly coupled nonlinear oscillators where a progressive and systematic change of the phase angle between input and oscillator happens), which occurs in experiments (Lewis et al. 2000; Barman and Gebber 2000).

Oscillations around 10 Hz are in contrast independent of respiration and heartbeat. They exist both in baroreceptor denervated and normal cats (Barman and Gebber 1992) and disappear after transsection of the cervical spinal cord above the level of preganglionic sympathetic neurons, suggesting necessary central nervous parts for the mechanism (Allen et al. 1993). The level of arterial pressure plays a role. It is a bidirectional influence; the patterns of the oscillation can also have influence on the BP (Barman and Gebber 2000). This is somehow surprising, because the high frequency of 10 Hz cannot be transmitted one to one to vasoconstriction patterns, because this effect is delayed and needs more time. Vascular smooth muscles act in reality like a low-pass filter with a cutoff clearly under 10 Hz. Is this 10 Hz oscillation-related to the old idea of a vasomotor center composed of neurons with intrinsic pacemaker properties? This has been proposed among others by Guyenet (e.g., Guyenet 1996), reinforcing the old observation by Dittmar (1873), who showed that ablation of a region in RVLM resulted in dramatic falls in BP. Barman and Gebber proposed a network of supraspinal centers responsible for it (Barman and Gebber 2000).

It seems obvious that the 10 Hz oscillation plays a certain role. A sudden appearance of it is accompanied by increased BP and its elimination by a fall (Zhong et al. 1993), but within physiologic boundaries. Barman's Model suggests that this system of coupled 10 Hz oscillators is able and probably necessary to generate different patters including the change from one to another. All that can be understood as a classical self-organized state. Absence of this oscillation according to the model would make it more difficult for the system to self organize, resulting in less adaptation in case of external perturbations.

Quantification of muscle sympathetic nerve activity (MSNA) in intraneural recordings is usually based on counting the neural bursts identified by inspection of a mean voltage neurogram. Burst area or amplitude can be measured to evaluate

changes in MSNA within a recording session; absolute measures of burst size cannot be used for interindividual comparisons for technical reasons (Vallbo et al. 1979; Sverrisdottir et al. 2000). As alternative analysis instrument, relative burst amplitude distribution has been proposed. It has been shown that before the occurrence of a significantly augmented burst frequency, the relative burst amplitude distribution is shifted toward larger bursts (Sverrisdottir et al. 1998). It was consequently possible to show that the distribution of multiunit MSNA burst amplitudes can discriminate between different conditions with similar MSNA burst frequencies (Sverrisdottir et al. 2000). Preganglionic activity of muscarinergic neurons can induce both brief excitatory postsynaptic potentials (EPSPs), which can last 20 ms, and longer lasting EPSPs and inhibitory postsynaptic potentials (IPSPs), which can last 500 ms or more (Iversen et al. 2000).

Vegetative Control of the Heart

The mammal heart has impressive properties to control itself. The well-known Starling mechanism (an isolated heart is capable of increasing its stroke volume by increasing the volume preload of the right ventricle) can increase the minute volume from resting levels of about 5 l per minute up to 13 l per minute without any influence of the nervous system. Stress conditions can initiate up to 20 l per minute in healthy individuals – the difference is based on vegetative control of the heart (Franchini and Cowley 2012).

The ANS is one of several systems with influence on the heart, but one of the most important ones. Both SNS and PNS influence the heart function. Early studies blocked SNS and PNS influences with medicaments (with help of propanolol and atropine), revealing an intrinsic heart rate, which is higher than in unblocked hearts (Jose and Collison 1970). This led to the hypothesis that the heart is under tonical influence of the PNS. In general, the sympathetic nerves to the heart are facilitatory, whereas the parasympathetic nerves have inhibitory effects. Efferent sympathetic neurons originate in cervical and thoracic sympathetic ganglia. Postganglionic neurons end in the sinoatrial and atrioventricular node, the conduction system, the myocardial fibers, and the coronary vessels themselves.

The sympathetic system increases heart rate and strength of contraction; the parasympathetic system slows down the heart, but has less effect on contraction. Sympathetic-released noradrenalin increases the force of contraction by acting on beta-adrenergic receptors that activate the cyclic adenosine monophosphate (cAMP) second messenger system, which in turn increases the long-lasting (L-type) Ca^{2+} channel current in the muscle. Activation of beta-receptors also decreases the threshold for firing the cardiac pacemaker cells in the sinoatrial node, thereby increasing heart rate. Circulating noradrenalin released from the adrenal medulla can probably increase this local effect of sympathetic-released noradrenalin. The inotropic effect is largely based on β_1 receptors, the chronotropic effect both on β_1 and β_2. Sympathetic effects on coronary vessels are based on α_1 receptors, α_2

receptors are nearly not existent in the heart. The coronary vasoconstrictive effect of stimulated α_1 receptors is also probably overestimated because local factors are stimulated due to increased oxygen demand, leading to a vasodilatatory effect (Franchini and Cowley 2012). Compared to the parasympathetic system, the cardiac sympathetic system has a delayed onset and return to prestimulation levels. Heart rate and contractility increase after a latent period of about 3 s, first approaching a steady state after 30 s. This is (partially) related to the relatively slow rate of noradrenalin inactivation in the cardiac tissue (Franchini and Cowley 2012).

As is typical for the parasympathetic system, the ganglion is located near its tissue target in the AV groove (epicardial neural plexus) in a region that is densely innervated by cardiac intrinsic neurons. Most parasympathetic neurons end in the nodal regions, but a smaller number is also situated within the atrial and ventricular myocardium. Parasympathetic acetylcholine is released from parasympathetic nerve terminals. It slows down the heart by acting on muscarinergic receptors in the cardiocytes of the sinoatrial and atrioventricular nodes, so increasing a resting K^+ conductance in these cells. This hyperpolarizes sinoatrial cells, slowing conductance through the atrioventricular node. Hyperpolarization of the sinoatrial cells appears to involve direct gating of a K^+ channel by a G protein activated by the muscarinergic receptor. Acetylcholine also decreases heart rate by increasing the threshold for firing the pacemaker cells opposite to the sympathetic influence. ACh can also reduce muscle contraction by decreasing intracellular cAMP, thus reducing the L-type Ca^{2+} current (Iversen et al. 2000). Vagal effects develop rapidly in contradiction to sympathetic effects. The vagus nerves, influenced by respiratory centers, can exert almost a beat-to-beat control of cardiac function (Franchini and Cowley 2012).

Sympathetic and parasympathetic systems in the heart interact in a complex rather than in a simple algebraic manner. Even acknowledging that noradrenalin and Ach are the main transmitter substances, several other mediators are also actively released during stimulation of the cardiac ANS, including vasoactive intestinal peptide (VIP), substance P, neuropeptide Y (NPY), and others; many of them also related to the intrinsic neurons of the heart. For instance, NPY released of SNS neurons can have inhibitory influence on PNS neurons.

Vegetative Control of Blood Pressure

Physiological Background

Blood pressure is a function of cardiac outcome and peripheral resistance, resulting in the (linear) equation:

$$BP = 80 \times \left(Cardiac\ output \times total\ peripheral\ resistance \right) + central\ venous\ pressure \tag{3.1}$$

Cardiac output again is dependent on stroke volume and heart rate, resulting in the linear equation:

$$CO = SV \times HR \tag{3.2}$$

Stroke volume is dependent on end-diastolic myocardial fiber length (preload), the force that resists muscle shortening during myocardial contraction (afterload), and myocardial contractility. When the end-diastolic volume rises, SV increases proportionally as does the systolic pressure and maximum rate of pressure development (dP/dT) up to a point. Many factors affect *preload* such as total blood volume, intrathoracic pressure, venous tone, afterload, body position, pulmonary vascular resistance, atrial contraction, and venous return. In principle, ventricular volume can be determined with echocardiography, angiography, or radionuclide scans. In practice, preload is also estimated frequently with the pulmonary artery catheter and PCWP. In the intact heart, *afterload* is the impedance to ejection or the stress on the ventricular wall. Impedance to ejection includes aortic pressure, the aortic valve, distensibility of the vascular system, and total peripheral resistance. Ventricular volume, left ventricular wall thickness, and systolic intraventricular pressure can be used as determinant for afterload. *Myocardial contractility* is the intrinsic myocardial ability to develop a tension from a given end-diastolic fiber length. There is no specific value that represents normal contractility. It is defined by measurements of cardiac performance in isolated muscles, hearts, and intact hearts. Definitions include rate of development of ventricular pressure (dP/dT), amount of shortening produced by isolated papillary muscle, or amount of work generated by isolated or whole heart preparations. Clinically, the ejection fraction is often used to estimate contractility. It is the slope of the plot of SV against end-diastolic volume and can again be determined with echocardiography, angiography, or radionuclide scans. It is affected by changes of preload and afterload but can be used as reliable and sensitive parameter of cardiac performance. Catecholamines, digitalis, and calcium ions increase contractility, hypoxia, and ischemia. Several drugs can decrease contractility. In contradiction to the Eqs. (3.1) and (3.2) every attempt to estimate stroke volume is necessarily nonlinear.

In Fig. 3.5 we show a curve illustrating the Frank–Starling law of the heart. The *Y* axis can describe the stroke volume, stroke work, or cardiac output and the *X* axis right atrial pressure, end-diastolic volume, or pulmonary capillary wedge pressure. The three curves illustrate how a change in preload can induce a change in afterload or contractility.

Neural Control of Blood Pressure

The neural control of circulation operates via parasympathetic neurons that innervate the heart and via the three main classes of sympathetic efferents mentioned above – barosensitive, thermosensitive, and glucosensitive cardiovascular – innervating

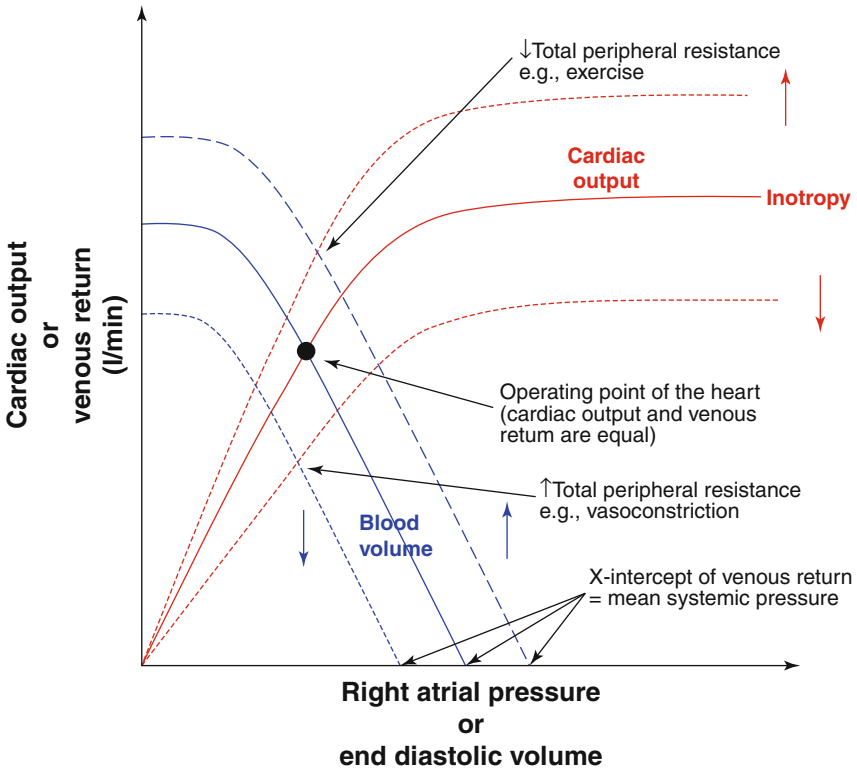

Fig. 3.5 Cardiac function curve illustrating the Frank–Starling law of the heart

blood vessels, the heart, the kidneys, and the adrenal medulla. The barosensitive sympathetic efferents are under the control of arterial baroreceptors. This large group of efferents plays a dominant role in both short-term and long-term blood pressure regulation. Their level of activity at rest is presumed to be the most crucial parameter for long-term blood pressure control. A core network of neurons sets this background activity in the rostral ventrolateral medulla (RVLM), the spinal cord, the hypothalamus, and the nucleus of the solitary tract. For rapid changes of blood pressure, primarily other structures like the limbic system, the forebrain, and midbrain are responsible, but play only a minor role in long-term control (Guyenet 2006). Possible mechanisms in chronic arterial hypertension include changed reflex circuits or activation of carotid body chemoreceptor afferents by hypoxia and hypercapnia. Notably, many overweight people have episodes of sleep apnea that can precisely induce these changes. Another possible mechanism is associated with a circuit involving atrial volume receptors, NTS, the paraventricular nucleus of the hypothalamus (PVH), and the real sympathetic nerves (see Figs. 3.6 and 2.6).

Increased sodium in plasma and brain, increased volume by dietary sodium, and blood volume leads to activation of pathways of the OVH through RVLM in the kidneys (increased sodium excretion) and muscles (peripheral resistance). This

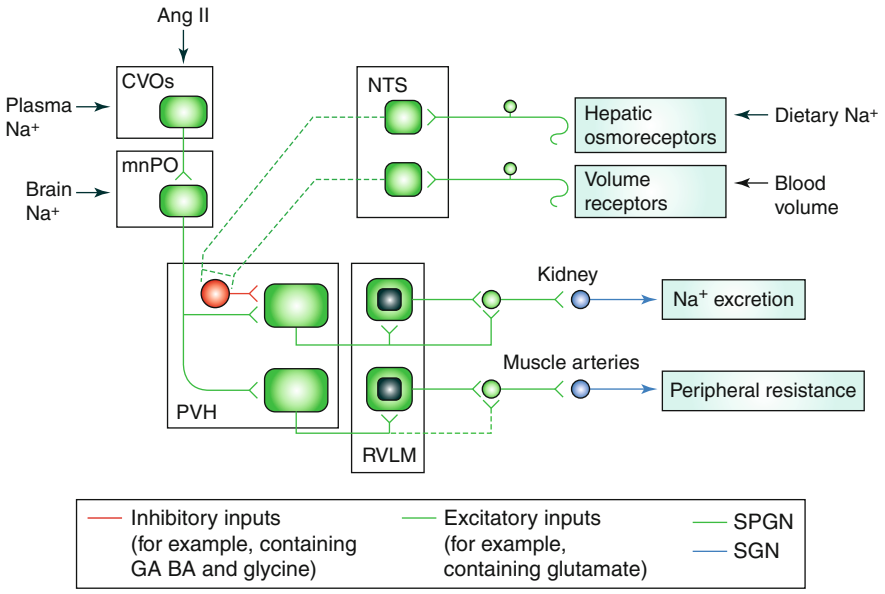

Fig. 3.6 Sodium, renal sympathetic control, and blood pressure control (Guyenet (2006), with friendly permission of Nature Publishing Group)

pathway again is blocked by neurons activated through NTS under activation of hepatic osmoreceptors and volume receptors in the carotids. Another pathway involved includes the dorsomedial hypothalamus and RVLM, which is activated by stress (for instance noise) and leads to tachycardia and chronic increase of real SNA. This might be dependent of genetic factors as experiments with rats have shown (DiBona and Kopp 1997).

There are several lines of evidence connecting ANS activity to the development of arterial hypertension (Esler 2000; Brook and Julius 2001; Palatini 2001). Sustained sympathetic stimulation of the kidney promotes sodium and fluid retention (Calhoun and Oparil 2012). Plasma noradrenalin spillover from the kidneys is increased in patients with hypertension (Jennings 1998). Sympathetic activation is a better predictor than overall heart reactivity to the immune response on short stressors (Berntson et al. 1996). Increased SNS activity is probably not an associated, but a causal factor as shown in population-based studies, were increased resting heart rate as a sign that sympathetic overactivity was present years before hypertension developed (Kim et al. 1999). Chronic hyperactivity of the SNS can also cause vascular remodelling. Noradrenaline promotes release of trophic substances in experimental models, like transforming growth factor-β, insulin-like growth factor or fibroblast growth factor (Calhoun and Oparil 2012). Different forms of inhibition of sympathetic overactivity prevent or diminish vascular hypertrophy (Calhoun and Oparil 2012). In addition, catecholaminergic receptors show increased sensitivity to adrenaline and noradrenaline (Calhoun and Oparil 2012).

Is There Something Like a General Sympathetic or Parasympathetic Activation? Recent Views on the Interaction Between the Sympathetic and the Parasympathetic Systems

The HRV literature is full of notions interpreting results as an increase in sympathetic activity or an increase in parasympathetic activity, implicitly, or sometimes explicitly assuming a SNS or PNS that reacts in a coordinated form. If this is the case, we should be able to find uniform changes in the activity of different vegetative efferents. In reality this is not so easy. In contrast to the cardiac SNS, several parts of the SNS do not have the same kind of oscillations or have none at all. For example, cutaneous vasoconstrictor fibers, sudomotor fibers, adrenaline-regulating adrenal preganglionic neurons, and nerves supplying the brown adipose tissue are generally devoid of this rhythm (Jänig et al. 1983; Macefield and Wallin 1996; Morrison 1999; Barman and Kenney 2007). There are many reasons to believe that at least the sympathetic output is not as uniform as many suppose (Morrison 2001).

The classical model of autonomic control describes a continuum with parasympathetic activation at one end and sympathetic activation at the other end, as the physiologist William Cannon had proposed. The mutual influence leads to a decreased parasympathetic activity in case of increased sympathetic activity and vice versa. This view has been challenged. In contrast to this linear-continuum model of autonomic control, descending influences from higher neural systems can evoke reciprocal, independent, or even coactive changes in the autonomic branches (Berntson and Cacioppo 2004, see Fig. 2.7). This is supported by studies in heart failure patients (Porter et al. 1990). According to Berntson, both divisions of the vegetative nervous system are tonically active and operate in conjunction with each other and with the somatic motor system to regulate most behavior, both in normal and in emergency conditions. Although one or the other division controls several visceral functions predominantly, and although both the sympathetic and the parasympathetic division often exert opposing effects on innervated target tissues, it is the balance of activity between the two that helps maintain an internal stable environment in the face of changing external conditions (Fig. 3.7) (Iversen et al. 2000).

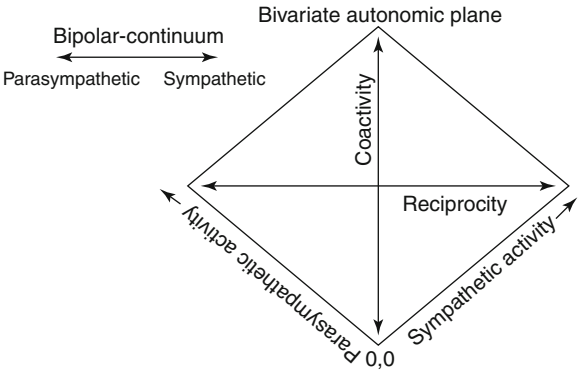

Fig. 3.7 Models of autonomic control (Modified after Berntson and Cacioppo (2004))

These views are supported by anatomical evidence showing that sympathetic ganglion cells innervate only one or few target tissues, for instance, regarding kidney and spleen (Meckler and Weaver 1984; Weaver et al. 1984), but also other differential innervations (Morrison 2001). It is difficult to characterize autonomic "fingerprints" of different organs in vivo and much research is based on rather artificial experimental preparations (Morrison 2001). There is also some support from findings suggesting that during stress responses the well-known cardiac stimulation, widespread visceral vasoconstriction, piloerection, and pupillary dilatation are caused by activated parts of the SNS (Coote et al. 1973); however, increased muscle blood flow, also characteristic, is mediated by activation of a cholinergic vasodilatator pathway, with little evidence for marked inhibitions of adrenergic pathways (Coote et al. 1973; Horeyseck et al. 1976). This can be one good example for activation of parts of both the sympathetic and parasympathetic systems in the same response pattern. One of these response patterns has been described as diving reflex. Submersion of the head under water elicits response of trigeminal afferents and leads to a powerful simultaneous reaction of SNS and PNS. The SNS increases in this situation, vascular constriction everywhere except brain and heart, the vagal activation elicits intense bradycardia and decreased cardiac contractility. All this results in a global reduction of energy demand in a stress situation with expected lack of oxygen in the body (Mantoni et al. 2006; Alboni et al. 2011). Such simultaneous activation of SNS and PNS is at the same time associated with a dramatic loss of fractal properties of the HRV signal (Tulppo et al. 2005).

Usually in science we look for simple concepts and models, such as the notion of an autonomic nervous system consisting of two parts in mutual dependence, where either one or the other part is predominant. This notion is often used for education and clinical explanations. In reality, however, a more complex model like the one delineated above might be more precise and this can have consequences for clinical practice.

Summary

The three divisions of the autonomic system comprise an integrated afferent/efferent system that acts in parallel with the somatic motor system. ANS is responsible for homeostases. The sympathetic and parasympathetic systems have partially opposed effects on each other, but this classical model has to be expanded by the possibility of a two-dimensional continuum model of different states of the sympathetic and parasympathetic systems. The vegetative nervous system is organized in different negative feedback and fast-forward circuits and other (negative) feedback mechanisms like parallel release of different transmitter substances. Central regions involved in cardiovascular control are the hypothalamus, the tractus of the solitary tract, and the rostral ventrolateral medulla. They contribute to a general sympathetic tone and a special renal sympathetic tone. Both short-term and long-term modulation mechanisms lead to oscillatory phenomena, which are dampened by negative feedback mechanisms.

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Chapter 4
Methodological Issues

Outline: In this chapter we provide information about different ways to process heart rate variability indices. We explain their mathematical background, provide their algorithms, and discuss their general relevance. In the second part we discuss standard test demands like validity and reliability. In the third part we discuss different physiological, pathophysiological, and pharmacological confounding factors that may have an impact on HRV calculations.

Introduction

The simple base of heart rate variability is the variation of the beat-to-beat time. This can be measured in different ways, e.g., with ECG, pulse waves, heart tones, or similar methods. In practice the most convenient and most precise method is to measure QRS-distances in milliseconds. The result is a series of three- and four-digit numbers depending on the measurement period. This is all. It may surprise the nonmathematician how many possible algorithms exist to process this time series (Fig. 4.1).

The second base is the time period. In principle, it is possible to measure HRV for minutes, hours, days, or even longer. In practice, HRV has been used for as short a time period as 2 min and rarely longer than 1 day. Based on this, usually two forms of HRV are distinguished, short-term HRV (usually 5 min, sometimes 10–20 min) and long-term HRV (usually 24 h, sometimes also only 12 h). The latter is based on

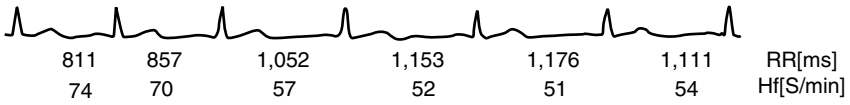

Fig. 4.1 HRV measured over a short period, with milliseconds between *R* and calculated heart frequency

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Holter monitoring, where the patient is connected to a small transportable registration unit that can be taken home.

Heart rhythm is traditionally characterized by a mean value of a certain period, possibly supplemented by range and qualitative descriptions. Some critics have pointed out that the usefulness of these measures depends on the properties of the data satisfying certain assumptions. If these assumptions are not fulfilled, then the analysis might be not meaningful. The basic assumption for the classical statistical measures is that the probability density function is integrable and that its second moment is finite. Physical processes with self-similar structures often do not fulfill this assumption. The power density function then has a power-law form (Liebovitch et al. 1999).

There are several possible ways to analyze the variability of time measures. Seely and Macklem (2004) differentiates between time domain, frequency domain, fractal analysis, and measures of entropy. All approaches rely on feasible algorithms and can be used with certain assumptions. Some of them need a higher amount of data points than others (power law, detrended fluctuation analysis); others are sensitive to artifacts or have a certain grade of arbitrariness (in time-domain analysis). In principle they can be distinguished as follows:

- Time-domain values are obtained by traditional descriptive statistics like mean and variation.
- Frequency domain is based on the relative portion of different frequency areas in the time series, which are usually calculated with the help of fast Fourier transformation.
- Different nonlinear methods.

An important achievement was the report from the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology published in 1996. In this report the following measures (to be explained in this chapter) are recommended: SDNN, HRV triangular index, SDANN, and rMSSD and VLF, LF, LFnu, HF, HFnu, and LF/HF. They concluded at the time that "HRV has considerable potential to assess the role of autonomic nervous system fluctuations in normal healthy individuals and in patients with various cardiovascular and noncardiovascular disorders" (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996). Today it is considered a gold standard to follow the Task Force's guidelines, and most published studies assert that they follow them. Recently, however, it has been shown that a great majority of research projects did not strictly adhere to the standards – only 44 of over 3,100 citations (Nunan et al. 2010).

Technical Requirements

In principle, any device able to measure heartbeat or its consequences (e.g., pulse) can be used, such as pulse oximetry, finger arterial BP (Finapres), invasive BP measurement. In reality, by far most commercial HRV devices are recording ECG

Table 4.1 HRV depending of sampling rate in a 75-year-old patient after myocardial infarction

Sampling rate (Hz)	TP	VLF	LF	HF	LF/HF	SDNN	rMSSD
500	25.1	18.19	3.74	3.17	1.181	6.23	4.91
246	24.3	17.45	3.75	3.10	1.207	6.23	4.98
125	28.3	19.63	4.66	4.03	1.155	6.66	8.19
62	40.7	24.55	7.00	9.09	0.771	7.80	8.06
31	64.1	21.58	23.19	19.28	1.203	10.92	12.66

Modified after Wittling and Wittling (2012, p. 151)

signals and code the QRS-distances in milliseconds. These are then consecutively used to calculate the different indices.

Several recommendations are made by both the Task Force and other groups and investigators: for short-term HRV generally stationarity of the heart rhythm is recommended. They should optimally not have ectopic beats, arrhythmic events, missing data, or noise (with exception of heart rate turbulence where ectopic beats are a prerequisite). Sampling rate should be between 250 and 500 Hz. A lower sampling rate is only acceptable if appropriate interpolation algorithms are used; a minimum sampling rate of 100 Hz is mandatory. Some years ago the increasing need for memory was a problem in higher sampling rates; however, with more sophisticated equipment, that problem is a minor one now.

Berntson et al. (1997, p. 633) discusses the issue of stationarity in some more detail: "Spectral analysis inherently assumes that the data series is at least weakly stationary. Strict stationarity requires that the distributional characteristics of a series (including all moments) be invariant over time, whereas weak stationarity requires only that the first and second moments (mean and covariance) are stable across time. Stationarity is an important consideration because the presence of slow or irregular trends in the series can potentially distort and can lead to misinterpretations. (…) This is a difficult issue, because violations of stationarity in actual heart period data might be quite common." This is not improbable. In fact, only very few studies test their time series on stationarity. The vast majority of the studies discussed in this book assume stationarity, mostly not even mentioning this as a possible problem. While short-term recordings might not be as affected, Holter monitoring approaches clearly are at risk of not being stationary. Also time series used under training are rather not stationary, but are calculated with algorithms that are based on it.

Wittling reported on the example a 75-year-old patient after myocardial infarction, showing that a sample rate below 246 Hz can already cause significant distortion (Wittling and Wittling 2012, p. 151) (Table 4.1).

As we see, most parameters taken with a sampling rate of >100 Hz are relatively close to each other, but even there LF, HF, and rMSSD have considerable differences. In this patient, results first seem valid at a sampling rate of >200 Hz.

The fiducial point recognized on the ECG tracing that identifies a QRS complex may be based on the maximum or baricentrum of the complex or on the determination of the maximum of an interpolating curve or found by matching with a template

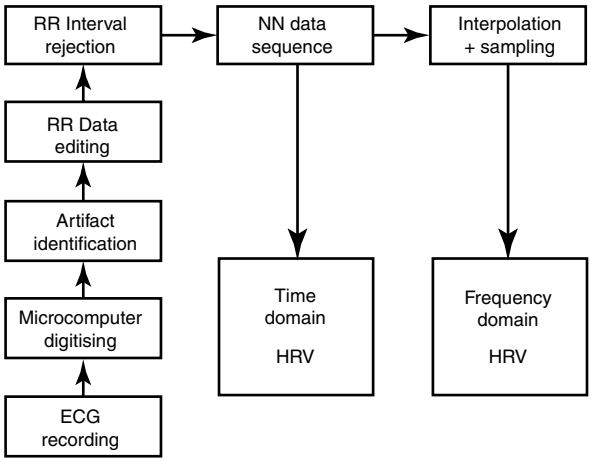

Fig. 4.2 Recommended steps for recording and processing of ECG signals to obtain HRV data (Modified after Task Force (1979), reproduced with friendly permission from Wolters Kluwer Health)

or other event markers (Task Force 1996, p.). Most investigators edit their raw data manually to ensure sufficient quality (Fig. 4.2).

Time-Domain Analysis

Time-domain analysis measures the variation in heart rate over time or the intervals between successive normal cardiac cycles. From a continuous ECG, QRS-distances are detected. Calculated time-domain variables include mean RR-distance. Standard deviation of NN intervals (SDNN, sometimes also called SDRR) is a global index of HRV and is formally the standard deviation of all normal QRS-distances. It correlates strongly with total power (TP), often $r>0.9$ (Wittling and Wittling 2012). The simplest form of time-domain analysis, still used occasionally (e.g., Sridhar et al. 2010), is to calculate the difference between the longest and the shortest RR-distance. It is also mentioned as simple test, e.g., for anesthesiologists to investigate autonomic failure in patients preoperatively (Lu et al. 2012).

Standard deviation of the average NN intervals (SDANN) is calculated over short periods, usually 5 min, and requires thus longer measuring periods. While SDANN5 is used in many studies, a variant has been mostly used in critical ill patients, called short-term HR volatility. Short-term HR volatility is computed for a given patient every 5 min by calculating the standard deviation of all HR samples collected during that time interval. The 5-min time interval follows established practices for collecting data for HR variability analysis. The difference from traditional HR variability analysis is, however, that precise instantaneous HR is not acquired at every beat. The system samples HR from a standard monitor every 1–4 s. Thus, a typical 5-min interval will contain between 100 and 150 HR data samples for a single patient. The standard deviation of these points is the basic parameter of short-term volatility (Grogan et al. 2004).

Table 4.2 Normal values of some time-domain values (Schumacher 2004)

Variable	Normal value (ms)
Mean RR interval	>750
SDNN	141 ± 39
SDANN	127 ± 35
rMSSD	27 ± 12

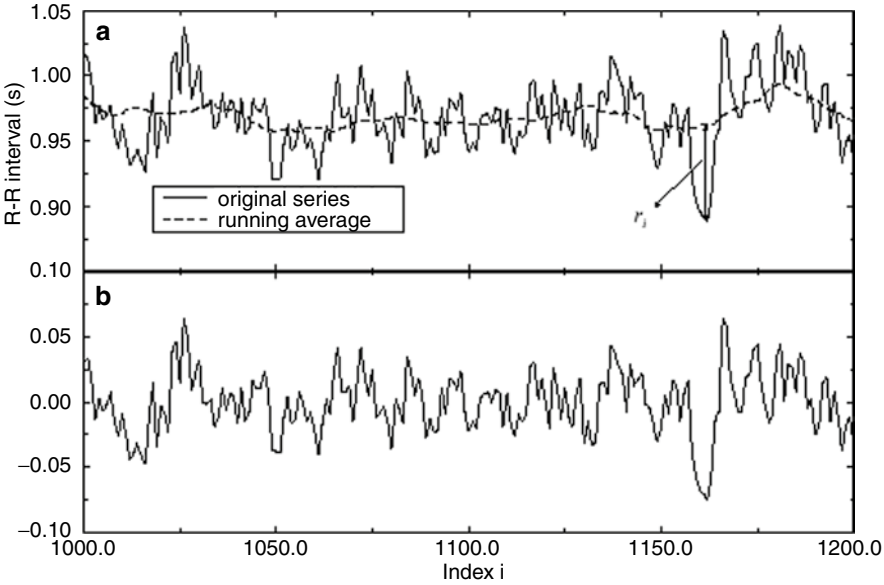

Fig. 4.3 Detrended time series (raw data, *solid curve*; running average, *broken curve*) (Ashkenazy et al. (1998), with permission)

pNN50 and rMSSD are short-term variables based on interval differences. NN50 is the number of pairs of successive NNs that differ by more than 50 ms, pNN50, the proportion of NN50 divided by total number of NNs over (normally) a 24 h-recording, and is thought to show cardiac parasympathetic activity (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996). rMSSD is calculated through squaring of each NN interval, thus calculating the mean value and drawing the square root, called root mean square successive difference (Frenneaux 2004) (Table 4.2).

A variation of time-domain analysis is the detrended time series. Here, from the time series of the raw data, a running average is constructed using an interval length of 2^m with m=4–5 (i.e., a window consisting of 16–32 heartbeats). Next, the running average is subtracted from the original time series (see Fig. 3.1). The difference between the two curves, denoted by r_i, is called the detrended time series (DTS), and it is generally assumed that in this curve noise and slow oscillations without significance for short-term HRV are removed. The standard deviation δ_d of DTS has been successfully used to discriminate between healthy patients and cardiologic patients in a small group of patients and can be used in brief time series (Ashkenazy et al. 1998) (Fig. 4.3).

Recently, remarkable correlations between SDNN and a 24-h minimum heart rate have been shown ($r = -0.8$) in a secondary analysis, and the latter has been proposed as an easy algorithm if there is no possibility to measure ordinary HRV (Burr et al. 2006).

Another index for sympathetic activation was used earlier, PEP (pre-ejection period). Briefly, it is calculated as the time interval in ms from the onset of the ECG Q-wave to the B-point of the dZ/dt wave (Berntson et al. 1996).

Geometric Analysis

Geometric methods are derived and constructed from the conversion of sequences of NN intervals. Different geometric methods include the 24-h histogram, the HRV triangular index, the triangular interpolation of NN interval histograms, and methods like the Poincaré plot.

The *triangular HRV* considers the major peak of the histogram as a triangle with its baseline width corresponding to the amount of RR interval variability and its height corresponding to the total number of all RR intervals use to construct it (Sztajzel 2004). It conforms to the integral of the density distribution (i.e., the number of all NN intervals) divided by the maximum of the density distribution. Using a measurement of NN intervals on a discrete scale, the measure is approximated by the value (total number of NN intervals)/(number of NN intervals in the modal bin), which is dependent on the length of the bin, that is, on the precision of the discrete scale of measurement (Task Force 1979) (Fig. 4.4).

Poincaré (or Lorenz) plots plot duplets of successive RR intervals with the implicit assumption that the next RR interval is significantly determined by the current one. This assumption lends itself to further generalization of Poincaré plots by plotting m-lagged plots where m represents the distance (in number of beats) between the duplet beats, that is, the lag of the second beat from the first. It has been observed in the context of short-term variability that the current RR interval can influence up to approximately eight subsequent RR intervals. Therefore, a series of lagged Poincaré plots can potentially provide more information about the behavior of Poincaré plot indices in health and disease than the conventional 1-lagged plot does (Lerma et al. 2003; Thakre and Smith 2006).

In healthy states, the disparity between the current and next NN intervals becomes progressively greater at higher NN intervals, whereas in disease states, this does not happen (Frenneaux 2004). Poincaré plots have been analyzed qualitatively, describing different shapes (Woo et al. 1992) (Fig. 4.5).

Stein and colleagues have recently quantified Poincaré plots using the SD12 index. SD12 is the ratio of length of the axis of an imaginary eclipse that has its center at the average RR interval and is fitted to the Poincaré plot (Stein and Reddy 2005). Poincaré plots are frequently also discussed as a nonlinear method (Fig. 4.6).

Time duration for geometric methods should be at least 10 min, which makes it less feasible for short-term applications.

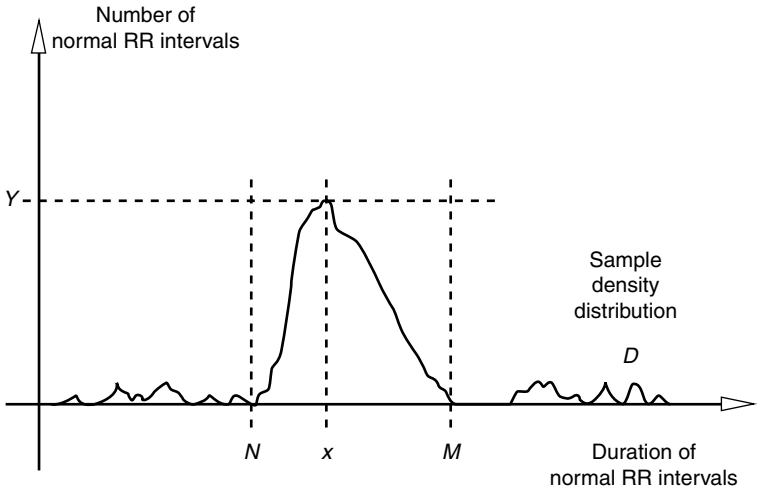

Fig. 4.4 To perform geometric measures on the NN interval histogram, the sample density distribution D is constructed, which assigns the number of equally long NN intervals to each value of their lengths. The most frequent NN interval length X is established, that is, $Y = D(X)$ is the maximum of the sample density distribution D. The HRV triangular index is the value obtained by dividing the area integral of D by the maximum Y. When the distribution D with a discrete scale is constructed on the horizontal axis, the value is obtained according to the formula HRV index = (total number of all NN intervals)/Y (Modified after Task Force (1979), reproduced with permission from Wolters Kluwer Health)

Esperer tried to group different heart rhythms with the help of Poincaré plots and found the following patterns: (1) comet shape, (2) torpedo shape, (3) H-fan shape, (4) SZ-fan shape, (5) double-side lobe pattern type A (DSLP-A), (6) double-side lobe pattern type B (DSLP-B), (7) triple-side lobe pattern type A (TSLP-A), (8) triple-side lobe pattern type B (TSLP-B), (9) island pattern type A (IP-A), and (10) island pattern type B (IP-B). Comet and torpedo shapes were associated with sinus rhythm, whereas a "fan shape" was associated with AF. They propose to use this kind of analysis to improve rhythm analysis of Holter recordings (Esperer et al. 2008).

Another numerical analysis of Poincaré plots is termed HRV fraction (*HRVF*). The scatter plot area (0.2–1.8 s) is divided into 256 boxes of 0.1 × 0.1 s, having an area of 0.01 s^2. In each box the number of paired NN intervals is counted and a 3-dimensional density graph is plotted. HRVF is then calculated with help of the formula:

$$\mathrm{HRVF} = \left(1 - \left(\mathrm{N1} + \mathrm{N2}\right) / \left(\mathrm{Total\ \ NN} - \mathrm{NN50}\right)\right) \times 100$$

where N1 and N2 are the two highest numbers of counts in any boxes. Total NN is the number of all heartbeats and NN50 is the number of intervals which differ >50 ms. HRVF correlated highly with SDNN ($r = 0.855$), SDNN ($r = 0.753$), and triangular index ($r = 0.834$) (Sosnowski 2005; Sosnowski et al. 2011). This method has been also proposed to characterize AF (Fig. 4.7).

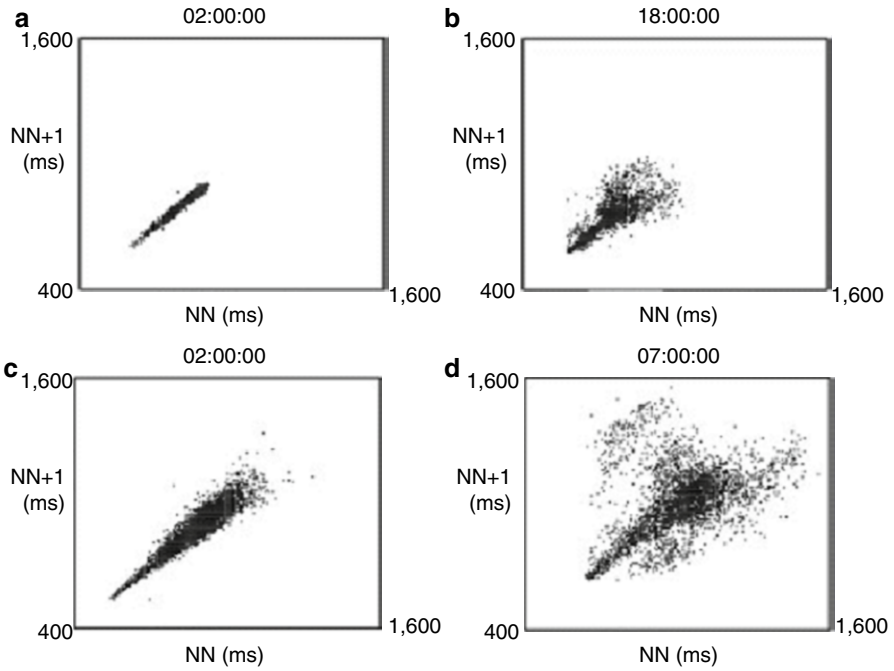

Fig. 4.5 Representative 1-h Poincaré plots. (**a**) and (**c**) show normal HRV; (**b**) and (**d**) show abnormal, complex HRV patterns (Stein and Reddy 2005; Stein et al. 2005) (Reproduced with permission of the author)

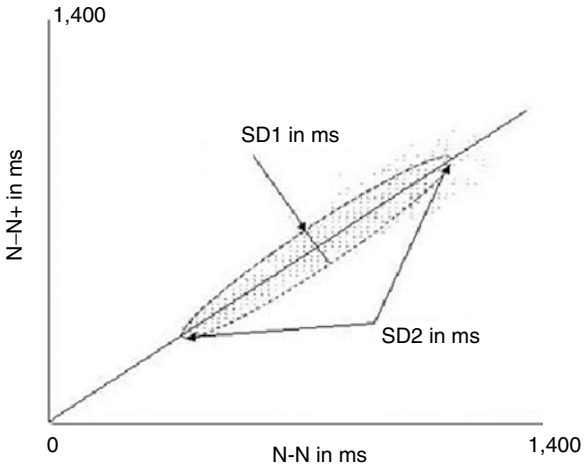

Fig. 4.6 Example of a Poincaré plot showing the calculation of SD1 and SD2 from an ellipse fitted to the plot (Stein and Reddy 2005; Stein et al. 2005) (Reproduced with permission of the author)

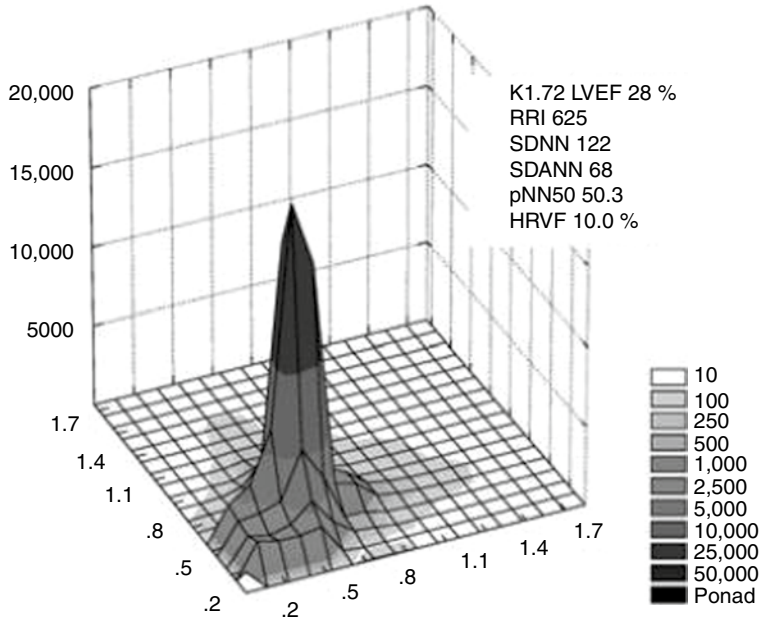

Fig. 4.7 Example for HRVF calculation (Modified from Sosnowski et al. (2011), with permission of John Wiley and Sons)

Frequency-Domain Analysis

LF, HF, and LF/HF

Frequency-domain (power spectral density) analysis describes in principle the periodic oscillations of the heart rate signal, decomposed at different frequencies and amplitudes, and provides information on the amount of their relative intensity (termed variance of power) in the sinus rhythm of the heart (Sztajzel 2004). It was introduced 1981 by Akselrod et al. (1981).

Frequency domain is based on the relative portion of different frequency areas in the time series. This can be calculated in different ways. Often, power spectral density is used, e.g., in the discrete Fourier transformation (most often nonparametric with the fast Fourier transformation). Other methods (rarely used in HRV) are the Lomb–Scargle (LS) periodogram (Işler and Kuntalp 2007). FFT-based methods like bispectral index of the EEG are more established than parametric methods that are model dependent and more complex. Both require stationarity that can induce problems in situations with fast changing RR-distances. This can be problematic because using only FFT can hide structures that could be identified, e.g., with wavelet analysis (Togo et al. 2006). An example for a parametric method is the autoregressive model estimation (Di Rienzo et al. 1989; Mainardi et al. 2002). Other algorithms

have been proposed and used (Huang et al. 1997). The pseudo-Wigner–Ville transformation (SPWVT) has been presented as an alternative to the fast Fourier transformation. It has the advantage of being feasible for relative nonstationary time series, and it allows the assessment of instant center frequency (ICF), which has been proposed as a new global index for the relationship between sympathetic and vagal modulation (Yoshiuchi et al. 2004).

Typical variables include total power, VLF (very low-frequency power, < 0.003–0.04 Hz), LF (low-frequency power, 0.04–0.15 Hz), and HF (high-frequency power, 0.15–0.4 Hz). A frequently used ratio is LF/HF. This variables are feasible both for short-term and long-term use. ULF (ultra low-frequency, <0.003 Hz) is only feasible for long-term use. Power is expressed in ms squared (ms^2) or normalized units (nu). Normalizing means here multiplying LF or HF by 100 and dividing the product by HRV – VLF. It is possible to use natural logarithms of the absolute values because of the skewness of the distributions. Details of the normalization algorithms can be found in Sztajzel 2004.

Occasionally also another band, mid-frequency, MF (0.08–0.15 Hz), is used (Huang et al. 1997). Oscillations in this also so-called 0.10-Hz component reflect both sympathetic and parasympathetic effects on sinus node activity (van Roon et al. 2004). It has been used to test effects of cardiovascular performance and autonomous state on cognitive performance (Duschek et al. 2009). A number of studies indicated the MF magnitude is inversely related to the individual degree of effort during execution of a cognitive task (e.g., Boucsein and Backs 2000; Van Roon et al. 2004). Others consider MF as a variation of LF and advice that MF should be abandoned (Berntson et al. 1997) (Tables 4.3 and 4.4).

HF is generally interpreted as a marker of vagal modulation and is respiration mediated, thus dependent on the respiration pattern (Frenneaux 2004). It is partially identical with the respiratory sinus arrhythmia (Hayano et al. 1996; Berntson and Cacioppo 1999) and correlates partially with it (in one study $r=0.9$, $p<0.0001$ (Weber et al. 2010)).

LF is modulated by both the sympathetic and parasympathetic systems. An increase of LF is often interpreted as a consequence of sympathetic activity (mental,

Table 4.3 Analysis of short-term recordings

Variable	Units	Description	Frequency range (Hz)
5-min total power	ms^2	The variance of NN intervals over the temporal segment	$\approx \leq 0.4$
VLF	ms^2	Power in VLF range	≤ 0.04
LF	ms^2	Power in LF range	0.04–0.15
LF norm	nu	LF power in normalized units LF/(total power − VLF) × 100	
HF	ms^2	Power in HF range	0.15–0.4
HF norm	nu	HF power in normalized units HF/(total power − VLF) × 100	
LF/HF		Ratio LF (ms^2)/HF (ms^2)	

Modified after Task Force (1979)

Table 4.4 Analysis of entire 24 h

Variable	Units	Description	Frequency range (Hz)
Total power	ms^2	Variance of all NN intervals	$\approx \leq 0.4$
ULF	ms^2	Power in the ULF range	≤ 0.003
VLF	ms^2	Power in the VLF range	0.003–0.04
LF	ms^2	Power in the LF range	0.04–0.15
HF	ms^2	Power in the HF range	0.15–0.4
α		Slope of the linear interpolation of the spectrum in a log–log scale	$\approx \leq 0.04$

Modified after Task Force (1979)

physical stress, sympathomimetic pharmacological agents). A beta-blockade leads to a decrease of LF. Another reason for decreased HF can be a relative resistance of the sinus node for sympathetic impulses. LF power probably reflects in large parts the baroreflex modulation of heart period in response to spontaneous changes in blood pressure by both vagal and sympathetic efferent mechanisms (Frenneaux 2004). As discussed earlier, LF is not necessarily correlated with increased sympathetic activity, but can in the case of congestive heart failure patients be inversely correlated with sympathetic activity, thus being an indicator for a loss of modulation of the sympathetic nervous system at the heart (Notarius et al. 1999; Notarius and Floras 2001).

The LF/HF ratio reflects the global sympathico-vagal balance and is normally in resting adults between 1 and 2.

VLF and ULF

Common to both components is that they have been associated with clinical data and used as predictive factors (Bigger et al. 1996). VLF has a cycle duration of 20 s to 5 min, and ULF from 5 min to 24 h. The measurement period should be at least twice as long as the cycle duration (Eller-Berndl 2010). VLF measurement should be therefore at least 5 and better 10 min minimum, whereas ULF only can be interpreted if it is recorded over 24 h.

The VLF component is a major determinant of physical activity and possibly reflects sympathetic activity, though its origin is controversial (Frenneaux 2004). It is not used as often, but has been associated to clinical consequences more strongly than LF in some studies (Hadase et al. 2004). Decreased VLF is associated with increased inflammatory parameters like CRP, Il-6, and WBC (Kop et al. 2010). Other explanations are as diverse as thermoregulatory processes, the renin–angiotensin system (e.g., Axelrod et al. 1981), hemodynamic feedback delays, mechanical and central neural effects of breathing patterns, a central oscillator, spinal reflexes, and vascular autorhythmicity (Berntson et al. 1997).

The ULF component introduced by Bigger et al. (1993) reflects circadian and neuroendocrine rhythms. ULF was associated with physical activity in one study

Table 4.5 Normal values for frequency-domain variables (Schumacher 2004)

Variable	Normal values
Total power (ms^2/Hz)	3,466 ± 1,018
ULF (Hz)	0.00–0.003
VLF (Hz)	0.003–0.04
LF (Hz)	0.04–0.15
LF power (ms^2/Hz)	1170 ± 416
LF power (nu)	54 ± 4
HF (Hz)	0.15–0.4
HF power (ms^2/Hz)	975 ± 203
HF power (nu)	29 ± 3
LF/HF ratio	1.5–2.0

Table 4.6 Reference values for time domain and frequency domain for healthy persons, patients with recent myocardial infarction, and 1 year after myocardial infarction (Sztajzel 2004)

Variable	Healthy subjects (n = 274)	Recent MI (n = 684)	1 year after MI (n = 278)
SDNN (ms)	141 ± 39	81 ± 30	112 ± 40
SDANN(ms)	127 ± 35	70 ± 27	99 ± 38
rMSSD (ms)	27 ± 12	23 ± 12	28 ± 15
pNN50 (%)	9 ± 7	7 ± 9	10 ± 11
Total power (ms^2)	21,222 ± 11,663	7323 ± 5720	14,303 ± 19,353
LF (ms^2)	791 ± 563	277 ± 335	511 ± 538
HF (ms^2)	229 ± 282	129 ± 203	201 ± 324
LF/HF ratio	4.61 ± 2.33	2.75 ± 2.13	3.60 ± 2.43

with five men and five women, which found significant differences between activities typical of daily life and rest for 2–3 h (Serrador et al. 1999) (Tables 4.5 and 4.6).

Other relevant reference values have been produced by a multicenter study focusing on genetic variations in 1,797 participants (Stolarz et al. 2004).

Free software solutions have been presented and published to analyze HRV data (in ms of RR-distance) with different methods (Niskanen et al. 2004).

Power-law slope is the slope the HRV power spectrum shows between 0.01 and 0.0001 Hz, when plotted on a log–log scale (Stein and Reddy 2005; Stein et al. 2005) (Fig. 4.8).

The potential prognostic value of the power-law slope has been evaluated by Bigger et al. (1996) and Huikuri et al. (1998), the latter finding a significantly increased risk associated with a power slope < -1.5 (see Fig. 3.4). Slope and frequency-domain values show only a low correlation (Bigger et al.1996) (Fig. 4.9).

Variants of Frequency-Domain Measures

A variant of frequency-domain measurement is V_{index}. Kiviniemi analyzed HF power from RR_i lengths where the relationship between HF power and RR_i is most linear to avoid the confounding effects of saturation, physical activity, and random RR_i

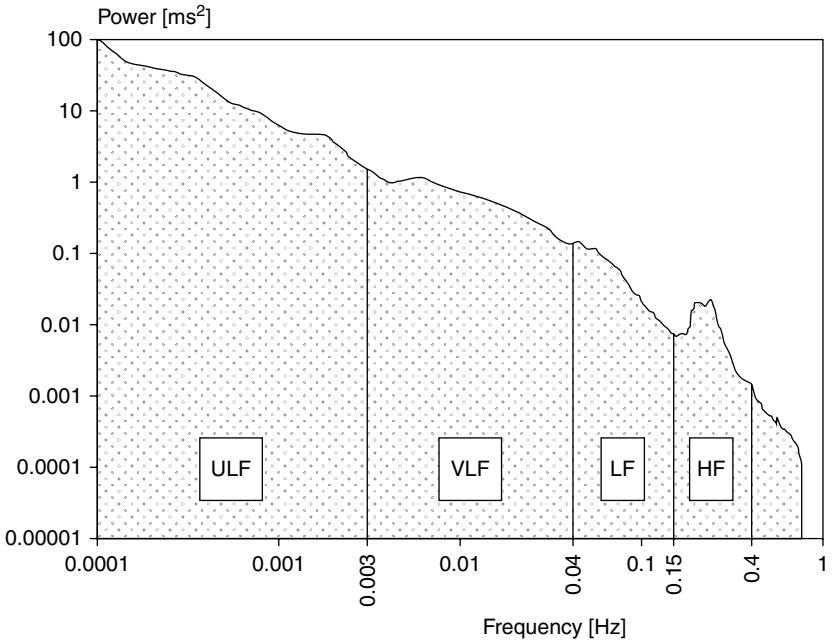

Fig. 4.8 Log–log plot of the HRV power spectrum over 24 h (Modified after Task Force (1979), reproduced with permission from Wolters Kluwer Health)

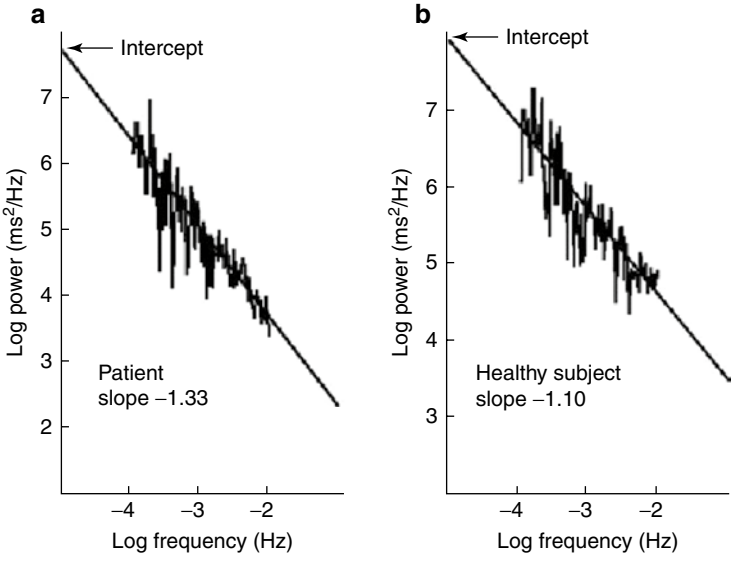

Fig. 4.9 Examples of the power-law slope in (**a**) a patient with cardiac disease and (**b**) a healthy person (Stein and Reddy 2005; Stein et al. 2005) (Reproduced with friendly permission of the author)

dynamics on the quantification of cardiac vagal outflow. The mean RR_i and the corresponding HF power are obtained in 5-min sequences over 24-h recordings. All valid 5-min values of HF power are plotted as a function of the corresponding mean RR_i values. The sigmoid regression model, based on automated mathematical computation, is used to detect the RR_i at which the relationship between the RR_i and the HF power is most linear. Due to the differences in 5-min mean RR_i values between the patients, the relative RR_i scale is used where the maximum 5-min mean RR_i value is defined as 100 %. Lower and higher deflection points are identified. For the purpose of the final analysis, the lower limit is calculated by adding standard deviation to the mean and the upper limit by subtracting standard deviation from the mean, all this in order to define a more stringent range of RR_i, in which the relationship between HF power and RR_i is most linear. All 5-min HF power values between 82 and 92 % of the maximum 5-min mean RR_i are averaged for each case to obtain V_{index} (Kiviniemi, Tulppo et al. 2007).

PLF index is analyzed from power spectra of all 5-min periods containing >95 % accepted and detrended RR_i data using the method of averaging periodograms based on discrete Fourier transformation. The frequencies of all maximum peaks within the LF band detected at 1/60 resolution are averaged over the whole recording to obtain the value of PLF. More than ten periods with detectable peaks per Holter recording are needed for a valid PLF calculation (Wichterle et al. 2004; Kiviniemi, Tulppo et al. 2007).

Correlations Between Time Domain and Frequency Domain

Several time-domain indices correlate with frequency-domain indices, and vice versa.

pNN50 and rMSSD correlate with HF power, SDNN and SDANN correlate with total power and ULF, and LF correlates with ASDNN (Frenneaux 2004) (Table 4.7).

In his dissertation Wittling examined different correlations, also observing the already mentioned high correlation coefficients between TP and SDNN, as well as HF and rMSSD (Wittling and Wittling 2012) (Tables 4.8 and 4.9).

Nonlinear Methods

Introduction

The difference between “linear” and “nonlinear” methods is not as clear as it may seem. Frequency-domain analysis is in principle based on predefined patterns. In Fourier transformations the assumed pattern is a sinusoidal wave, and in wavelet analysis a specific wavelet function. By contrast, nonlinear methods can start

Table 4.7 Approximate correspondence of time-domain and frequency-domain methods applied to 24-h ECG recordings

Time-domain variable	Approximate frequency-domain correlate
SDNN	Total power
HRV triangular index	Total power
TINN	Total power
SDANN	ULF
SDNN index	Mean of 5-min total power
rMSSD	HF
SDSD	HF
NN50 count	HF
pNN50	HF
Differential index	HF
Logarithmic index	HF

Modified after Task Force (1979)

Table 4.8 Correlation between different time- and frequency-domain values

	TP	SDNN	VLF	LF	HF	rMSSD	LF/HF
TP		0.87	0.80	0.89	0.75	0.80	0.02
SDNN	0.92		0.79	0.70	0.62	0.71	0.02
VLF	0.80	0.79		0.52	0.37	0.48	–0.03
LF	0.88	0.70	0.52		0.60	0.65	0.23
HF	0.75	0.62	0.37	0.60		0.93	–0.26
rMSSD	0.80	0.71	0.48	0.65	0.93		–0.18
LF/HF	0.2	0.02	–0.03	0.23	–0.26	0.18	

Adapted after Wittling and Wittling (2012, p. 138)

Table 4.9 Correlations between different time- and frequency-domain indices

	ln LF	ln HF	ln TP	ln LF/HF	ln SDNN	ln pNN50	ln rMSSD	ln mean heart rate
ln VLF	0.85	0.61	0.96	0.32	0.86	0.47	0.48	–0.55
ln LF		0.77	0.94	0.30	0.75	0.57	0.60	–0.39
ln HF			0.76	–0.38	0.63	0.87	0.93	–0.39
ln TP				0.22	0.86	0.59	0.62	–0.54
ln LF/HF					0.15	–0.48	–0.52	0.02
ln SDNN						0.53	0.54	–0.51
ln pNN50							0.94	–0.39
ln rMSSD								–0.43

Modified from Tsuji et al. (1994)

without specifying any pattern simply by looking at similarities in the signals. This can be related to the entropy itself (which usually, but not entirely correctly, is described as a measure for regularity) or to self-similarities, which can be studied with the help of fractal methods.

Take a look at four different artificial time series showed in Fig. 3.1. The qualitative patterns are obviously different; however, some time domain and in cases c and d even

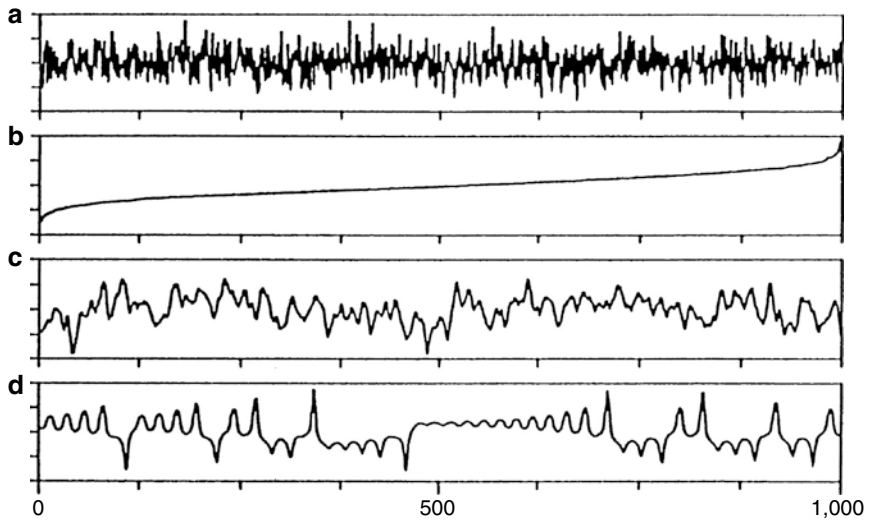

Fig. 4.10 Example of four synthesized time series with identical means, standard deviations, and ranges (**a**–**d**). Series (**c**) and (**d**) also have identical autocorrelation functions and therefore identical power spectra (Modified after Task Force (1979), reproduced with friendly permission from Wolters Kluwer Health)

some frequency-domain values are the same. How to catch the differences anyway? This is the beginning point for nonlinear methods. Most established are entropy and fractal approaches, but there are also several others. Until today their significance is not completely clear. In meta-analysis there are still too few high-quality longitudinal studies to make it possible to reach a convincing conclusion on this.

To sound a note of warning, it is important to use some expressions from the nonlinear field with caution. It is quite usual to misunderstand ideas like entropy, fractality, fuzziness, and complexity. Entropy, for example, is frequently described as a disorder, which ignores its fundamental relationship to degrees of freedom. All these expressions are based on advanced theoretical concepts that cannot easily be simplified (Fig. 4.10).

Entropy

Approximate Entropy

Different measures of entropy are increasingly being used, among other things, because they need fewer data points than other nonlinear measures. One example of this is approximate entropy (ApEn). Pincus first presented this algorithm in 1991. It evaluates data sets for recurrent patterns and for the likelihood that other runs in the data set with the same length are similar. The input variables r and m must be fixed

to calculate ApEN. The variable r sets the tolerance limits and the variable m the window length for the comparisons of the RR interval runs. It is defined by

$$\mathrm{ApEn} = \Phi^m(r) - \Phi^{m+1}(r)$$

where

$$\Phi^m(r) = (N - m + 1)^{-1} \sum_{i=1}^{N-m+1} \log\left(C_i^m(r)\right)$$

(Kaplan et al. 1991).

Healthy middle-aged subjects have approximate entropy of RR intervals somewhat over or 1. Approximate entropy (ApEN) achieves a number between 0 and about 1. Small values of ApEn indicate regularity, whereas higher numbers indicate a lower fraction of order or patterns in the data set. It has been shown that ApEN can be used reliably down to 1,000 data points (Pincus 1994). ApEN has been used successfully in such different fields as the investigation of cortisol and ACTH secretion in patients with major depressive disorders (Posener et al. 2004), nonlinear dynamics of heart rate in patients with major depression and unstable angina pectoris (Vigo et al. 2004), changes of respiration in patients with panic disorders (Yeragani et al. 2004), or heart rate variability of children (Srinivasan 2004) treated with antidepressant medicaments. It was also used for the analysis for the circadian temperature curve (Varela et al. 2003), the intracranial pressure (Beaumont and Marmarou 2002), or insulin oscillations (Feneberg et al. 2002). Recently ApEN was used to analyze discharges of wide dynamic range neurons in the dorsal horn of rats. Different neurons showed constant values of ApEn over an hour. Using a low dose of morphine leads to a differentiated inhibition of the WDR neurons that correlated with ApEN. The authors concluded that the complexity of the signal output does not correlate with the nociceptive input and that the average firing rate does not describe adequately what happens at the dorsal horn (Zheng et al. 2004).

The main advantage of using tools like ApEN is the possibility of discovering unexpected interactions between apparently unconnected systems. It was possible to show, for instance, that cachectic patients with chronic obstructive pulmonary disease have an absent circadian rhythm of circulating leptin in contrast to noncachectic patients with similar diseased and healthy controls. The same absence of circadian changes was noted in heart rate variations described by time- and frequency-domain analysis and another entropy parameter (maximal entropy). This means that heart rate variations and the circadian leptin rhythm are directly or indirectly coupled (Takabatake et al. 2001). In cocaine-exposed neonates' HRV analysis including spectral power distribution, ApEn, correlation dimension, and nonlinear predictability, no differences were found between them and a group of healthy neonates. Using a rescaling method to obtain "surrogate data" (LaViolette et al. 2004) from the original time series, however, revealed that large intersubject variability can mask small differences in heart rate dynamics between the groups (Garde et al. 2001). ApEN is also increasingly used in (small) time series for psychological data.

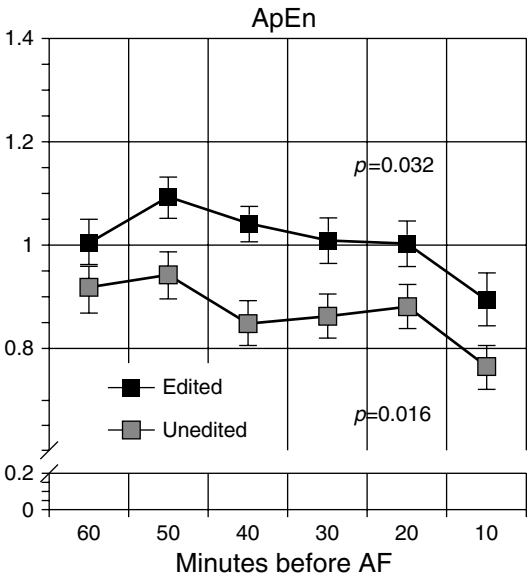

Fig. 4.11 Influence of editing on ApEN before onset of AF (Shin et al. 2006, with permission)

In one example it was used in a randomized study comparing two medicaments and placebo with all 56 data points (VAS scales). Despite similar mean and standard deviation, ApEN revealed differences between one and the two other groups that were not noted with traditional statistics (Yeragani et al. 2003).

ApEN has been criticized mainly because a lack of internal consistency and modified (Richman and Moorman 2000) or alternative (Wessel et al. 2000) algorithms. Correlations between nonlinear measures themselves can be weak (Storella et al. 1998).

Systems have been developed that record simultaneously data from ICU patients to be stored and analyzed. Also bedside systems have been described to obtain and process data of single patients (Goldstein et al. 2003). There are computer algorithms to obtain and process dynamical raw data, mainly based on the MATLAB programming language and usually freely available on the Internet (Aboy et al. 2002; Goldberger et al. 2000, www.physionet.org). There is some evidence that editing has minor influence on ApEn and SampEn results (Shin et al. 2006). Different levels of noise in experimental models show only a small to moderate influence on nonlinear dynamical measures in multivariate discrimination (Rapp et al. 2002) (Fig. 4.11).

Sample Entropy

Sample entropy (SampEn) is an advancement of approximate entropy that is meant to overcome ApEN's weak points. Like ApEn it determines the probability of finding specific patterns or matches in a short-time series. By definition, SampEn is a

negative natural logarithm of an estimate for predictability in finding specific matches in a short-time series. To characterize the stringency of match recognition, the length (m) of the subseries and the tolerance (r) of the matches are previously set. Its results are between 0 and 2, whereby 0, for example, represents a sinus curve and 2 a complete chaos. Two parameters need to be declared: the embedding dimension and a filter parameter. The embedding dimension m represents the length of sequences to be compared and ranges between 2 and 10. Often fixing m to 2 is suggested (e.g., in Kuusela et al. 2002). The filter parameter r represents tolerance for accepted matches and is often set to a value related to 20 % of standard deviation of the whole time series. It has been suggested that SampEn needs at least 200 data points to allow lower confidence intervals (Kuusela et al. 2002), and it has been used in time series with 200–250 data points (e.g., in Heffernan et al. 2007). In an intervention study, HF did not explain significant parts of variance, but with sample entropy added to the regression model, variance increased considerably (Bornas et al. 2007).

In conclusion, ApEN and SampEn are promising algorithms that likely have some clinical value (Huikuri 2003a; Perkiömäki et al. 2005).

Lempel–Ziv Entropy

Lempel–Ziv entropy is based on Kolmogorov estimates and counts the numbers of different and repeating patterns, from short to long in the time series, and generates a string of symbols using binary coding: 1 for a value above the mean and 0 for a value below. The binary sequence is constructed by insertion of symbols to form a subcue and copying of this subcue. With the use of a comparison and accumulation method, LZEn is computed on the basis of the number of such insertion and copying operations needed to generate the original sequence (Batchinsky et al. 2007b; Heffernan et al. 2007).

Multiscale Entropy

Diseased systems typically show reduced entropy values. Some cardiac pathology such as atrial fibrillation is associated with highly erratic fluctuations and statistical properties similar to uncorrelated noise. Traditional algorithms, like approximate and sample entropy, show an increase in entropy values for such noisy time series when compared with healthy dynamics, even though the latter represents more physically complex states. This obvious inconsistency may be related to the fact that the entropy measures used are based on single-scale analysis without considering the complex temporal fluctuations of a healthy physiological control system. Instead of computing one single-scale entropy measure for the time series, the signal can be analyzed using a multiscale approach (Laitio et al. 2007). Consider a nonoverlapping window analysis of the original time series, where the sample mean inside each window is computed. This set of sample means constitutes a new time

series. Repeating the process N times with a set of window lengths starting from 1 to a certain length N will produce a set of N time series of sample means. The multiscale entropy is obtained by computing any entropy measure (sample entropy is suggested) for each time series and displaying it as a function of the number of data points N inside the window (i.e., of the scale) (Costa et al. 2008; Bravi et al. 2011).

Other Entropy Indices

Multi-lag tone–entropy has been proposed as an alternative to other nonlinear parameters, tested in a cohort with diabetic patients (Karmakar et al. 2012).

To avoid the sensitivity to the threshold r (ApEn or sample entropy), a new entropy called *fuzzy entropy* was developed. All the computational steps are the same, with the difference that sample entropy uses r to produce a binary classification of the distance between two windows (zero if they are more distant than r, one otherwise), while fuzzy entropy uses a fuzzy membership function to evaluate the distance. This continuous function scores as one if the distance between two windows is infinitesimal and decays exponentially to zero the more distant the vectors are. This improvement avoids the discontinuity of the binary classification, therefore lowering the sensitivity to the threshold (Chen et al. 2009; Bravi et al. 2011). Other forms of entropy used in time series are Kullback–Leibler permutation entropy, conditional entropy, compression entropy, diffusion entropy, Kolmogorov–Sinai entropy, and Shannon entropy, the latter coming from information theory (Bravi et al. 2011).

Fractal Analysis

Short-Term Fractal Scaling Exponent (Detrended Fluctuation Analysis)

The short-term fractal scaling exponent (also termed α1) measured by the detrended fluctuation analysis has been feasible to predict fatal cardiac events in various populations (Huikuri et al. 2003a, b; Perkiömäki et al. 2005). It was introduced by Peng et al. (1994, 1995) and can be used for nonstationary data from time series. The raw data are first preprocessed as follows:

$$X(T) = \sum_{t=1}^{T} \left(x(t) - \bar{x} \right)$$

where $x(t)$ is the tth t-interval and x is the average RR interval of the series (Echeverria et al. 2003). After preprocessing, the RR interval data series is divided in the windows of same size. The RR interval variability is then analyzed in relation to a local trend in each window. This process is repeated for all different window sizes. The variability is shown on a log–log scale as a function of the size of the observation window. In the presence of scaling, this slope is linear and describes

fractal-like correlation properties of the signal. The first part of the slope (for window sizes < 11 beats, called α_1) corresponds to the short-term scaling exponent; the second part (for window sizes > 11 beats, called α_2) to the intermediate scaling exponent (Perkiömäki et al. 2005). This algorithm was proposed by Peng (1995) and has been calculated from all RR intervals or from only normal intervals. It needs at least 1,000 beats and reflects the amount of randomness in the heart rate time series, with the lowest values (~0.5) associated with a completely random series and the highest values (1.5) associated with a time series that is totally correlated (Stein and Reddy 2005; Stein et al. 2005). A filter has been proposed to estimate the power law as a function of time scales. This αβ filter is a simplified version of a Kalman filter that provides a good compromise between performance and computational load and is described more thoroughly in Echeverria et al. (2003).

A spectral DFA has been proposed recently. It involves calculating sd(m), m as Fourier coefficient for several values of m; plotting the curve of log (sd(m)) in terms of log ($1/m$) = −log(m); and obtaining the slope γ, which has a similar role as the parameter α in the traditional DFA (da Fontoura Costa et al. 2005).

A recent review has concluded that fractal scaling exponents might provide more powerful prognostic information than traditional heart rate variability indexes (Perkiömäki et al. 2005).

Coarse-Grained Spectral Analysis

Corse-grained spectral analysis is used to reveal the percent fractal component in total HRV power (%fractal) and the spectral exponent β of each bin. The random fractal component is extracted from a given time series through computations in frequency domain (Yamamoto and Hughson 1991; Yamamoto et al. 1992).

Long-time data (8,500 beat) have been compared to short-time data (512, respectively 256 beats), and significant differences have been shown for %fractals (considerably lower in short-term series). Average fractal% has been 85 % in human data (Yamamoto and Hughson 1994).

Fano Factor

The Fano factor is defined as the variance of the number of signals divided by the mean number of signals in a time window of length T:

$$F = \frac{\sigma_w^2}{\mu_w}$$

where σ_w^2 is the number of signals in the ith window of length T. The Fano factor curve is constructed by plotting $F(T)$ as a function of the window size on a log–log scale. For a data block of length T_{max}, the window size T is progressively increased from a minimum of a single bin to a maximum of $T_{max}/10$ so that >10

nonoverlapping windows are used for each measure of $F(T)$. For a random process in which fluctuations in signals counts are uncorrelated, $F(T)$ is 1 for all window sizes. For a periodic process, the variance decreases and $F(T)$ approaches 0 as the window size is increased. For a fractal process, $F(T)$ increases as a power of the window size and may reach values >1. Whether a power-law relationship in the Fano factor curve truly reflects a fractal process, and thus long-range correlations of events, is finally tested by constructing surrogate data sets in which signal distances are randomly shuffled. If shuffling of the signals eliminates the power-law relationship, then it can be concluded that the signal intervals in the original times series were ordered and independent (Das et al. 2003).

Dispersional Analysis

Dispersional analysis involves calculation of the SD of the mean values of signal distances for groups of data points of a specified number m. Specifically the mean distance for each group of m data points is obtained, and the SD of these values is calculated for the total number of groups. The process is repeated each time m is increased progressively from the minimum of one data point to a maximum of one-quarter of the total number of data points. SD is then plotted against m on a log–log scale yielding a straight line with a negative slope. The lope is used to calculate the Hurst (H) exponent using the formula

$$H = \text{Slope} + 1$$

The value of the H exponent (0–1.0 range) indicates whether the time series is a fractal. The H exponent is 0.5 for a time series in which events are uncorrelated (i.e., random Poisson process). An H exponent $\neq 0.5$ implies that the time series are fractal. When $H > 0.5$, the long-range correlations among the events are positive (persistence: values larger (smaller) than the mean tend to be followed by values also larger (smaller) than the mean). When $H < 0.5$, the correlations are negative (antipersistence: values larger than the mean tend to be followed by values lower than the mean, and vice versa). To test the validity, the DA curve for the original time series is compared with shuffled data series (Bassingthwaighte and Raymond 1995; Das et al. 2003).

Fractal Dimension

The Hurst exponent (see above) is related to the fractal dimension (FD): $H = E + 1 + \text{FD}$, where E is the Euclidean dimension ($E = 0$ for point, 1 for line, and 2 for surface). The relation between H and FD of the graph of a random fractal is $\text{FD} = 2H$ for one-dimensional signal. While H varies from 0 to 1, FD decreases from 2 to 1 (Krstacic et al. 2001).

Correlation Dimension

The correlation dimension of a data sequence is typically calculated according to the Grassberger–Procaccia algorithm. In a reconstructed phase space of dimensionality D, the correlation sum $C = \sum_{ij} \theta(r - \left| {}_i - r_j \right|)$ is calculated as a function of the radius r and is expected to behave as a power-law $C \propto r^{\nu(D)}$. Here, r_i denotes the D-dimensional radius vector of the ith data point and $\theta(r)$ stands for the Heaviside function. The correlation dimension dc is found as the limit of ν at large volumes of D (in fact, it is expected that for $D > d_c$ the exponent ν is independent of D, and in that case $\nu = d_c$). For the reliable calculation of the correlation dimension, the length is often inadequate for high-values $d_c > 6$. Other problems besides noise and non-stationarity are some inputs of the autonomic nervous system, which can lead to quasiperiodic signals (Kalda and Säkki 2003).

Largest Lyapunov Exponent (LLE)

Lyapunov exponent (λ) is a quantitative measure of the sensitive dependence on the initial conditions. It defines the average rage of divergence of two neighboring trajectories. An exponential divergence of initially close trajectories in phase space coupled with folding of trajectories, to ensure that the solutions will remain finite, is the general mechanism for generating deterministic randomness and unpredictability. Therefore, the existence of a positive λ for almost all initial conditions in a bounded dynamical system is a widely used definition for deterministic chaos. For dynamical systems, sensitivity to initial conditions is quantified by the Lyapunov exponent. A negative exponent implies that the orbits approach a common fixed point. A zero exponent means the orbits maintain their relative positions; they are on a stable attractor. Finally, a positive exponent implies the orbits are on a chaotic attractor (Acharya 2004). A feasible algorithm has been proposed by Wolf et al. (1985) for EEG data and has been applied by Acharya (2004) for HRV data. Regarding the problems of missing data, it has been estimated with help of artificial data sets that estimates of λ_1 can readily be recovered with 15–20 % amounts of missing data (Kreindler and Lumsden 2007).

Other Nonlinear Methods

An algorithm using non-Markovian effects was recently introduced to study age-related alterations of relaxation processes ECG time series (Yulmetyev et al. 2006).

Scale-independent methods have been used to analyze nonlinear properties of HRV, in particular wavelet analysis (Thurner 1998b). They have been criticized as a merely fine-tuning of SDNN (Kalsa and Säkki 2003). The *wavelet coefficient* $W_{m,j}$ is identified where m is a scale parameter and j is a position parameter (the scale m is related to the number of data points in the window by $n = 2^m$) by means of a wavelet transform. The standard deviation $\sigma_{wav}(m)$ of the wavelet coefficients $W_{m,j}$ across the

parameter *j* is used as a parameter to separate healthy from sick subjects. The corresponding scaling exponent is denoted by α_{wav} (Ashkenazy et al. 2000).

A variation of wavelet analysis is the *cumulative variation amplitude analysis* (*CVAA*). Briefly, this technique is based on consecutive wavelet and Hilbert transforms and can be used for nonstationary time series. Mathematically, CVAA consists of several steps:

1. Choose adequate scales to analyze the data.
2. From the original series, obtain a set of series each at a different scale using a continuous wavelet transform. (There are many wavelet families to choose from for this step, and several have been tried out. Each family eliminates local polynomial trends from the signal in a different way. The coefficients c of the wavelet transformation in each scale reflect the cumulative variation of the signal.)
3. Then, process each of the new time series with a Hilbert transform to extract the instantaneous amplitudes h of the variations at each point of the series.
4. Construct the time series $y = c + ih$ and calculate the amplitudes $A = \sqrt{\left(c^2 + h^2\right)}$.
5. Finally, normalize the histogram of these amplitudes to 1 to form a probability distribution, $P(x)$, which is then rescaled such that $x \to xP_{max}$ and $P(x) \to P(x)/P_{max}$ (Ritto et al. 2004).

In a study analyzing 428 heart patients after MI, 105 healthy subjects and 11 "cardiac-impaired" patients, DFA, DTS, and wavelet analysis were compared. It turned out that DTS performed better as a diagnostic tool, whereas the scaling exponents of wavelet and DFA analysis were better risk stratification tools (Ashkenazy et al. 2000).

Another recently presented approach uses *Zipf's law* to establish a rank order of low-variability periods. Local variability for each interbeat interval is calculated, a low-variability threshold is defined, and its length τ is measured in number of heartbeats. The rank of a low-variability period is plotted versus its length in a logarithmic graph. Failure of power law is correlated weakly with pathological heart conditions. However, τ_{end} distinguished between patients and healthy controls. The calculation of τ_{end} is not easy, but alternatives are τ_{max} (the longest low-variability period in the time series) with a considerable diagnostic value but low reliability because of fluctuations, the overall number of low-variability periods r_{max}. But the best alternative was to choose a set of critical ranks and determine the respective lengths, or to choose a set of critical length values and to determine the respective rank numbers. Both techniques were feasible for distinguishing between patients and healthy controls (Kalda et al. 2001).

A further approach is to use *recurrence quantification analysis* (RQA), also called *recurrence plots*. RQA was first introduced in physics by Eckmann in 1987. RQA is particularly useful in quantifying transient behavior far from equilibrium. It is based on the computation of a distance matrix between the rows (epoch) of the embedding matrix of the tachogram at unitary lag. This matrix represents the autocorrelation of the signal in all possible time scales. In other words, RQA

searches for repeating data sequences, which allows the data to be reconstructed as a time-ordered sequence of vectors. The resulting vector matrices are then indexed and compared on all possible *I*, *J* vector coordinate combinations, producing the qualitative recurrence plot. The recurrence plot is a visual representation of the vectored data sequences, illustrating changes in the system as it evolves in time (Schumacher 2004).

In the recurrence plot, two points are considered recurring if the distance between them is less than a preset radius. The plot's diagonal lines denote trajectories: two vectors (data sequences) starting from two close points, remain close together over a subsequent time period. In other words, the trajectory of one vector parallels the other over that distance in time. Recurrence plots dramatically illustrate one's data. However, since statistical analysis is necessary for experimentation, RQA quantifies the information contained within the recurrence plots. To this end, only the upper triangle is used for variable calculations since the recurrence plot is symmetrical. (The central line of identity splits the two triangular halves.) Alongside each recurrence plot is a list of the parameter values used to generate the individual plot, the resulting variable values, and a histogram showing the various lengths of the line segments. RQA produces five variables: %recurrence, %determinism, entropy, maxline, and trend. Once a time series has been analyzed with RQA, statistical analysis is performed on these variables to examine the relationships with other pertinent variables or the significance of experimental results (Schumacher 2004). There are indexes for this: percentage of recurrence index and percentage of determinism index. Usually the Shannon entropy is used (Giuliani et al. 1998; Marwan et al. 2002). RPs have been used to identify retrospectively structures in patients developing VT (Marwan et al. 2002).

One approach focuses specially on nonstationary signals where a short-time HRV and a short-time scale variability parameter are measured. The slope of changes is then linear and might provide information about the physiological state of the subjects (Siegel et al. 2004).

Large-scale dimension densities have been proposed as an analysis algorithm. This is estimated from a time series using a normalized Grassberger–Procaccia algorithm that enabled the analysis of nonstationary, rather short and unfiltered, data and made it possible to distinguish AF, CHF, older, and younger controls in a small study (Raab et al. 2006).

Another approach does not analyze RR-distances, but the times between events that disrupt the normal rhythm of the heart (for instance, ventricular tachycardia episodes or premature ventricular contractions). The authors calculated probability density functions of the events and conducted a Hurst analysis to look at fractal properties. They found a power-law form of the probability density functions and a fractal pattern for the disruption of normal sinus rhythm (Liebovitch et al. 1999).

An alternative nonlinear algorithm that has been named complexity rate information (symbolic dynamic system complexity rate information) uses the Lempel–Ziv complexity measure (Lempel and Ziv 1976). The Lempel–Ziv complexity is calculated for subsets of the time series. The complexity rate of the whole time sequence can be calculated from the slope rate of a sequence fitting polynomial. In addition the

authors defined complexity saturation as a phenomenon when a deterministic system enters into chaos, then randomness. This complexity then is definite and does not rely on the starting point. This algorithm has been used on VT and VF data and it was possible to distinguish them by complexity rate information (Zhang 2000).

The *non-Gaussianity index* (λ) is a new index of heart rate variability (HRV) that characterizes increased probability of the large heart rate deviations from its trend.

The analysis of non-Gaussianity of HRV is divided into four steps, as the authors describe them:

In step 1, time series of normal-to-normal R–R intervals are interpolated with a cubic spline function and resampled at an interval(Δt) of 250 ms(4 Hz), yielding interpolated time series $b(t)$. After subtracting average interval b(ave), integrated time series $B(t)$ are obtained by integrating $b(t)$ over the entire length.

In step 2, the local trend of $\{B(t)\}$ is eliminated by third-order polynomial that is fit to $\{B(t)\}$ within moving windows of length 2 s, where s is the scale of analysis.

In step 3, $\Delta_s B$ is normalized by the SD to quantify the probability density function(PDF). Then, the non-Gaussianity index, λ_s, is estimated.

In step 4, intermittent deviation $\Delta_s B(t)$ is measured as the increment with a time lag s of the detrended time series $\{B*(t)\}$:

$$\lambda_s = \sqrt{\frac{2}{q(q-2)}\left[\ln\left(\frac{\sqrt{\pi\left(\left|\Delta_s B\right|\right)^q}}{2^{q/2}} - \ln\Gamma\left(\frac{q+1}{2}\right)\right)\right]}$$

where $<|\Delta_s B|^q>$ denotes an estimated value of the q-th-order absolute moment of $\{\Delta_s B\}$. If the λ_s is close to zero, the observed PDF is close to a Gaussian distribution. On the other hand, a larger value of λ_s means that the observed PDF has flatter tails and a sharper peak in comparison with the Gaussian distribution. This method has been tested in a large study with 570 post-AMI patients and showed predictive power (Hayano et al. 2011).

Heart Rate Turbulence (HRT)

A German research group led by Schmidt developed an interesting method to analyze heart rate (Schmidt 1999). Heart rate turbulence is not a classical HRV method, but shares some physiological mechanisms and can be used in similar ways. Last not least it is also dependent on Holter monitoring. We discuss therefore HRT as a complement of HRV measures and mention it in clinical sections.

Briefly, the method is based (and dependent) on the occurrence of ventricular extra systoles and observes the heart rate changes afterwards. Directly following the VES an increase of heart rate can be observed, followed eventually by a decrease. This pattern is diminished or nonexistent in patients with recent myocardial infarction.

The method is based on Holter monitoring and averages heart frequency changes after VES. With the help of an algorithm, two parameters are calculated, turbulence onset (TO) and turbulence slope (Bauer et al. 2008). Turbulence onset is calculated by subtracting the sum of the two preceding QRS-distances from the sum of the first two QRS-distances after the VES, divided by the sum of the last two preceding QRS-distances and multiplied by 100:

$$\mathrm{TO} = \left[\left(\mathrm{RR}_1 + \mathrm{RR}_2\right) - \left(\mathrm{RR}_{-1} + \mathrm{RR}_{-2}\right) / \left(\mathrm{RR}_{-1} + \mathrm{RR}_{-2}\right)\right] \times 100[\%].$$

Turbulence slope is defined as the maximum positive regression slope assessed over any five consecutive sinus rhythm RR intervals within the first 15 sinus rhythm RR intervals after the VES (Bauer et al. 2008). In healthy volunteers TO ranges from −2.7 to −2.3 %, and TS ranges from 11.0 to 19.2 ms/RR interval (Grimm et al. 2003c; Lindgren et al. 2003; Diaz et al. 2002; Tuomainen et al. 2005).

In risk stratification studies (see the subsequent section), HRT values are usually classified into three categories: (1) HRT category 0 means TO and TS are normal, (2) HRT category 1 means 1 of TO or TS is abnormal, and (3) HRT category 2 means both TO and TS are abnormal. If HRT cannot be calculated because no or too few suitable VPC tachograms are found in the recording, patients who are otherwise in sinus rhythm are classified as HRT category 0 (Barthel et al. 2003; Bauer et al. 2008) (Figs. 4.12 and 4.13).

Heart rate turbulence is also interesting from a theoretical point of view. Systems near transition points can be tested by small perturbations and the reaction of the

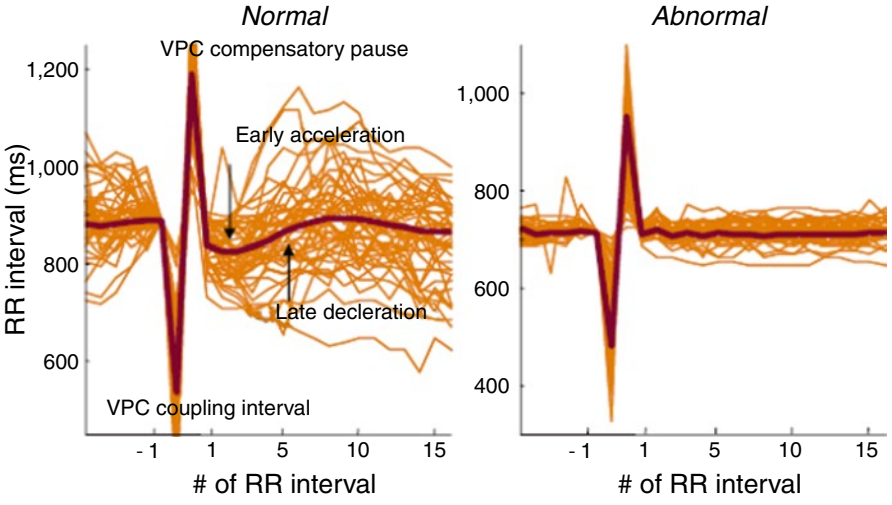

Fig. 4.12 Physiological and pathological heart rate turbulence (Reproduced with friendly permission of Elsevier from Bauer et al. (2008)) (Note that in spite of optical similarity, this is not a QRS complex!)

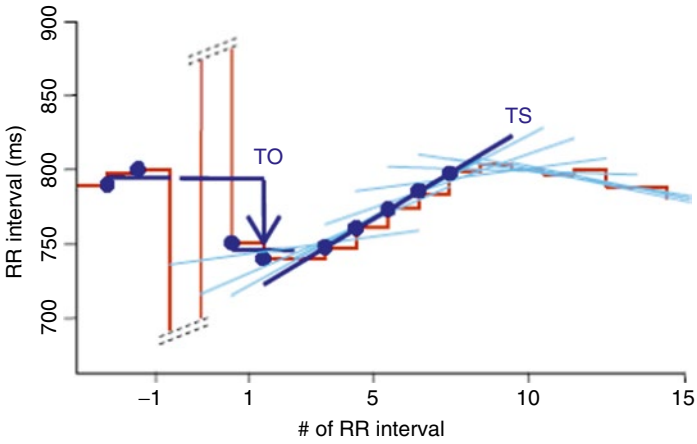

Fig. 4.13 Calculation of the HRT parameters turbulence onset (*TO*) and turbulence slope (*TS*). Turbulence onset is the relative change of RR intervals from before to after the VPC. Turbulence slope is the slope of the steepest regression line fitted over the sequences of five consecutive sinus rhythm RR intervals within the 15 RR intervals after the VPC. Eleven possible regression lines are shown. The steepest one is used for TS calculation (Reproduced from Bauer et al. (2008), with permission of Elsevier)

system afterwards as we described it in Chap. 2 as a "critical slowing down" phenomenon (Wissel 1984). The idea for real systems is to use this phenomenon inducing small perturbations that are not sufficient to drive the system over the transition point and then to measure the rates of change. Otherwise it may be possible to observe the effects of natural perturbations on the exchange rates. But characteristic for these phenomena is that changes persist after perturbation. Like in the critical slowing down approach, HRT uses naturally occurring perturbations, but in contrast a decreased reaction pattern is observed.

HRT seems to share some of the physiological background of HRV, among others, the involvement of the baroreceptor system. Early acceleration of heart rate during HRT might be related to vagal withdrawal in response to the missed baroreflex afferent input due to reduced ventricular contraction after VES that causes decreased systolic and diastolic blood pressure. This drop also causes increased activity of the SNS. The late HRT phase is then caused by overcompensation, by an early sympathetic activation with delayed vasomotor response, as well as by vagal activation (Bauer et al. 2008).

HRT indices are influenced by the systolic function of the heart, especially the left ventricular ejection fraction (LVEF). Not surprisingly, HRT is reduced in patients with congestive heart failure (Koyama et al. 2002) but also in the case of structural heart disease with preserved LVEF (Sestito et al. 2004). It can be eliminated nearly completely through the use of atropine, but not of beta-blockers (Lin et al. 2002) (Table 4.10).

Interesting are fast changes of HRT after complete or incomplete restoration of coronary perfusion (Bonnemeier et al. 2003b) (Fig. 4.14).

Table 4.10 Factors influencing HRT

Factor	Effect	Reference
Gender	No effect	Grimm et al. (2003a, b, c); Jeron et al. (2003)
Age	Decrease	Schwab et al. (2005)
Heart Rate	Decrease	Schwab et al. (2004a); Cygankiewicz et al. (2004)
Origin of VES	No effect	Schwab et al. (2004b)
Beta-blockade	No effect	Lin et al. (2002)
ACE hemmer	Increase	Chowdhary et al. (2000); Ozdemir et al. (2007)
Atropine	Decrease	Lin et al. (2002)
Amiodarone	Unclear	Grimm et al. (2003a, b, c)
Coronary reperfusion	TS increase, TO decrease	Bonnemeier et al. (2003a, b)

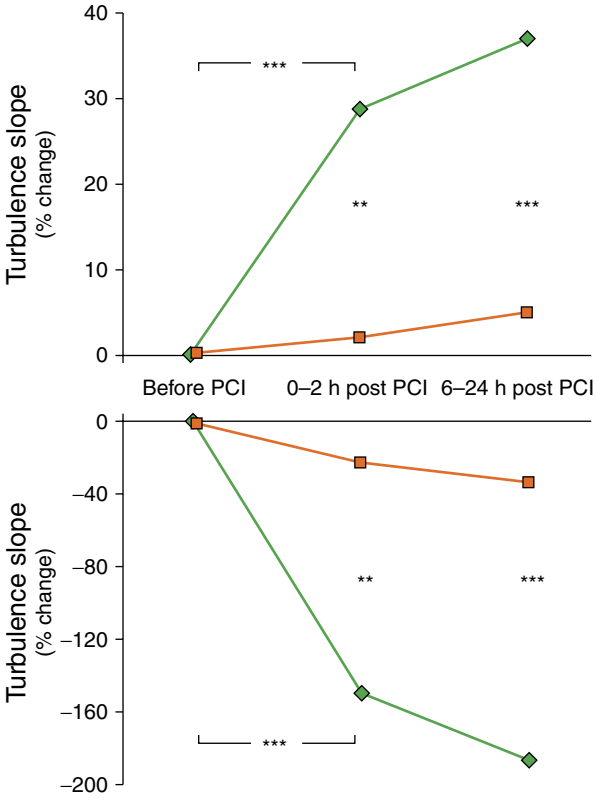

Fig. 4.14 Effect of complete and incomplete coronary reperfusion. TS increases, and TO decreases significantly faster (Bonnemeier et al. 2003a, b)

There are modest correlations between HRV and HRT probably due to the common physiological mechanisms already mentioned (Ghuran et al. 2002; Sestito et al. 2004; Cygankiewicz et al. 2004).

Further Methods Combining HRV and Other Measured Parameters

R-Wave to Pulse Interval (RPI)

Sympathetic cardiovascular tone may be estimated based on the measurement of R-wave to pulse interval (Contrada et al. 1995; Hugdahl 2001). This is probably not a pure sympathetic parameter (Duschek et al. 2009). The magnitude of RPI is predominantly determined by beta-adrenergic effects on myocardial contractility (Furedy et al. 1996; Hugdahl 2001).

During acute illnesses, patients in intensive care units are monitored 24 h. Several groups have worked with continuous signal analysis. As an example thereof, we present here an approach published recently by Ahmad: continuous individualized multiorgan variability analysis, or CIMVA (2009).

"To accomplish continuous variability analysis over time, CIMVA employs a moving window approach, whereby a window (interval-in-time) of user specified width and step marches through the input signal, computing and time-stamping different variability metrics at each step, thus making it possible to monitor a change in HRV over time. A standard RR cleaning algorithm (22) is employed inside each window to detect gross artifact or noise, and HRV analysis is performed on the cleaned data. The cleaning algorithm excludes RR intervals less than 0.25 s and greater than 2.5 s, as well as those that differ by more than 15 % from the previous one. The CIMVA system stores the number of samples lost due to RR cleaning in each window instance, thus keeping track of signal quality." A window width of 1,200 samples (~10 min) and steps of 200 samples (~2 min) are used to compute HRV over time (Fig. 4.15).

Concluding Remarks

A recent review argued that although concepts of chaos theory, fractal mathematics, and complexity measures of heart rate behavior are still far off from clinical medicine, they are a fruitful area for future research (Perkiömäki et al. 2005). A study including a cohort of CHF patients examined 20 nonlinear parameters, some of them rarely used in HRV and identified only two relevant parameters that add additional information to clinical models: the ratio between the power associated with the first mode with frequency <LF1 and the modes with frequencies higher than LF1 and one variation pattern (from symbolic dynamics). Other parameters studied earlier, like sample entropy, 1/*f* slope, or different ways to analyze Poincaré plots, did not add any relevant information in the model (Maestri et al. 2007).

Bravi, Longtin, and Seely have recently provided an excellent overview of techniques for variability analysis (Bravi et al. 2011), describing no fewer than 39 different features consisting of even more algorithms. All of them have been used to test physiological time series, even though some were only used in pilot studies or open source data, e.g., from PhysioNet. Only few were used repeatedly. Bravi also tried recently to

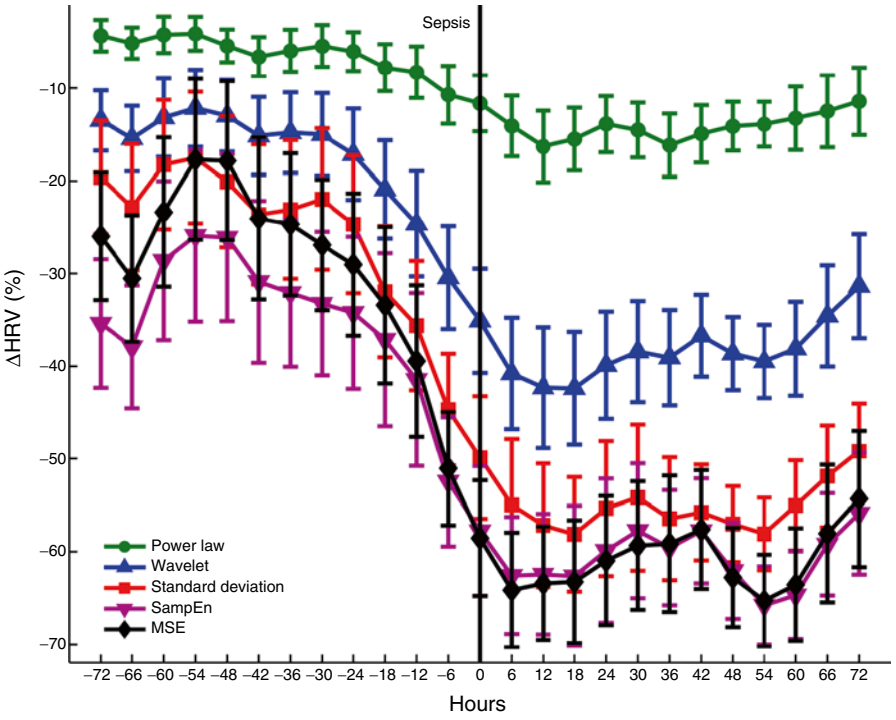

Fig. 4.15 Changes of diverse continuous HRV indices before onset of sepsis (Ahmad et al. (2009b), with friendly permission)

construct a composite measure that can be used for early detection of sepsis development (Bravi et al. 2012, see Chap 4). At the moment, most algorithms have not been sufficiently tested to allow for any conclusions. Most developed are several forms of entropy analysis and some fractal algorithms, which were discussed above. It is very likely that even more algorithms will eventually be published along with promising preliminary results, though often we will not know how feasible they are in clinical practice. To this day, the best tested and most relevant are the so-called linear measures, which should be a standard part of any studies or clinical work-ups with help of HRV.

Modulating and Confounding Factors

General Reliability

Early reports testing the feasibility of different methods to assess the sympathovagal balance in congestive heart failure noted the complete lack of correlation between time-domain and frequency-domain HRV, noradrenaline spillover, submaximal

Table 4.11 Short-time stability in 50 healthy persons after different time periods (Wittling and Wittling 2012)

	TP	HF	LF	LF/HF	SDNN	rMSSD
10 min	0.75	0.93	0.68	0.92	0.76	0.89
20 min	0.82	0.96	0.78	0.83	0.87	0.81
30 min	0.84	0.88	0.82	0.78	0.84	0.93
60 min	0.65	0.86	0.75	0.74	0.62	0.82
2 days	0.84	0.81	0.75	0.52	0.68	0.69

Table 4.12 Correlation of HRV parameter in 16 persons after 2 months (Wittling and Wittling 2012)

	TP	HF	LF	VLF	LF/HF	SDNN	rMSSD
r	0.90	0.95	0.86	0.72	0.56	0.79	0.96

heart rate training, and 24-h daytime and nighttime heart frequency (Adamopoulos 1992). Also recent reports raised some doubts about the reliability of short-term measures of HRV. Variation ranged from 1 to 100 %. Patient position and medication had significant consequences on the variables, whereas reliability increased under resting conditions (Sandercock et al. 2005). The standard test battery for patients with DN showed a reliability of 4.3 % for metronomic breathing, 6.26 % for Valsalva test, and 6.66 % for stand (postural) test (Risk et al. 2001). Correlations between 24-h and short-term spectral indices were generally >0.75 in a post-MI study (Bigger et al. 1993).

Wittling studied both short-time and long-time reliability. They observed changes in 5-min HRV uptakes after 10, 20, 30, 60 min, and 2 days (Table 4.11).

They investigated also changes in 16 persons after 2 months with the same conditions, showing a high level of stability (Table 4.12).

Stress and distraction can change HRV indices (Madden and Savard 1995). However, a longitudinal study revealed high test–retest correlations in frequency domain in a group of older subjects both at baseline and with mental stressors retested after a year (Cacioppo 1994).

In relation to a longitudinal study on patients with stable coronary artery disease, Tarkiainen followed 89 subjects over a period of 3–4 months, measuring seven times short-term HRV, including paced breathing. The mean of the RR intervals and the total power showed the highest stability over time; SDNN tended to be unstable, whereas frequency-domain values showed acceptable stability (Tarkiainen et al. 2005).

In an evaluation study, test–retest reliability was assessed for rMSSD, Valsalva maneuver, orthostatic challenge (to calculate posture index), and paced breathing (with help of a feedback box). rMSSD was reliable, and all other measures also showed good reliability with the exception of the Valsalva maneuver, which was estimated as moderate (Haegele-Link et al. 2008).

Koskinen reports reference values for young adults in a Finnish study. It included 1,780 healthy subjects between 24 and 39 years and computed frequency- and

time-domain indices. In addition the study used the deep breathing test. Age and higher heart rate were inversely associated with all indices. Women had higher HF and lower LF, as well as a higher resting heart rate. According to the authors, age, sex, and heart rate have to be considered in reference values, but reproducibility is good (Koskinen et al. 2009b).

In younger diabetic patients, differences between two short-term HRV were not statistically significant; the 95 % limits of random variation however were quite high (Sacre et al. 2012).

It is unclear whether a "white coat effect" exists in short-term HRV. In a small study, patients were educated to take short-term HRV at home on several days, with acceptable reliability and no differences between measurements in hospital and at home (Fleischer et al. 2011).

One problematic point is the great variance within patient groups, which leads to overlaps with healthy controls in many studies (e.g., Orlov et al. 2012).

But, in conclusion, even taking into account the critical remarks by Sandercock et al. (2005), large studies have now shown reasonable reliability under different conditions. It is clearly important not to compare results of studies using different lengths of measurement. It is also important to include major confounding factors into the protocol both in studies and clinically. Taken all together, reliability of HRV measurements is acceptable.

Short Term Versus Holter Monitoring

The research literature shows that two kinds of heart rate variability methods are generally used. Short-time variability is usually defined as a heart rate series taken for a time period of 5–20 min (mostly 10, but in studies even with 2-min (e.g., Schroeder et al. 2003) or 3-min (e.g., Gerritsen et al. 2001) measurement time has been published). In addition some studies have only used 10-s stripes (Carnethon et al. 2006).

Mostly in cardiology 24-h Holter monitoring has been used in a plethora of studies. In the time domain, 5 min and 24 h appear to be equally appropriate (Mazzeo et al. 2011). This notion is based on a repeatability study showing that even some repeated 10-s series achieve similar results – in healthy persons and with some caveats – as 6-min intervals. This study however did not compare Holter monitoring with short-term monitoring (Schroeder et al. 2004). Another study compared 1-min and 5-min HRV in diabetic patients and found good correlations for time-domain indices (Nussinovitch et al. 2012). Even 15- to 30-s strips have been used in depression patients, showing sensible results (Kamphuis et al. 2007). Correlations between 24-h and short-term spectral indices were generally >0.75 in a post-MI study (Bigger et al. 1993). So, generally, time-domain variables might be similar, whereas frequency domain might possibly differ more.

Different Forms of Measurement

Another interesting point is the post hoc analysis of ECG stripes in paper form. Automatic, computer-based analysis has been shown to be superior to manual analysis, but paper ECGs could be considered more often for retrospective analysis (Fleischer et al. 2012). Another study only used 10-s digitalized stripes to calculate SDNN and rMSSD (Carnethon et al. 2006). One study showed no differences between post-event and real-time analysis (Migliaro et al. 2004).

Pulse watches have been used in several studies, especially in training, but also in psychological investigations. This is of some interest, since the equipment is much cheaper. The Task Force does not endorse methods other than ECG. Some studies have compared pulse watches with regular approaches. The Polar S810 (Suunto, Finland) watch was used under resting conditions to test validity and reliability of a short-term HRV of 5 min. The watch demonstrated a good to near-perfect validity, but the reliability in regard of LF and HFnu was not high (Nunan et al. 2009). Another study compared Polar S810i and t6 (Suunto, Finland) and Cardiolite (Medset, Hamburg). Generally there were no major differences between the three different devices. In detail, the relative differences in LF were lower than 5 %. HF showed more differences, mostly 5 %, but in single patients up to 30 %. The variation was generally higher at higher heart frequencies (Weippert 2004). In one multicenter depression study, pulse-based and ECG-based HRV were used simultaneously. ECG measurements were obtained by 15- to 30-s strips and pulse-based HRV by measuring radialis pulse manually over 30 s; SDNN was then calculated. SDNN values were similar between the methods. Interestingly, they do not discuss problems related to the measurement period at all (Kamphuis et al. 2007).

Schäfer and Vagedes have written a comprehensive review on the accuracy of pulse wave-based measurement compared with traditional forms of HRV. They conclude that pulse measurement as an estimate of HRV has been proved to be sufficiently accurate only for healthy (and mostly younger) subjects at rest. They quote some studies showing that pulse-based techniques tend to overestimate HRV somewhat in variables associated with short-term variability (e.g., rMSSD, HF). More crucially, they found that "moderate physical or mental stress tends to diminish agreement between PRV and HRV to an extent that is or is not acceptable" and call for more exact studies (Schäfer and Vagedes 2013).

Confounding Factors

Genetic Factors

A problem in many clinical studies is the registration of subjects as of "Caucasian," "Asian," or "African" origin or "phenotype." Many studies, especially those relating to FDA criteria, register their participants under these

categories. Sometimes results are reported in connection with these categories (e.g., Reed et al. 2006, see below). In terms of science, this is problematic. One of us (GE) has reviewed research protocols submitted to an ethical review board for a decade. But I cannot remember any clear definition as to who is "Caucasian" and who isn't. One would certainly expect clear definitions in multicenter studies, but they also fail to provide them. There is no clear genetic concept for "races" or, for the supposedly nicer word, "ethnicities." With some exceptions, we have no clear evidence for genetic differences between "races." On the contrary, there is a line of evidence showing that the genetic differences *within* this constructed groups are higher than the genetic differences *between* them (Heinz and Kluge 2012).

A twin study showed that genetic polymorphism is important in the regulation of ambulatory HRV. For SDNN, heritability in the model had an influence of 34–47 % on variance, and for rMSSD 40–48 % (Kupper et al. 2004). Comparing HRV (frequency domain) of siblings and spouses (682, respectively 517 each), genes have been calculated to contribute for 13–23 % of variation (Singh et al. 2001). Genetic variation in CYP11B2 and AT1R had a correlation with LF/HF in supine position in subjects with sodium excretion >190 mmol/day, but not in subjects with lower sodium excretion (Stolarz et al. 2004). Variations in apolipoprotein phenotypes showed different changes in HRV under mental stress (Ravaja et al. 1997). In a comparison of "Caucasian" and "Asian" children ($n = 62$) of a same community in Canada, Asian children had a higher LF/HF ratio (Reed et al. 2006). Angiotensin II receptor type 1 polymorphism (A11666C) was associated with a higher SDNN compared with patients with other polymorphism patterns (Mitro et al. 2008). A polymorphism in the glutathione S-transferase gene (homozygous GSTT 1 null) exhibits an average of 10 % lower TP and LF. Together with passive smoking >2 h/day, TP was 26 % lower in these individuals, with obesity 22 % lower. Glutathione S-transferase is oxidant scavenging and the authors discuss the possibility that lower HRV in individuals with GSTT 1 null could be due to oxidative stress on the autonomic system (Probst-Hensch et al. 2008).

Another polymorphism exists in the dual-specific kinase-anchoring protein 2 (AKAP 10 (A/G) I646V). The 646 V alleles exist in about 40 %. A sample of 122 humans with known coronary heart disease was associated with increased resting HR and decreased HRV (SDNN) (Tingley et al. 2007). In a large sample ($n = 1{,}033$) of healthy humans between 30 and 54, this polymorphism was associated with greater resting heart rate and diminished HRV. The authors suggest that this variant may modulate the sensitivity of cardiac pacemaker cells to autonomic inputs (Neumann et al. 2009).

In a sample of 1,095 trauma patients with a mortality of 14.2 %, an association between changes in HRV and survival has been shown. Genetic polymorphisms to the beta-2-adrenergic receptor, the alpha-1-adrenergic receptor, and the catechol-O-methyltransferase (COMT) gene were tested. In particular, a beta-2-receptor polymorphism in 15.5 % of the study population was associated with increased survival (Morris et al. 2009)

Physiological Factors

Endocrinological and Neurohumoral Factors

LF and LF/HF ratio tend to increase and HF to become reduced during the luteal phase compared to the follicular phase, which can be interpreted as a higher activity of the sympathetic system. This might be caused by *estrogen* activation of the parasympathetic system and by *progesterone*-dependent activation of the sympathetic nervous system (Saeki et al. 1997; Sato and Miyake 2005). A recent study, however, was not able to show HRV differences with respect to the menstrual cycle, but the number of subjects included was very low ($n = 11$) (Nagakawa 2006). Women with estrogen replacement therapy have higher BRS and total HR variance than women without (Huikuri et al. 1996a).

Neurohumoral factors like oscillations of *adrenaline*, *noradrenaline*, *and angiotensin* may be responsible for HRV variations with periods in the minute range (Moser et al. 1994). Sympathetic tone increases with stimulation of the renin–angiotensin system and is under the influence of salt intake (DiBona 2002).

Exercise leading to an increase of more than 1.5 METS causes a significant increase in SDNN, SDANN index, SDNN index, pNN50, TP, and HF (Pardo et al. 2000). Similar results have been recorded in groups of young and old men. SDNN was lower in the older group, both groups had increased SDNN after 6 months of training, and the effect was larger in the older group (Levy et al. 1998). Similar changes were shown in an RCT including older men and women where the intervention group (6 months of training for 45 min and thrice a week) showed increased frequency-domain values compared to the control group (Schuit et al. 1999). Nakamura showed a first decrease of PNS activity in subjects with up to moderate activity in a treadmill experiment, whereas SNS was activated more when they had moderate to heavy exercise. A fractal component increased at the same time (Nakamura et al. 1993). In patients with persistent atrial fibrillation undergoing training, SDNN recorded with Holter monitoring was the only independent predictor of good exercise (Matsumoto et al. 2004). Exercise led to an increase in time-domain measures in patients with end-stage renal disease (Cashion et al. 2000); the same increase was observed in 12 chronic heart failure patients (Adamopoulos et al. 1995). Exercise training in subjects after PTCA increased significantly HF compared with a control group (Tsai et al. 2006). A 160-km ultramarathon did not induce changes in short-term HRV in 25 athletes (Scott et al. 2009). I discuss this as a confounding factor, especially when healthy controls are used. Investigators should have an idea about training manners and fitness of healthy participants in any HRV study. (HRV and physical exercise is discussed more extensively in a later chapter.)

Stress is often but not always associated with an increase in sympathetic cardiac control, a decrease in parasympathetic control, or both (Berntson and Cacioppo 2004). This was reported for acute stress paradigms in laboratory (e.g., arithmetic tests or reaction time tasks (Berntson et al. 1994; Delaney and Brodie 2000), acute

stressor in real life like college examinations (Lucini et al. 2002), and chronic perceived stress (Dishman et al. 2000)). By contrast, some experiments showed an increase in HF (e.g., forehead cold pressure manipulation (Hughes and Stoney 2000) or water immersion (Schipke and Pelzer 2001)). Different tasks can lead to different responses. An arithmetic task led to sympathetic changes in PEP and decreased HF, whereas an illusion task led to increases in HF in the same group of test persons (Berntson et al. 1996). The concept of stress is exceedingly broad and poorly defined (Berntson and Cacioppo 2004), which makes it difficult to compare different experimental or observational settings. Another caveat exists regarding the reaction to psychological stressors that lead to wide interindividual differences in the mode of response, with some subjects consistently showing predominantly sympathetic activation, others primarily vagal withdrawal, and still others a reciprocal pattern of autonomic response (Berntson et al. 1994). Cacioppo's study mentioned above, however, revealed high test–retest correlations in frequency domain in a group of older subjects both at baseline and with mental stressors (Cacioppo 1994). The relation between stress, cardiac disease, and HRV changes is discussed in following chapters.

Sleep: In REM sleep, TP, VLF, and LF increase, and LF decreases. In non-REM sleep phases, TP, VLF, LF decrease, and LF increases. Accordingly, LF/HF ratio was lowest in the non-REM phase. LF/HF increases already before the onset of REM phase, in stage two of non-REM sleep (Busek et al. 2005). During an awake state, 70 % of total HRV in the power spectrum was fractal; in deep sleep the ratio decreased significantly to 40 % (measured with coarse-graining spectral analysis) (Togo and Yamamoto 2000). In another study, low HRV levels were observed during slow-wave sleep, and high levels during REM sleep and intrasleep awakenings (Viola et al. 2002).

Of special interest is deep sleep (NREM sleep, Stage III/IV sleep) because it should be the least influenced by external and internal factors. A typical HF peak exists in the power spectrum, but oscillations in LF and VLF disappeared. It has been postulated that this is not due to a lack of oscillatory rhythms in vivo, but due to non-stationarity of the oscillations, which makes HRV analysis with help of Fourier analysis difficult. By using wavelet analysis (continuous wavelet transformation), a nonstationary periodicity in VLF was observed that was not detectable by Fourier analysis (Togo et al. 2006).

The effect of sleep on HRV is also influenced by ambient temperature. In 8 healthy male subjects, no differences were observed during REM sleep or wakefulness. In NREM sleep, however, LFnu decreased with 3 and 10 °C in NREM sleep phases (Okamoto-Mizuno et al. 2009).

In light sleep, SDNN, LF, and LF/HF values are similar to wakefulness; in slow-wave sleep the parameter decreases ($n = 387$ with or without sleep apnea) (Kesek et al. 2009).

Sleep deprivation was associated with an increase in LF and a decrease of HF (Zhong et al. 2005). In a field study with 147 engineers, LF/HF ratio changed in subjects with higher working hours and lower sleeping periods (Sasaki et al. 1999). There are also more conflicting results from other small studies (Muenter et al.

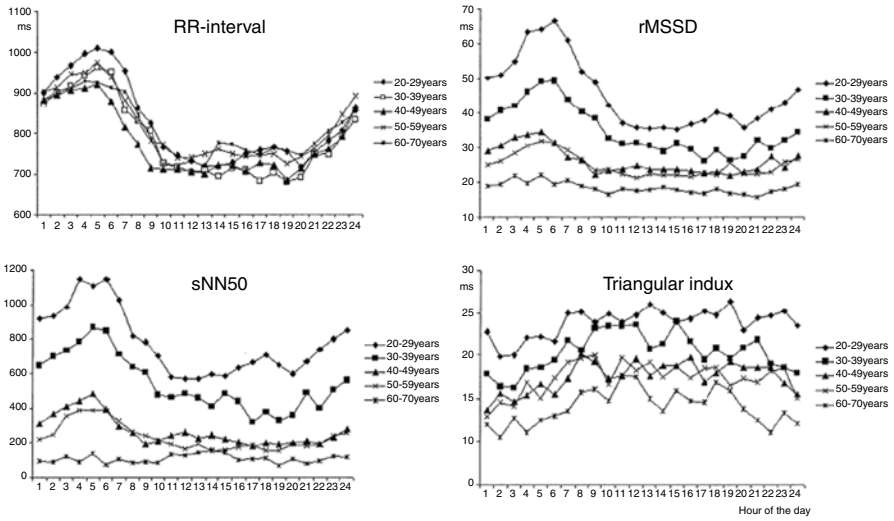

Fig. 4.16 Circadian variations of different time-domain indices (Bonnemeier et al. (2003a, b), with permission of John Wiley and Sons)

2000; Viola et al. 2002; Van den Berg et al. 2005). Compared to daytime nurses, permanent night-shift nurses showed an increased LF and LF/HF (Chung et al. 2009). In a study we conducted on 16 nurses, we took short-term HRV before and after a night shift and did not find differences between the evening before and the morning after, even when we included subjective sleepiness into the model (Ernst and Rostrup 2013a).

Circadian Influences: Most cardiovascular activities show a circadian rhythm. Almost all noninvasive electrophysiological phenomena, such as electrocardiographic indices, cardiac refractoriness and conduction, pacing, defibrillation threshold, heart rate indices, QT-dispersion, and T-wave alternans, show diurnal variability (Guo and Stein 2002). Changes or deregulation of this variability has been associated with pathological developments. Most HRV measures did not change during sleep deprivation and were mainly sleep-stage dependent. Only one linear parameter, SDNN, showed a nocturnal 140 % increase (Viola et al. 2002). Bonnemeier showed the effects of the circadian rhythm in 166 healthy volunteers investigated with Holter monitoring (Bonnemeier et al. 2003a, b) (Fig. 4.16).

Respiration: HRV was originally discovered in relation to respiration-dependent variability (RSA). Thus, it is not surprising that many studies found differences, and until today approaches recommend paced breathing to eliminate respiration-dependent effects. Both frequency and depth of ventilation can have effects on HF (Nakatsuka et al. 2002; Kanaya et al. 2003). Usually, with increased breathing frequency, LF and HF are reduced (Brown et al. 1993). In several studies, respiration was maintained with different frequencies (with help of a metronome, called paced breathing), e.g., 12/min (Druschky et al. 2001). Altered breathing patterns, as may be seen in Cheyne–Stokes respiration, shift spectral power into the very

low-frequency range (<0.05 Hz) in patients with moderate to severe heart failure (Mortara et al. 1997). Controlling ventilation for both rate and depth is likely to improve the reproducibility of measuring the heart rate variability associated with respiration; however, it remains to be established whether such controls are viable when comparing across different patient groups (Malpas 2002). Mean RR interval at a P_aCO_2 between 40 and 50 mmHg did not differ (controlling breathing frequency and tidal volume), but decreased at a P_aCO_2 of 30 mmHg. RSA magnitude increased progressively with $P_{ET}CO_2$ (Sasano et al. 2002). Individual differences in breathing have probably more effect in short-term HRV and most on parasympathetic measures like HF and the LF/HF ratio. To avoid this influences several groups use paced breathing protocols, where patients are asked to breath to a rhythm presented through a computer (e.g., Neumann et al. 2009). Paced breathing has particularly been used in diabetic autonomic neuropathy test batteries. However, recent data and reviews argue that the effect of respiration patterns and consecutively the effect of paced breathing have probably been overestimated. Respiration frequencies between 9 and 24/min have been discussed as unproblematic (Wittling and Wittling 2012), and a recent review concluded that variations in respiratory frequency are probably responsible for less than 2 % of variance of the HRV power (Denver et al. 2007). Paced breathing is still used in cohort studies, sometimes due to historical reasons (e.g., Pop-Busui et al. 2009).

Gender: Healthy women have a significantly lower HRV than healthy men (Bonnemeier et al. 2003a, b; Stein et al. 1997b). These effects can disappear in disease (congestive heart failure (Stein et al. 1997a)). In a bigger study, middle-aged women showed lower BRS (8.0 ± 4.6 ms/mmHg vs. 10.5 ± 4.6 ms/mmHg). LF and LF/HF were lower and HF was higher than in men. The differences remained after adjustment of the variables such as blood pressure, HR, smoking, alcohol consumption, and psychosocial score (Huikuri et al. 1996a, b). In a study comparing ten men and ten women, men had two to sixfold the adrenaline concentration of women in blood. There was no difference in frequency-domain values in resting subjects. Beta-blockade increased LF and HF in women, but not in men. Muscarinergic blockade reduced TP to almost zero. Women had a more negative slope. The authors conclude that men probably have a predominance of sympathetic vascular regulation, whereas women have a dominant parasympathetic influence on heart rate regulation (Evans et al. 2001). Younger women have a higher LF and lower HF ($n = 1{,}780$) (Koskinen et al. 2009a, b). Women with a new diagnosed essential hypertension had a lower SDNN and LF and a generally lower HRV during paced breathing (Pavithran et al. 2008).

Age has clear effects on HRV, but these effects can disappear in disease (congestive heart failure (Stein et al. 1997a)). HRV time-domain and frequency-domain values are all decreased in older men and partially decreased in women (Stein et al. 1997b). VLF, LF, and HF decreased with age, but not ULF (Holter ECGs (Bigger et al. 1995)).

In a study with 141 healthy individuals, the investigators aimed to find parameters for a "cardiac age." They used cluster analysis to identify different groups (5 in all) and found a correlation between frequency-domain values and different age

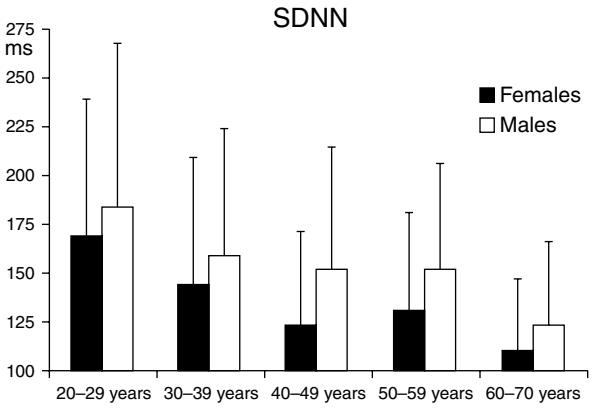

Fig. 4.17 SDNN changes with age (Bonnemeier et al. (2003a, b), with permission of John Wiley and Sons)

Table 4.13 Time-domain changes with age

Decade (years)	RR interval (ms)	rMSSD (ms)	sNN50	TI (ms)	SDNN (ms)	SDNNi (ms)	SDANN (ms)
20–29	800.2 ± 89.1	46.3 ± 17.9	810.1 ± 395.6	49.3 ± 11.4	177.4 ± 36.9	77.7 ± 18.4	157.5 ± 37.2
30–39	770.9 ± 77.2	35.5 ± 15.0	555.1 ± 419.6	41.4 ± 11.7	147.9 ± 33.9	63.5 ± 19.5	133.2 ± 32.0
40–49	764.7 ± 91.7	26.1 ± 9.1	273.7 ± 208.9	36.7 ± 10.9	141.3 ± 36.5	54.4 ± 15.6	127.1 ± 33.4
50–59	799.5 ± 77.4	24.2 ± 10.9	218.3 ± 279.8	34.9 ± 7.4	134.9 ± 34.2	52.9 ± 13.6	130.1 ± 37.7
60–70	802.9 ± 93.9	18.8 ± 6.8	109.4 ± 155.8	32.2 ± 7.1	117.6 ± 26.9	39.1 ± 9.6	106.8 ± 26.0

Modified from Bonnemeier et al. (2003a, b) with friendly permission of John Wiley and Sons

groups. They propose differences in chronological and neuroautonomic aging, calling the latter also the cardiac age. Neuroautonomic changes correlate with age until the sixth decade and then reach a plateau state (Colosimo et al. 1997). Bonnemeier showed clear age effects in 166 healthy volunteers investigated with Holter monitoring (Bonnemeier et al. 2003a, b) (Fig. 4.17, Table 4.13).

A decrease in complexity of short-term heart rate measures with age was shown as early as 1991 after the introduction of approximate entropy (Kaplan et al. 1991). In a study with 150 subjects between 5 and 70 years, HRV was recorded in sitting and lying positions for 20 min and four different age groups. For analysis, linear (SDNN, rMSSD, Pnn50, triangular index, TINN, ULF, VLF, LF, HF) and nonlinear (Poincaré plot analysis, approximate entropy, largest Lyapunov exponent, detrended fluctuation analysis) algorithms were used. In summary, HRV were less chaotic/more ordered with higher age and linear measures for variability reduced (Acharya 2004). Giuliani et al used a different approach, representing cardiac dynamics in terms of a first-order Markov model, considering heartbeat dynamics as a random walk. Older healthy subjects showed less stochasticity and more determinism than younger subjects (Giuliani et al. 1998) (Tables 4.14, 4.15, and 4.16).

Older otherwise healthy persons showed a decline in rMSSD in 5-min HRV measures (Haegele-Link et al. 2008). HRV decreases already in healthy age groups between 24 and 39 years ($n = 1{,}780$) (Koskinen et al. 2009a, b) (Fig. 4.18).

Table 4.14 Linear measures of HRV for various age groups (some values truncated) (Acharya 2004)

Parameters	10 ± 5 years	25 ± 10 years	40 ± 15 years	60 ± 5 years	*p* value
SDNN	92.96 ≤ 48.60357	81.30984 ≤ 38.87531	49.3888 ≤ 21.5635	70.89301 ≤ 61.20758	0.0007
SDSD	89.24 ≤ 64.86	80.56024 ≤ 62.02868	37.58513 ≤ 20.31	78.50874 ≤ 93.46987	0.0067
rMSSD	88.482 ≤ 65.6591	80.1892 ≤ 62.338	37.56944 ≤ 20.31	78.43348 ≤ 93.34064	0.008
Pnn50	12.9144 ≤ 8.469	15.2694 ≤ 9.97441	3.17521 ≤ 4.08388	9.77243 ≤ 19.8519	<0.0001
Triangle index	0.018 ≤ 0.0049	0.0163 ≤ 0.0047	0.0123 ≤ 0.0046	0.017 ≤ 0.01482	0.0038
TiNN	121.51 ≤ 234	154.188 ≤ 372.983	421.607 ≤ 619.87	113 ≤ 648	0.024

Table 4.15 LF/HF in various age groups (Acharya 2004)

Parameters	10 ± 5	25 ± 10	40 ± 15	60 ± 5	*p* value
LF/HF	1.425 = 1.0591	1.26798 = 0.88745	2.29766 = 2.59557	1.57 = 1.867	0.018

These results are frequently supported by newer data such as in Abhishekh et al. (2013), who once again showed decreasing SDNN, rMSSD, HF, and TP with age, whereas LF/HF increased.

Weight: Anorexia nervosa patients with less than 75 % of their ideal weight showed reduced frequency-domain values. Anorexia nervosa patients with restored weight showed no differences to the controls (Rechlin et al. 1998). To analyze the effect of ANS activity levels on postmenopausal obesity-related factors, 175 women were divided in a low TP group (<220 ms^2) and a high TP group (>220 ms^2). There was no difference in age, age at menopause, or years after menopause between the two groups. Body mass index, percentage of body fat, and blood pressure was higher in the low TP group, as well as triglycerides, cholesterol, and LDL (Kimura et al. 2006). In a small study, BMI < 20 was associated with elevated HF (Molfino et al. 2009). Weight loss of 10 % induced increased HF (Poirier et al. 2003).

Food Intake: Ingestion of meals in 15 healthy subjects did not lead to changes in HRV values recorded over 5 min in a time period of 2 h (Ambarish et al. 2005). Longer-lasting dietary restriction leads to an increase in HF and a decrease in LF (Vögele et al. 2009). High-carbohydrate/high-fat nutrition in an experimental study revealed an increased LF/HF, which was associated with an increased respiratory quotient (Millis et al. 2009).

Cognitive Performance: Psychological research has focused repeatedly on the interaction between states of the autonomic nervous system and cognitive performance. The basic idea has been that best functional results will be obtained if the cardiovascular system is neither too relaxed nor too stressed (underarousal and overarousal). Porges postulated an association between the resting cardiac vagal tone and the extent of cardiovascular reactivity (Porges 1992), which again may correlate with cognitive performance. An increase in blood pressure correlated with performance on five attentional tasks (Duschek et al. 2005) and decreases of RSA during a task were related to higher cognitive functional levels in children (DeGangi et al. 1991). It was not always possible to replicate these findings in other studies (e.g., Backs and Seljos 1994; Duschek et al. 2009; Wright et al. 2005), which may be explained through different attentional tasks demanding different cognitive patterns (Duschek et al. 2009).

On the other hand, increased cognitive activity can lead to reductions in heart rate variability (Althaus et al. 1998; van Roon et al. 1995). The MF band is sensitive to the amount of mental workload (Boucsein and Backs 2000). In fact, MF is more closely related to attentional processing than HF (Althaus et al. 1998). MF reductions have also been shown in complex, more naturalistic attentional tasks like flight simulation or car steering (Mulders et al. 1982; Veltman and Gaillard 1993, 1998). As mentioned above, MF and LF have some similar though not identical properties.

Table 4.16 Nonlinear measures of HRV for various age groups (some values truncated) (Acharya 2004)

Parameters	10 ± 5	25 ± 10	40 ± 15	60 ± 5	*p* value
SD1/SD2	0.5169 ≤ 0.193551	0.5265 ≤ 0.2357	0.4298 ≤ 0.191684	0.6055 ≤ 0.286834	0.12
ApEn	1.903 ≤ 0.34597	2.0722 ≤ 0.1849	1.8746 ≤ 0.3475	1.6837 ≤ 0.4083	< 0.0001
LLE	0.6852 ≤ 0.2012	0.6392 ≤ 0.0895	0.4387 ≤ 0.1779	0.4342 ≤ 0.2945	< 0.0001
αs	0.579 ≤ 0.35056	0.4121 ≤ 0.204	0.1386 ≤ 0.2160	0.2244 ≤ 0.3280	< 0.0001
αl	2.0062 ≤ 0.33472	1.8309 ≤ 0.1495	1.6741 ≤ 0.2057	1.7148 ≤ 0.2222	< 0.0001

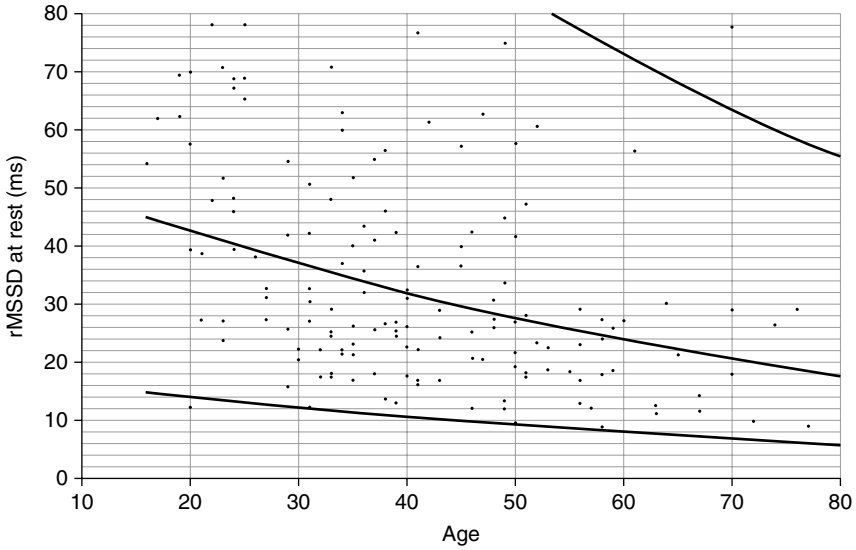

Fig. 4.18 rMSSD decline in healthy persons dependent of age ($n = 190$) (Haegele-Link et al. (2008), with friendly permission)

In a visual attention test conducted on 60 healthy subjects, R-wave to pulse interval (RPI), RSA, HRV in the mid-frequency band, and sensitivity of the cardiac baroreflex (BRS) were assessed at rest and during the test. RPI, RSA, HRV, and BRS were inversely related to the attentional functioning and discussed as a bottom-up modulation of cerebral function by baroreceptor activity. HF and RSA accounted for the largest portion of test score variance among all on-task parameters. The authors argue that enhanced sympathetic and reduced vagal cardiovascular influences as well as baroreflex inhibition may induce an adaptive state associated with improved cognitive–attentional functioning. Reduced cardiac inhibition is of particular importance for the establishment of a physiological condition optimal for the mental process required by attentional tasks (Duschek et al. 2009).

Ethnicity

As suggested above, ethnicity is a problematic concept. In cardiovascular medicine it has been used to identify subgroups of African American origin that have an increased prevalence of hypertension (e.g., Wali and Weir 1999). The word "ethnicity" is often used as a supposedly less problematic expression than "race" but is actually an equivalent term. However, there is no clear scientific basis for the concept of ethnicity. Genetic variation within ethnicities is often bigger than between ethnicities. Summarizing all with black skin under "African Americans" is a very special idea regarding the fact that Africans are widely different in phenotypes. There is also no convincing genetic definition of ethnicity (compare a broader

discussion in Heinz and Kluge 2012). Choi's study is a good example for how "ethnicity" can be used to draw rather special conclusions. For it, researchers invited "African Americans" and "Caucasians" to participate in an HRV study. They claim that they assessed social class ("Social class was determined using the clinician-rated Hollingshead two-factor index."), but this does not appear in any statistical model. One may take social differences between groups into account by looking at weight differences, which are often associated with social class. On this base the authors of the study find and describe "ethnic differences" and discuss them again without considering the problematic idea of ethnicity or possible social differences that might explain the results. Based on this they conclude, "These results suggest that young AA individuals might exhibit signs of premature aging in their autonomic nervous system" (Choi et al. 2006). If ethnicity is a useful concept at all, studies need much better theoretical frameworks and methodological concepts before achieving reliable results.

Pathophysiological Factors

Persistent atrial fibrillation is closely related to disturbances of the autonomic nervous system. AF requires usually one or several triggering factors and a vulnerable electrophysiological or anatomic substrate for maintenance. Once established, AF alters atrial electrical and structural properties (called atrial remodelation), which promotes its own maintenance and recurrences and may alter the response to antiarrhythmic drugs (Chen and Tan 2007). Most patients with idiopathic paroxysmal AF appear to be vagally dependent, with heightened susceptibility to vasovagal cardiovascular response. In patients with organic heart disease, paroxysmal AF appears more likely to be sympathetically induced (Huang et al. 1998). Already early studies documented that in patient subgroups RR intervals and pulse are mainly nonrandom (Rawles and Rowland 1986). The relevance and significance of traditional time-domain and spectral HRV parameters in chronic AF is uncertain. However, although RR intervals are intrinsically irregular in AF, this irregularity is not random; it is complex and is dependent on a number of factors: the refractory period and conductivity of the AV node, the degree of concealed conduction and the irregularity, and frequency and direction of atrial wave fronts impacting on the AV node (Khand et al. 2006). HRV in AF has been stated to be highly rate dependent (Friedman 2004).

Garfinkel et al. studied atrial fibrillation in humans, in a stabilized form of canine ventricular fibrillation, and in fibrillation-like activity of tin sheets of canine and human ventricular tissue, with the hypothesis of AF as deterministic chaos arising via a quasiperiodic transition.[1] They analyzed data with help of

[1] A system's behavior is said to be quasiperiodic if it displays several independent frequencies, for example, an oscillation at one frequency that is amplitude modulated at another frequency. When a quasiperiodic system becomes chaotic, the quasiperiodic frequencies often remain detectable in the chaotic regimen (Garfinkel et al. 1997).

Poincaré plots where consecutive points were connected and the distance measured. Fifteen of 19 plots of humans showed a clear ring structure. Quasiperiodicity was detected with the help of a Fourier analysis of the intervals (not to be confused with a Fourier analysis of QRS-distances). The Lyapunov exponent was calculated with a range of 0.08–0.14 in a computer simulation, but it was not possible to calculate the Lyapunov exponent in the biological samples. The authors considered the behavior to suggest chaos in analogy to models of fluid turbulence (Garfinkel et al. 1997).

Holter monitoring has been used in patients with *permanent AF* to test HRV (Piot et al. 1998). In a small study, 500 RR intervals were studied in 16 patients with permanent AF and 12 healthy controls using SDNN, coefficient of variance, rMSSD, LF, and HF as feasible markers (van den Berg et al. 1997b).

Patients with AF are usually excluded in studies. However, in some studies, they have been used. Kamata analyzed with the help of Holter monitoring 12 patients after 1, 6, and 12 months following Maze interventions (ablation) and seven patients without, using RR intervals and computing time-domain (SDRR) and frequency-domain (HF, LF, TP) values. The circadian variation 1 month after surgery was significantly disturbed but restored after 6 and 12 months, possibly due to vegetative reinnervation of the sinus node (Kamata 1997). 24 patients with persistent AF were tested with continuous ECGs during bicycle exercise testing, their ventricular response was characterized by time-domain HRV indices, based on QRS-distances (Husser et al. 2007).

Stein and Borer conducted a landmark study in 21 patients with atrial fibrillation due to chronic severe mitral regurgitation using Holter monitoring and following the patients for up to 9 years (end points: mortality, surgery). They used time- and frequency-domain measurements and compared them with resting ventricular function measured by radionuclide cineangiography and the outcome. Reductions in frequency-domain measurements of ultra low- and high-frequency HR variability were significant predictors of the combined risk of mortality or requirement for surgery (Stein et al. 1994).

Friedman used a method to calculate regressions and examine the differences between the measured HRV and the expected HRV (Friedman 2004). Mostly, premature beats are removed and AF episodes ignored, using only SR periods (e.g., Vikman et al. 1999). SDNN and SDANN as indices for the ventricular response interval have been used in patients with persistent atrial fibrillation. They showed correlation to good exercise capacity during treadmill exercise testing, whereas LVEF (and age, BMI) did not correlate (Matsumoto et al. 2004).

In a study including 40 patients with AF, QRS intervals labelled in 5th RR percentile intervals in each hour were calculated. This parameter has been shown to approximate the functional refractory period (FRP) of the atrioventricular node. In addition they used SDARR (the equivalent of SDANN), which has been shown to predict mortality in patients with chronic AF and heart failure. FRP did correlate with SDARR, mean RR interval, and NYHA class of heart failure (Khand et al. 2006).

Exercise improved health and quality of life in patients with chronic AF compared to controls; this correlated with HF in a 15-min frequency-domain HRV (Hegbom et al. 2006).

Segerson and colleagues measured short-term HRV in patients with paroxysmal AF during sinus rhythm and ventricular cycle length entropy during AF phases, using data from PhysioNet. Short-term HRV parameters were SDNN, rMSSD, SDANN, pNN50, and interbeat correlation coefficient (ICC) from 30-min short-term HRV and entropy measures (Shannon informational entropy and ApEN) from 5-min AF. Reductions in rMSSD and increases in ICC were correlated with reductions of entropy during AF. They conclude that entropy during AF is possibly modulated by vagal activity (Segerson et al. 2008).

Esperer and colleagues used Poincaré plot patterns (here called Lorentz plots) to test their associations with different heart rhythms. They grouped the patterns in (1) comet shape, (2) torpedo shape, (3) H-fan shape, (4) SZ-fan shape, (5) double-side lobe pattern type A (DSLP-A), (6) double-side lobe pattern type B (DSLP-B), (7) triple-side lobe pattern type A (TSLP-A), (8) triple-side lobe pattern type B (TSLP-B), (9) island pattern type A (IP-A), and (10) island pattern type B (IP-B). Comet and torpedo shapes were associated with sinus rhythm, whereas a "fan shape" was associated with AF. They propose to use this kind of analysis to improve rhythm analysis of Holter recordings (Esperer et al. 2008). Kikillus used a similar kind of analysis in 60-min measures and was able to show that it is possible to identify patients with paroxysmal AF even if they don't show this at the time of measurement and state a sensitivity of 83 % (Kikillus et al. 2008).

In conclusion, using HRV in patients with persistent AF remains controversial. Some studies have revealed associations between exercise capacity, quality of life, and HRV (e.g., Stein et al. 1994); other studies did not find correlations between traditional heart measures and HRV (Friedman 2004). Clinical aspects are discussed in more detail in part II, Chap. 2.

Depression is a significant factor in frequency-domain HRV. Depending on the amount, HRV values decrease significantly more in depressed coronary patients than in nondepressed (Carney et al. 2005b). However, in a sleep study with female IBS patients, depressed patients showed no difference compared to nondepressed patients and healthy controls (Robert et al. 2004).

Growth hormone deficiencies led to decrease in LF, increase in HF, decrease in VLF, and decrease in LF/HF (Leong et al. 2000).

Isocapnic hypoxia in dogs leads to progressive decrease of HF during moderate to severe hypoxia (measured through invasive blood pressure oscillations, verified by ECG) (Yasumo 2000).

Total *cholesterol* and *low-density lipoprotein* correlated inversely with HRV-based measurements and did not normalize after 3 months of diet; hence, serum lipids decreased (Danev et al. 1997).

Smoking: HF (0.25 Hz) decreased 3 min after smoking a cigarette following an abstinence of 8 h under controlled respiration conditions (Hayano et al. 1990). Long-term effects of smoking in 81 subjects (25 nonsmokers, 31 moderate, and 25 heavy smokers) were observable in younger smokers by a decrease of the HF

component and reduced postural changes in all smokers (Hayano et al. 1990). Heavy smokers (20–40 cigarettes a day) who stopped smoking for 3 days showed a reduction of HRV parameters (Holter monitoring) (Munjal et al. 2009).

Pollution: In treated stable heart failure patients ($n = 132$), heart rate variability measures (Holter monitoring) were independent of daily area PM10, particle number concentration, nitrogen oxides, daily estimated PM 2,5, PNC exposures, and 3-day cumulative nitrogen dioxide (N_2O) (Barclay et al. 2009). In a study, five asthmatic adults were exposed to carbon and ammonium nitrate particles and ozone or filtered air over 4 h. SDNN, LF, and HF were reduced in 20-min HRV (Power et al. 2008). In a group of 22 workers exposed to lead, a negative correlation between SDNN, TP, and LF and lead concentration was found ($r = -0.48$, -0.48, and -0.47, respectively), whereas overall HRV indices were not different to a control group of 13 age-matched healthy test persons (Gajek et al. 2004).

CRP: In 531 patients with unstable angina pectoris, high CRP correlated with low HRV. SDNN and VLF were the best predictors of high CRP (Lanza et al. 2006). In patients after acute myocardial infection, a strong inverse relation between several HRV indices (SDNN, TP, HF, LF) and CRP was observed that remains also after adjustment for left ventricular function (Psychari et al. 2007). In stable coronary heart disease, mixed results were presented. In a study with Holter monitoring, a high correlation was observed (Madsen et al. 2007). In another study with short-term data (5 min), no correlation was observed (Yue et al. 2007). In a further study that selected a small sample with low and higher CRP values using short-term HRV, HF was decreased in the high-CRP group (Nolan et al. 2007). In healthy persons, no association was found between CRP and HRV changes after a mental stress test (Owen and Streptoe 2003). Using only a 2-min HRV in 823 subjects without heart disease, Kon and colleagues showed that CRP predicted independently a low SDNN index (Kon et al. 2006). Sloan included 757 young healthy subjects in a 10-min ECG, and HF and LF were inversely correlated with HF and LF (Sloan et al. 2007). A recent review concluded that there is clear evidence for an association between ongoing subclinical inflammation and decreased heart rate variability (Haensel et al. 2008).

Medicaments

Antiarrhythmics

Amiodarone: Patients with a decreased HRV index < 20 had showed better response to treatment with amiodarone than patients with a higher HRV (Malik et al. 2000). Amiodarone reduced HRV indices in patients with paroxysmal AF and a predominant sympathetic type, whereas it did not change HRV in patients with vagal tone or mixed type (Shabalin et al. 2002).

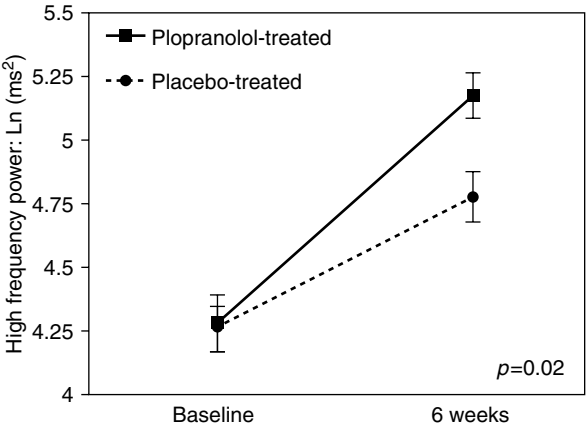

Fig. 4.19 Effects of propranolol on HF power in MI patients after 6 weeks of treatment (Lampert et al. (2003), with friendly permission of Elsevier)

Antihypertensive Drugs

Angiotensin II Receptor Antagonists: All time- and frequency-domain values increased after a treatment with losartan. Decreasing effects of volume load disappeared (Petretta et al. 2000).

ACE Inhibitors: 32 patients with chronic cardiac failure underwent Holter ECG and were treated with captopril or placebo. pNN50 increased from 482 (23–6,120) to 1,032 (48–7,437) (Flapan et al. 1992). In a small RCT, patients with congestive heart failure received either an ACE inhibitor (zofenopril) or a placebo. After 12 weeks, total power was increased by 50 % and HF increased twofold in the group receiving zofenopril (Binckley et al. 1993). 40 patients with a first uncomplicated MI got either captopril or placebo and were studied baseline and 3 days after with a Holter ECG. In the captopril group SDNN increased (from 90 ± 29 to 105 ± 30), SDANN increased (74 ± 24 to 90 ± 26), and SDNN 5 min increased (45 ± 17 to 49 ± 17). rMSSD and pNN50 remained unchanged. TP increased (8.28 ± 0.42 to 8.47 ± 0.3); ULF, VLF, and LF increased; HF remained unchanged (Bonaduce et al. 1994).

Beta-Blockers: Beta-blockers induced increasing values in TP, HF, LF, and VLF in long-time treatment (Lin et al. 1999). Metoprolol, but not celiprolol, restored BRS and HF in heart failure patients (Sanderson et al. 1999). Bisoprolol increased rMSSD, pNN50, SDNN (daytime), and HF (daytime) (Pousset et al. 1996). Propranolol did not lead to notable changes in coarse-graining spectral analysis (Yamamoto and Hughson 1994). Beta-blockers possibly increased the coupling of HRV and SPV (Gonzalez et al. 2000). Beta-blockers increased HRV indices in patients with MODS and increased survival (retrospective study (Hennen et al. 2008)). The effect of beta-blockers on the recovery of HF power was studied in an RCT of postinfarction patients. HF recovered in all patients but more profoundly in patients treated with beta-blockers (Lampert et al. 2003). *Propranolol* increased HRV measures (Van den Berg et al. 1997a, b) in general as well as in patients with permanent AF (Van den Berg et al. 1997a, b). It increased (pathologically decreased) HF in patients with end-stage renal disease (Tory et al. 2004) (Fig. 4.19).

Antidepressive

Bupropion: Decreased values for HRV both in rest and in response to mental and physical stressors (Straneva-Meuse et al. 2004).

Doxepine: Decreased SDNN after 14 days (Rechlin 1994; Rechlin et al. 1994), see also fluoxetine.

Fluoxetine: In a small study ($n = 14$), responders on fluoxetine (or doxepin) had an increase in SDANN of 17 %, and nonresponders a decrease in SDANN and a 22 % decrease in SDNN. pNN50 and rMSSD remained unchanged (Khaikin et al. 1998). SSRIs generally led to a decrease of SDNN and RAS in a large cross-sectional study (Licht et al. 2008).

Fluvoxamine: No change of SDNN after 2 weeks of treatment (Rechlin 1994; Rechlin et al. 1994).

Paroxetine: Unchanged values for HRV both in rest and in response to mental and physical stressors (Straneva-Meuse et al. 2004). Unchanged SDNN after 14 days of treatment (Rechlin 1994; Rechlin et al. 1994).

Sertraline: Decreased HRV did not change after treatment with sertraline, but ultra low frequency was increased (Glassman et al. 2007).

SSRI General: Patients with depressions showed a similar HRV than controls, but HRV decreased 2 days after using SSRIs (Bär et al. 2004).

Tricyclic Antidepressants: The mean consecutive difference between RR intervals was reduced in patients treated with different tricyclics (Jakobsen et al. 1984). 150 mg amitriptyline per day reduced, after 14 days of treatment, heart rate and heart rate variability and all indices of frequency-domain HRV (Rechlin 1994; Rechlin et al. 1994). In a large cross-sectional study, patients with TCAs had a significantly lower SDNN and RSA (Licht et al. 2008).

Other Psychopharmacological Drugs

Atypical Antipsychotics: In schizophrenic patients, already abnormal suppressed RR intervals (specially in LF) were further decreased with the use of atypical antipsychotics (Mujica-Parodi et al. 2005).

Caffeine: Caffeine intake increased HRV measures in both diabetic patients and the control group (Richardson et al. 2004). Caffeine intake increased ApEN and frequency-domain values of HRV (Yeragani et al. 2005). Blood pressure variability in healthy objects consuming 240-mg caffeine or placebo was assessed with ApEN and DFA (α exponent). ApEN did not change after caffeine intake, but the long-time scaling exponent α did increase from 0.99 to 1.04 (Papaioannou et al. 2006). In healthy participants, intake of 100- or 200-mg caffeine did not change HRV (Rauh et al. 2006). Caffeine intake in cardiologic patients with acute STEMI was investigated in an RCT, where one group had unlimited access to caffeinated coffee and one to decaffeinated coffee. In the caffeine group SDNN after 5 days was higher

(97.7 ± 29.0 vs. 85.0 ± 18.5), also rMSSD (26.5 (21.7–31.2) vs. 19.4 (16.7–22.2)). No adverse cardiovascular effects associated with caffeine ingestion in the periinfarct period were observed, in particular no predisposition to tachydysrhythmias (Richardson et al. 2009). Caffeine had no effect on SDNN in a small study (Karapetian et al. 2012).

Gabapentin: SDNN and HF increased significantly or LF/HF ratio decreased and LF remained unchanged after 3-month therapy in diabetic patients with peripheral polyneuropathy (Ermis et al. 2010).

Nicotine: Holter monitoring in subjects going over from smoking to nicotine patches to abstinence showed an increase in all frequency-domain variables of HRV (Stein et al. 1996).

Olanzapine: In 15 patients, some complexity measures (approximate entropy, compression entropy, fractal dimension) and the QT-variability were obtained and compared with matched controls. Untreated patients had reduced complexity indices; the QT-variability was increased. After initiation of treatment, complexity was reduced, and QT-variability unchanged (Bär et al. 2008).

Catecholamines

Dobutamine: CHF and healthy controls underwent dobutamine infusions and were scanned with help of Swan–Ganz catheters, ECG, and MSNA. In controls, dobutamine inhibited MSNA probably due to the activation of arterial baroreceptors – if there was no increased blood pressure, the MSNA reaction was absent. A similar reaction was observed in CHF patients (Velez-Roa et al. 2003).

Adrenaline: Infusion of noradrenaline and adrenaline did not induce changes in frequency-domain values of short-term HRV (1 h each) in healthy subjects (Tulen et al. 1994).

Noradrenaline: Infusion of noradrenaline and adrenaline did not induce changes in frequency-domain values of short-term HRV (1 h each) in healthy subjects (Tulen et al. 1994).

Anesthesiological Drugs

Fentanyl: No effects on frequency-domain variables were detected (Galletly et al. 1994a). It decreased absolute TP and LF, not HF. No effect on normalized measurements of LF, HF, and LF/HF ratio (Riznyk et al. 2005). 1 ug/kg fentanyl decreases LFnu without increases of HFnu, in addition to decrease of TP from 3,345 ± 3,333 to 1,806 ± 1,328 ms^2 (Vettorello et al. 2008).

Midazolam: Slight depression of HF and LF and unchanged LF/HF ratio (Michaloudis et al. 1998). Depression of HF in deep-sedated ICU patients (Unoki et al. 2009).

Nitrous Oxide: N_2O in healthy subjects led to a reduction in HF and to a rise in LF/HF ratio (Galletly et al. 1993). Inhalation of nitrous oxide by healthy volunteers attenuated the increase of LF due to the procedure (compared with controls), whereas HF remained high, such as LF/HF increased by use of nitrous oxide (Okushima et al. 2008).

Propofol: Decreased LF, MF, and HF, LF to a lesser extent than the latter two (Galletly et al. 1994b). Decreased TP and HF and increased LF/HF ratio (Howell et al. 1995). Absolute TP and HF decreased (Riznyk et al. 2005).

Thiopental: Decreased TP and HF and increased LF/HF ratio (Howell et al. 1995). Absolute TP, HF, and LF decreased. LFnu increased and HFnu decreased. Increase of LF/HF ratio (Riznyk et al. 2005).

Other Drugs

Allopurinol: No effect on time-domain values (Shehab et al. 2001).

Atropine: Decreased HRV (Van den Berg et al. 1997a, b). Decreased coupling between HRV and SPV (Gonzalez et al. 2000). Increased short-term scaling exponent alpha-1 (Hautala et al. 2003a).

Beta-agonists: Beta-agonists had no effect on HRV in a study with COPD patients (Bédard et al. 2010).

Digoxin: In a study with 26 patients with heart failure recently set on digoxin, HF increased from 84 ± 24 to 212 ± 72 ms^2, rMSSD increased from 20.3 ± 1.8 to 27.0 ± 3.4 ms, and LF increased from 239 ± 80 to 483 ± 144 ms^2 (Krum et al. 1995). Similarly, MSNA decreased in heart failure patients, but not in healthy controls (Ferguson et al. 1989).

Metformin: Metformin increased HRV after 4 months of treatment in obese diabetic patients (Manzella et al. 2004).

Omega-3 Fatty Acids: A crossover study with post-MI patients showed increased HF but no other HRV parameters in patients taking for 4 months omega-3 fatty acids (O'Keefe et al. 2006). On the other hand, a meta-analysis showed reduced basal heart rate in patients taking omega-3 fatty acids (in mean 1.6 bpm) (Mozaffarian et al. 2005). In a population-based study recording intake of tuna and other fish products, short-term SDNN and rMSSD was higher in persons consuming them regularly. Also HF was increased (and LF reduced), resulting also in a lower LF/HF ratio. In addition higher fish intake was associated with lower Poincaré ratio and higher DFA1 and VLF (Mozaffarian et al. 2008).

Proton-Pump Inhibitors: Use of esomeprazole did not induce changes in HRV (Yi et al. 2008).

Raloxifene: In one study time-domain values remained the same after 6 months of treatment, but HF increased and LF/HF decreased in this treatment period (Gol et al. 2006).

Simvastatin: 25 patients with a non-dilated cardiomyopathy were measured before and after a 6-week course of simvastatin. A 5-min ECG was used to determine frequency-domain values. There were no differences on baseline HRV, but a

modest relationship between the extent of LDL reduction and Lfa (Gentlesk et al. 2005).

Spironolactone: 31 patients with chronic heart failure were treated with spirinolactone or placebo in addition to diuretics and ACE inhibitors. Spironolactone reduced a marker of vascular collagen turnover and increased time-domain parameters of heart rate variability (MacFadyen et al. 1997). It reduced HRV in diabetic patients (rMSSD, Lf, and HF) (Davies et al. 2004).

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Chapter 5
HRV and Alterations in the Vegetative Nervous System

Introduction

Heart rate variability is often discussed synonymously with imbalance within the autonomous system. HRV has been seen not only as an indicator for probable disturbances in the autonomous system. In a significant number of publications, it is even regarded as proof for ANS dysfunction without other kind of evidence (e.g., in Mazzeo et al. 2011). In this chapter I intend to review this hypothesis.

One basic problem is to find methods to examine the autonomic nervous system. There is no gold standard to evaluate the ANS, and it is rather arguable whether there are evaluation methods that can display the real situation of the ANS.

Dysfunction of ANS can be caused or impaired by several clinical and subclinical conditions, summarized in the following Table 5.1.

We still have an insufficient understanding of the exact underlying mechanisms that induce alterations of HRV in CHF (Tulppo and Huikuri 2004) or in healthy persons.

Is There an Accordance Between Anatomical Structures Involved in HRV and Supraspinal Structures Related to ANV?

Given the increased possibilities of in vivo studies of the human brain, it is not surprising that several studies have been conducted focusing on HRV.

Critchley used functional MRI experiments with simultaneous electrocardiography to examine regional brain activity associated with autonomic cardiovascular control during performance of cognitive and motor tasks. Activity in the dorsal anterior cingulate cortex (ACC) related to sympathetic modulation of heart rate was observed using indices of heart rate variability and high- and low-frequency power in the cardiac rhythm. This could indicate that during effortful cognitive and motor

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Table 5.1 Principal causes of autonomic nervous system dysfunction

Degenerative disorders	Acute and subacute disease	Chronic diseases	Others
Pure autonomic failure (PAF)	Heart failure	Diabetes mellitus	Drugs acting on ANS
Multiple system atrophy (MSA)	Myocardial infarction	Hypertension	Cardiac transplant
Parkinson's disease	Severe brain injury	Idiopathic orthostatic hypotension	
	Spinal cord injuries	Increased intracranial pressure	
	Guillain–Barré	Hereditary neuropathies	
	Paraneoplastic neuropathies	Dopamine beta-hydroxylase deficiency	
	Botulism	Uremia	
	Drug-induced neuropathies	Alcoholism	
	Toxic neuropathies	Liver disease	
	Porphyria	Chronic pulmonary diseases	
	Immune autonomic neuropathies	Amyloidosis	
		Infective neuropathies	
		Chronic immune demyelinating polyneuropathies	
		Connective tissue diseases	

Modified from Mazzeo et al. (2011)

behavior, the dorsal ACC supports the generation of associated autonomic states of cardiovascular arousal. This idea was tested on three patients with damaged ACC regions who, in contrast to healthy volunteers, showed blunted autonomic arousal to mental stress (Critchley et al. 2003).

Matthews used a test that presented incongruent (INC) and congruent (CON) stimuli at two speeds to probe dorsal (dACC) and ventral (vACC) using functional magnetic resonance imaging (fMRI). He was able to distinguish functional subdivisions within the ACC and to link the processes of cognitive interference and parasympathetic modulation with activation in specific subregions of the ACC, a structure that is critical for the interface between cognition and emotion. This activation correlated significantly with HF and might represent the parasympathetic modulatory role of the vACC (Matthews et al. 2004).

Napadow and colleagues developed and implemented a new method that relates cardiac-gated fMRI time series with continuous-time heart rate variability (HRV) to estimate central autonomic processing. The ECG was analyzed with a novel point process adaptive-filter algorithm for computation of HF simultaneously. This combined HRV–fMRI approach demonstrated HF correlation with fMRI activity in the hypothalamus, cerebellum, parabrachial nucleus/locus coeruleus, periaqueductal gray, amygdala, hippocampus, thalamus, and dorsomedial/dorsolateral prefrontal, posterior insular, and middle temporal cortices (Napadow et al. 2008).

Lane correlated HF-HRV with measures of regional cerebral blood flow (rCBF) derived from positron emission tomography (PET) and (15)O-water in 12 healthy women during different emotional states. Three different emotional states and three neutral conditions were each induced by videos or through recall of personal experiences. A 60-s HRV was analyzed with the help of frequency domain. The six emotional and six neutral conditions were grouped together and contrasted. Substantial overlap was found between emotion-specific rCBF and the correlation between emotion-specific rCBF and HF-HRV, particularly in the medial prefrontal cortex. The study also observed that the elements of cognitive control had clear neural substrates that correlated with HF-HRV and to a large extent differed from the emotion-specific correlates of HF-HRV. The study proposed that the medial visceromotor network is a final common pathway by which emotional and cognitive functions recruit autonomic support (Lane et al. 2009).

Thayer and colleagues executed a meta-analysis of this and four other imaging studies using Multilevel Kernel Density Analysis (MDKA). The study treats MDKA contrast maps as the unit of analysis and is therefore suitable for evaluating the consistency of activation across studies (Thayer et al. 2012). They identified three regions associated with emotion tasks investigated in earlier studies together with HRV (Thayer 2006), the right pregenual cingulate (BA 24/32) in the medial prefrontal cortex, the right subgenual cingulate (BA 25), and the left sublenticular extended amygdale/ventral striatum (SLEA). The latter region extends into the basolateral amygdale complex, the superior amygdale (central nucleus), and into the ventral striatum. Especially the involvement of SLEA is in accordance to its central role in ANS. One problem is that due to temporal aspects of the imaging investigations, only HF (needing the shortest time periods) could be tested.

In conclusion, newer studies support the assumption developed in animal studies that ANV correlates in the brain and structures involved in HRV are largely similar.

Is There General Increased Autonomic Activity That Might Correlate with HRV Measures?

In frequency-domain analysis the idea of a possible correlation between alterations of the HF, or LF component and parasympathetic, or sympathetic activity comes largely from pharmacological studies in both humans and other animals. The basic idea that HRV measures could correlate with the functional state of the vegetative nervous system assumes a synchronicity between different parts of it. In other words it assumes that the vegetative nervous system is in either a sympathetic or parasympathetic state, and this regards all parts simultaneously. This is probably only partially true. There is evidence for quantitative regional differences in sympathetic outflow, particularly in patients with heart failure, with a bigger activation at the heart compared to the real noradrenaline spillover (Hasking et al. 1986). These differences occur not only between different functional systems but also temporally. The increase in cardiac adrenergic drive precedes the rise in sympathetic nerve traffic to the skeletal muscle measured by MSNA (Rundqvist et al. 1997). Therefore, it

is difficult to sustain the idea of a generalized sympathetic or parasympathetic state. HRV might or might not mirror a generalized state, but it may also simply show just the sympathetic or parasympathetic state of the parts of the ANS involved in HRV (and not, for instance, ANV states in peripheral nerves).

Does HF Correlate with Parasympathetic Tone?

[*Pros*:] Early evidence was interpreted to suggest that HF power can be promoted as a noninvasive index of vagal-cardiac nerve traffic in humans (Eckberg 1983; Fouad et al. 1984). Administration of atropine or other parasympathetic blocking agents can abolish the high-frequency component of heart rate variability (Rimoldi et al. 1990). High-dose atropine was thought to block vagal parasympathetic activity, and it was shown to eliminate nearly all HF (and LF) in studies (Pomeranz et al. 1985; Koh et al. 1994). Using an experimental approach in which sympathetic influence was blocked by propranolol and vagal influence was blocked gradually with atropine under controlled respiration, HF (both calculated with autoregressive spectrum analysis and fast Fourier transformation) correlated strongly with vagal tone (Hayano et al. 1991). In volunteers after beta-adrenergic blockade with propranolol, phenylephrine and nitroprusside were used to achieve baroreflex-mediated increases and decreases of the parasympathetic activity, with a dose–response experiment. In the analysis, which used linear and quadratic models, quadratic models proved superior. The authors conclude that the relationship between HRV parasympathetic activities can be described best by a function with an ascending part that goes over to a plateau level (Goldberger et al. 2001). In post-AMI patients, plasma noradrenaline correlates with HF (Oya et al. 1999).

[*Cons*:] Kollai and Mizsei compared respiratory peak minus valley RR interval changes with RR interval shortening provoked by large-dose atropine after β-adrenergic blockade. Although their study supported the use of respiratory RR interval fluctuations as indexes of vagal-cardiac nerve traffic, it showed that this measure is not a perfect index (Kollai and Mizsei 1990). After β-adrenergic blockade, there was a reasonable correspondence between RR interval fluctuations and vagal-cardiac neural outflow but only when respiration was controlled. When respiration was not controlled, respiratory frequency RR interval fluctuations bore no significant relation to tonic vagal-cardiac nerve activity (Grossman et al. 1991). Casadei noted a difference between absolute power of the HF component and the normalized power. The former increased, but the latter decreased at the onset of exercise (Casadei et al. 1995).

Does LF Correlate with Sympathetic Tone?

[*Pros*:] Low frequency is thought to be associated with changes of sympathetic outflow. In dogs, an increase in low-frequency power was observed during baroreceptor unloading with nitroglycerin and was prevented by prior bilateral

stellectomy (Rimoldi et al. 1990). In four of ten subjects studied, a significant correlation between sympathetic nerve activity and normalized LF was found (Saul et al. 1990). Malliani and coworkers argued with parallel changes of increased sympathetic activity and LF increase (Malliani et al. 1991); their review and data however have been recalculated and challenged (Eckberg 1997). In decerebrated cats, increased activity of cardiac sympathetic nerves and reflex sympathetic excitation induced an increase in LF and a reduction in HF, the opposite effect occurring in sympathetic reflex inhibition (Montano et al. 1992). Another argument for the correlation of LF and sympathetic outflow came from studies showing synchronous changes of LF and HF oscillations of MSNA recordings and HRV recordings under stimulation with nitroprusside (Pagani et al. 1997).

[*Cons*:] Pagani reported that propranolol 0.2 mg/kg iv does not reduce normalized 0.1-Hz RR interval spectral power (Pagani et al. 1986). Low-dose scopolamine as cholinergic blocking drug increases LF (Vibyral 1990). In healthy supine subjects there was no significant correlation between myocardial noradrenaline spillover and absolute or relative 0.1-Hz RR interval spectral power (Kingwell et al. 1994). High-dose atropine should block vagal parasympathetic activity and thus increase sympathetic activity. By contrast, high-dose atropine abolished nearly all LF (and HF) in studies (Pomeranz et al. 1985; Koh et al. 1994). Heart rate variability recorded during severe exercise in healthy subjects (a condition known to increase sympathetic outflow) has been shown to decrease (Casadei et al. 1995). Two groups measured RR interval spectral power before and after high spinal anesthesia. Sympathetic blockade in the supine position did not alter absolute or relative 0.1-Hz RR interval spectral power significantly (Hopf et al. 1995; Introna et al. 1995). Short-term β-blockade can increase HF power (Jokkel 1995). In a mice model, cardiac-specific GTP-binding protein, $G_s\alpha$, which plays an important role in β-adrenergic signal transduction, was overexpressed. Contrary to expectations, the LF component was reduced in the mutant mice compared to wild-type mice, and the LF/HF ratio was also reduced (Uechi et al. 1998). LF however contains also vagal influence (Eckberg 1997). MIBG-SPECT used to examine postganglionic sympathetic innervation showed reduced activity, whereas frequency-domain and time-domain values did not differ to the controls apart from a subgroup of patients (Druschky et al. 2001).

Some of the studies reporting associations between LF and sympathetic outflow have been criticized. The study of Saul et al. (1990) was not able to show the correlation in six of ten subjects. The study of Pagani et al. (1997) was criticized for not using fixed breath frequencies, using wrong statistic algorithms, and not normalizing the data (Eckberg 1997).

To explain the disconcordance of LF and known conditions with high sympathetic outflow, the hypothesis was developed stating that under conditions of complete receptor saturation or blockade, the modulation of autonomic activity is abolished and the relevant frequency band disappears (Malik and Camm 1993). The loss of LF in chronic heart failure can be viewed as evidence for a decrease in modulation of sinoatrial discharge, which may be due to constancy of sympathetic and parasympathetic firing rates or to a loss of pacemaker responsiveness to neurally released noradrenaline and acetylcholine (Notarius and Floras 2001).

In patients with severe heart failure, the LF pattern can be virtually absent in muscle sympathetic nerve activity, which correlates again close with HRV LF (van de Borne et al. 1997). A breakdown of fractal properties of HRV is often related to an unfavorable prognosis. In a study using an experimental stress model, fractal breakdown was associated with simultaneous activation of SNS and PNS (Tulppo et al. 2005).

In rats, there is a correlation between sympathetic nerve activity and blood pressure in power spectra at 0.4 Hz, but not with heart rate (where the majority of spectral power was lower than 0.4 Hz) (Brown et al. 1994).

Baroreflex Gain

The baroreflex manages blood pressure homeostasis in different body positions. Baroreceptors located in major systemic arteries monitor blood pressure. If PB decreases, sensory impulses transmitted to the vasomotor center in the brainstem also decrease, resulting in adjustment of ANS activity to increase heart rate and vascular resistance. This basic reflex can be attenuated by higher brain centers and the limbic system. Blushing during an embarrassing moment involves the vasomotor center but originates in the frontal association cortex, much like fainting reactions, cold sweating, and racing heart rate.

The baroreflex feedback theory describes low oscillations observed as a consequence of changes in blood pressure (e.g., due to respiration). Arterial baroreceptors detect such changes and lead the central nervous system to adjust the heart rate through both fast vagal action and slower sympathetic action. The baroreflex also adjusts sympathetic outflow to the vasculature and therefore peripheral resistance, leading to a change in blood pressure in an attempt to buffer the initial change in blood pressure (Malpas 2002). The critical point is that the combination of a series of time delays present among baroreceptors, the central nervous system, sympathetic outflow, and the response of the vasculature means that the input change in blood pressure results in an output change in vasculature resistance that is slightly delayed in time. Instead of buffering the initial change in blood pressure, this leads to the development of yet another change in blood pressure. This was showed in a model that accounted for oscillations at 0.1 Hz in the human (DeBoer et al. 1987). Sympathecomy or combined alpha- and beta-adrenergic blockade leading to reductions of the spectral power at 0.1 Hz may be interpreted as interruption of the reflex feedback loop (Malpas 2002). Some refined models have been presented to show this. Linear models seem to require strict relationships between the vasculature and the central nervous system (Burgess et al. 1997). A nonlinear model, however, needed only a set of rather mild assumptions to show a similar behavior of the system (Ringwood and Malpas 2001). But even if the baroreceptor reflex is removed by denervation, a reasonable amount of variability remains around this frequency (Cerutti et al. 1994; Julien et al. 1995). This can be due to other reflex pathways or central nervous system components (Malpas 2002).

LF spectral power is influenced by the baroreflex function, cardiac beta-adrenoreceptor sensitivity, post-receptor signal transduction and parasympathetic modulation (Adamopoulos et al. 1992; Saul et al. 1990). By contrast, values for cardiac noradrenaline spillover are not affected by postsynaptic mechanisms, but may be influenced by changes in reuptake of noradrenaline (Notarius and Floras 2001).

Frequency-domain measures have been challenged as too insensitive for individual measures because of relatively large intersubject variability and dependency on the measurement conditions (Gregoire et al. 1996; Notarius and Floras 2001).

Coupling between the three main rhythms of respiration, HF and LF oscillations were determined to be weak (Janson et al. 2001). However, they tend to synchronize (Prokhorov et al. 2003). The high degree of nonlinear coordination between HRV and SPV may be mainly influenced by the respiratory component. If this was filtered, the coupling was significantly reduced in an animal model (Gonzalez et al. 2000).

Conclusion

In a critical review, Eckberg considers the existing evidence about how heart rate variability reflects the sympathovagal balance. He comes to the following conclusions:

- Vagal contributions to baseline LF RR interval fluctuations are great, and there is no evidence that baseline LF RR interval spectral power is related quantitatively to sympathetic-cardiac nerve traffic.
- Most evidence refutes the notion that LF RR interval spectral power tracks baroreflex-mediated changes of sympathetic nerve activity.
- Baseline respiratory frequency RR interval fluctuations are related significantly but imperfectly to the level of human vagal-cardiac nerve traffic.
- Moderate changes of arterial pressure, which alter vagal-cardiac nerve activity, do not change HF RR interval fluctuations, and changes of breathing frequency and depth, which profoundly alter HF RR interval fluctuations, may not change vagal-cardiac nerve activity at all.
- Some physiological interventions provoke parallel, not reciprocal, changes of vagal and sympathetic nerve activity, and other interventions, such as baroreceptor stimulation, provoke reciprocal changes but only over a very limited range of arterial pressure.
- Measures of sympathovagal balance are not valid in heart failure patients and may not be valid in hypertensive or sleep apnea patients.
- Neither upright tilt nor light or heavy exercise provokes the reciprocal changes of sympathetic and vagal nerve traffic predicted by calculations of sympathovagal balance.

He does not dispute the value of heart rate variability in stratifying risk in patients with cardiovascular diseases or in better understanding autonomic mechanisms, but argues against using the term “sympathovagal balance” because this relationship is not proven (Eckberg 1997).

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Chapter 6
Pathophysiological and Systems Biology Considerations

Outline: In this chapter some general arguments about the significance of changed time series patterns as a surrogate of a system are presented. I introduce the idea of decreased heart rate variability as a sign for illness and emphasize specially entropy and other nonlinear parameters. In the next section several subsystems of the body that may influence heart rate variability are discussed. I include commonly known (and already mentioned) elements, like the autonomic nervous system, the lung and the circulatory system, as well as other peripheral parts, such as the endocrinological system in general or the immune system. This discussion will be essential for the next chapter, in which I present and discuss different models for heart rate variability.

General Considerations

Systems biology is a biology-based interdisciplinary field of study that focuses on complex interactions within biological systems, using a more holistic perspective approach to biological and biomedical research. Usual tools in systems biology are mathematical models and time series analysis. Basically, systems biology analyses different parts of the body as a kind of network. Most research efforts are on the subcellular level, where gene networks or metabolic networks are summarized and then analyzed with the help of sophisticated network methods or mathematical models, which in turn are compared to real work data. Network analysis or models can be used even if the quantitative relationships are not known (using Boolean networks). Usually they can be used quantitatively even if some exact data are lacking.

Investigating quantitative relationships can also be based on different kind of models. Few models rely on linear quantitative relations between their parts; most however include at least some nonlinear relations. On an abstract level, network nodes can be characterized as oscillators that resonate all the time around one or

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more mean values. Through this, a network of coupled (nonlinear) oscillators is generated. Understanding a larger number of coupled oscillators is still a challenge for theoretical physicists.

Usually, systems biology is epistemological; it is seen as a method of generating, not testing, hypotheses. Therefore, results are only valid if they can be replicated with real observational data. The evidence increases strikingly when real systems and model systems are challenged with the same kind or perturbations and react in the same way, something regarded as a gold standard in modeling today.

Time series of biological markers are considered surrogates of the particular system. Frequently the markers investigated include blood samples with different molecules and physical measurements like heartbeat, blood pressure, and EEG but also gait and eye blinking. An isolated marker can give information if it is elevated over a certain level that has been defined as abnormal or pathological. This applies to most but not all markers (e.g., not gait), as well as to heartbeat, for which tachycardia (heart frequency over 100) or bradycardia (heart frequency below 60) is regarded as pathological. There are exceptions, for instance, athletes who frequently have frequencies below 50, which are not seen as pathological. Heart frequencies over 100 are only considered pathological if they are measured without physical activity and psychic stress.

Small time series can also give information about a system. If they are not stationary, they might indicate increasing pathological states but also a return to normality. For instance, isolated measured values of kidney markers like creatinine may give less information about the system compared to short time series where the slope of the curve is more informative than the absolute value. In acute kidney damage, fast increasing creatinine is important, even if the absolute level is (still) low; stationary pathological value might indicate stabilizing illness even if the absolute level is high; and a negative slope might indicate recovery even if it is far from normal values.

For many decades now, scientists and clinicians have ignored other qualities of time series. These are usually analyzed according to very simplistic criteria: pathological or not, stationary, or increasing or decreasing? Inherent characteristics such as variability have been ignored. It was only in the 1990s that scientists began to look at further properties of times series and proposed new ideas. Ari Goldberger suggested that increased regularity of signals may represent a decomplexification through illness. Thus, health is more complex and illness shows decreased variability, caused by reduction in the number of structural components and alterations in the coupling function between these components (Lipsitz and Goldberger 1992; Goldberger 1997). This notion has been extensively used in the analysis of heart rate variability. Pincus hypothesizes that decreased complexity and greater regularity correspond to greater component autonomy and isolation. “The idea is that healthy systems have good lines of communication, marked both by numbers of external influences that interact and by the extent of interactions. Contrapuntally, disease and pathology would represent system decoupling and/or lessening external inputs, in effect isolating a central system component from its ambient universe” (Pincus 1994, p. 162). This again leads to decreased reaction in the organism to changing

challenges; this decrease is therefore not only a surrogate but a relevant (secondary) pathogenetic factor. Complexity of physiological control systems serves an important purpose; that is, it enables the organism to mount a focused response on a number of different time scales in order to return to a new steady state (Lipsitz 2002).

Coming from a complexity theory paradigm, another group has proposed HRV as measure of the degree to which a system provides flexible adaptive regulation of its component systems (Thayer and Friedman 2002). They describe their view as follows: "When processes mutually constrain one another, the system as a whole tends to oscillate spontaneously within a range of states. The various processes are balanced in their control of the whole system, and thus the system can respond flexibly to a range of inputs. However, such systems can also become unbalanced, and a particular process can come to dominate the system's behaviour, rendering it unresponsive to the normal range of inputs (…) A system, which is 'locked in' to a particular pattern, is dysregulated" (Thayer et al. 2012).

Other scientists observed both decreased and increased complexity and approximate entropy in several disease states (Vaillancourt and Newell 2002). Of particular importance is the concept of changed variability in age, based probably on reduced number of system components and reduced coupling between elements (Lipsitz and Goldberger 1992; Vaillancourt and Newell 2002). Increased complexity was observed mainly in endocrinological diseases. Patients with acromegaly induced by increased levels of growth hormone showed growth hormone release patterns over 24 h with higher approximate complexity compared to healthy controls (Hartman et al. 1994). Similar changes were observed in patients with Cushing's syndrome, where time series of ACTH and cortisol concentration levels increased approximate complexity compared to healthy persons (Van den Berg et al. 1997a). Older males showed a more complex pattern of releasing luteinizing hormone and testosterone (Pincus et al. 1996). According to Kauffman's argument about life being at the edge of chaos, some authors argue on an abstract level that "health is defined by a certain distance from thermodynamic equilibrium; too close (decreased variation, too little energy dissipation, low entropy) or too far (increased variation and energy dissipation, high entropy) each represents pathological alterations" (Buccelletti et al. 2012, p. 1).

Some Physiological Systems with Influence on Heart Rate Variability

Sinoatrial Node

The pacemaker cells of the sinoatrial node are usually regarded as a population of electrically coupled oscillators, synchronized by a mechanism of mutual entrainment or phase locking (Bergfeldt and Haga 2003). Cardiac mitochondria itself can behave as individual oscillators and interact. When the mitochondrial network of cardiomyocytes is stressed to a critical state, the cardiomyocytes exhibit

high-amplitude self-sustained oscillations. The temporal behavior of the mitochondria membrane potential in cardiomyocytes under physiological conditions is oscillatory and shows a power law with a spectral component (Aon et al. 2006).

Left ventricular assist devices were used in two patients with stable heart failure. Through this, the influence of cardiac baroreceptors was diminished, and thus, the oscillations were determined mainly by the LVAD device. The normal heart continued to be innervated and controlled by the autonomic nervous system. LF, which was absent in the severe heart failure patients, was restored during the circulatory support with the LVAD. This restored LF was evident in the absence of any similar oscillation in blood pressure. The authors concluded that LF oscillations represent partly a central oscillation in autonomic outflow, which works without perturbations of blood pressure oscillations, albeit blood pressure oscillations can contribute to the LF component (Cooley et al. 1998).

Respiratory System

There is good evidence from both human and other animal experiments that a major cause of sinus arrhythmia is central coupling of respiratory drive to cardiac-vagal motor neurons (Pilowsky 1995; Hayano et al. 1996; Malpas 2002). Inputs from medullary respiratory neurons to medullary sympathetic premotor neurons are a possible mechanism (Pilowsky 1995). Cheyne–Stokes respiration patterns are present in more than 50 % of patients with congestive heart failure (Sin et al. 1999). Probably it is an effort to improve the efficacy of pulmonary gas exchange by entraining heartbeats with phasic hyperpnea within each cycle length of Cheyne–Stokes respiration (Yasuma and Hayano 2004). Cheyne–Stokes respiration again can affect not only sinus rhythms but also AF, which otherwise does not react to normal ventilation, probably due to modulation of the atrioventricular nodal refractory period and concealed conduction (Leung et al. 2005).

Endocrinological System

An increased number of CYP11B2-344T alleles in subjects with increased sodium excretion led to increased LF/HF ratio, but not in carriers of the AT1R 1166C allele. This result is discussed as an effect of an expanded plasma volume increasing the parasympathetic tone (Stolarz et al. 2004).

17 patients with hypertension due to primary or secondary hyperaldosteronism were compared to 11 primary hypertensive subjects and 10 healthy controls. Frequency-domain variables of systolic and diastolic blood pressure were measured in supine and passive 60° head-up tilt position (20, respectively 10 min measuring each). LF and LF/HF were higher in patients with hypertension regardless of etiology (Veglio et al. 1995).

There is a reverse relationship between cortisol and HRV in healthy adults (Thayer and Sternberg 2006).

Controlled hypoglycemia in an experimental study (with 15 min HRV) caused decrease in HF and SD1 (derived from Poincaré plots), but no (significant) changes in LF and SD2 (Koivikko et al. 2005).

Sex hormones like estrogens might activate the parasympathetic system, and progesterone might activate the sympathetic nervous system (Saeki et al. 1997; Sato and Miyake 2005).

The neuropeptides orexin A and orexin B are produced by about 7,000 cells in the human brain. Orexin pathways project widely to the entire neuroaxis excluding the cerebellum. The densest staining of orexin-immunoreactive nerve endings in the brain is found in the paraventricular nucleus of the thalamus, the arcuate nucleus, the locus coeruleus (containing noradrenergic neurons), dorsal raphe (containing serotonergic neurons), and tuberomammillary nucleus (containing histaminergic neurons) (Date et al. 1999).

Orexins have a role in regulating autonomic function. Injections increase heart rate and blood pressure, which indicates that orexins physiologically stimulate sympathetic outflow and increase food intake and metabolic rate (Sakurai 2007).

In recent years, oxytocin's role in human social behavior was investigated in several studies, mostly on observable social behaviors. In a study with 26 male participants, application of oxytocin did not have an effect on mood, but HRV changed. These effects were visible in HF and detrended fluctuation scaling exponent (but rather moderate) (Kemp et al. 2012).

Immunological System

Inflammation is a normal response to disturbed homeostasis caused by infection, injury, and trauma. The host responds with a complex series of immune reactions to neutralize invading pathogens, repair injured tissues, and promote wound healing (Baumann and Gauldie 1994). The beginning of inflammation is characterized by release of pro-inflammatory mediators including, interleukin (IL)-1, adhesion molecules, vasoactive mediators, tumor necrosis factor (TNF), and reactive oxygen species. The early release of pro-inflammatory cytokines by activated macrophages has a crucial role in triggering the local inflammatory response. Excessive production of cytokines, such as TNF, IL-1beta, and high-mobility group B1 (HMGB1), however, may be more damaging than the inciting event, causing diffuse coagulation, tissue injury, hypotension, and death (Wang et al. 2001). The inflammatory response is balanced by anti-inflammatory factors including the cytokines IL-10 and IL-4, soluble TNF receptors, and transforming growth factor (TGF beta). Although simplistic, the pro-/anti-terminology is widely used in the discussion of the complex cytokine network. Apart from their involvement in local inflammation, TNF and IL-1β are signal molecules for activation of brain-derived neuroendocrine immunomodulatory responses. Neuroendocrine pathways, such as the hypothalamic–pituitary–adrenal

(HPA) axis and the sympathetic division of the autonomic nervous system (SNS) (Rivest 2001; Elenkov et al. 2000), control inflammation as an anti-inflammatory balancing mechanism. The host thereby mobilizes the immunomodulatory resources of the nervous and endocrine systems to regulate inflammation (Pavlov et al. 2003).

The cross talk between the immune system and the brain relies on classical humoral pathways and more recently discovered neural pathways.

The neural mechanism relies upon the activation of vagus nerve afferent sensory fibers that communicate to the brain that inflammation is occurring. Immunogenic stimuli activate vagal afferents either directly by cytokines released from dendritic cells, macrophages, and other vagal-associated immune cells or indirectly through the chemoreceptive cells located in vagal paraganglia. For instance, intraperitoneal administration of endotoxin can induce IL-1β immunoreactivity in dendritic cells and macrophages within connective tissues associated with the abdominal vagus nerve and subsequently in vagal paraganglia (Goehler et al. 2000) and afferent fibers (Goehler et al. 1999). Visceral vagus afferent fibers, residing in the nodose ganglion, terminate primarily within the dorsal vagal complex (DVC) of the medulla oblongata (see Chap. 3). The transmission of cytokine signals to the brain through the vagal sensory neurons depends upon the magnitude of the immune challenge. Subdiaphragmatic vagotomy inhibits the stimulation of the HPA axis (Gaykema et al. 1995) and noradrenaline (NE) release in hypothalamic nuclei (Ishizuka et al. 1997) in response to intraperitoneal administration of endotoxin or IL-1β. Vagotomy fails to suppress high-dose endotoxin-induced IL-1β immunoreactivity in the brain (Van Dam et al. 2000) and increases blood corticosterone levels (Hansen et al. 2000). Intravenous endotoxin administration induces expression of the neural activation marker c-Fos in the brainstem medulla, regardless of the integrity of the vagus nerve (Herrmann et al. 2001). It is possible that the vagal afferent neural pathway plays a dominant role in mild to moderate peripheral inflammatory responses, whereas acute, robust inflammatory responses signal the brain primarily via humoral mechanisms (Pavlov et al. 2003).

Acetylcholine is an important neurotransmitter and neuromodulator in the brain. It mediates neural transmission in the ganglion synapses of both sympathetic and parasympathetic neurons and is the principle neurotransmitter in the postganglionic parasympathetic/vagal efferent neurons. Acetylcholine acts through two types of receptors: muscarinic (metabotropic) and nicotinic (ionotropic). In addition to the brain and "wire-innervated" peripheral structures, the RNA for these receptor subtypes (muscarinic) and subunits (nicotinic) has been detected on mixed populations of lymphocytes and other immune and nonimmune cytokine-producing cells (Sato et al. 1999; Tayebati et al. 2002). Most of these cells can also produce acetylcholine (Kawashima and Fuji 2000). Acetylcholine significantly and concentration dependently decreases TNF production by endotoxin-stimulated human macrophage cultures via a posttranscriptional mechanism. Acetylcholine is also effective in suppressing other endotoxin-inducible pro-inflammatory cytokines, such as IL-1β, IL-6, and IL-18, by a posttranscriptional mechanism; release of the anti-inflammatory cytokine IL-10 from endotoxin-stimulated macrophages is not affected by acetylcholine (Borovikova et al. 2000; Wang et al. 2004). In experimental models for sepsis, myocardial ischemia, and pancreatitis, vagus stimulation blocked cytokine activity (Mioni et al. 2005; Saeed et al. 2005; van Westerloo et al. 2006).

Changed activity of the vagal system thus modulates the inflammatory response significantly, which can be blocked or enhanced by local or systemic use of transmitter substances like noradrenaline, acetylcholine, or nicotine. But this is no one-way street; inflammatory influences can also enhance or block the sensory vagus activity. Pro-inflammatory cytokines released upon immune challenge can activate vagal afferent signaling and subsequent direct or indirect (through NTS neurons) activation of vagal efferents in the DMN. Thus, the sensory vagal afferents, together with the regulatory vagus efferents, form an inflammatory reflex that continually monitors and modulates the inflammatory status in the periphery (Tracey 2002). Consequently, animals with bilateral cervical vagotomy are more sensitive to endotoxemic shock (Pavlov et al. 2003). The cholinergic anti-inflammatory pathway can also be activated by the area postrema, e.g., via increased blood concentrations of IL-1beta (Herrmann et al. 2001).

Soluble TNF-α receptors and IL-6 correlate (negatively) with time-domain HRV variables (SDNN, SDANN) (Malave et al. 2003; Straburzynska-Migaj et al. 2005; Mani et al. 2009), likewise endothelin 1 (including negative correlations with TP and ULF) (Aronson et al. 2001a). In the same study, TNF-α did not correlate with HRV variables, but also with IL-6 (Aronson et al. 2001b). An association between decreased linear HRV measures and increased CRP, which is again related to increased IL-1 and IL-6, among others, has been observed in several studies (Kon et al. 2006; Araujo et al. 2006; Carney et al. 2007; Ziegler et al. 2008).

In diabetic patients, both in newly diagnosed and in a chronic phase, increased IL-6 was correlated with decreased time-domain (SDNN) and frequency-domain parameters (Lieb et al. 2012), and in another study with decreased E/I ratio in pace breathing (González-Clemente et al. 2007).

In a long-time cohort study (follow-up 15 years), Holter monitoring with linear indices and DFA was associated to inflammatory parameters at baseline. Inverse associations were found between VLF and LF, TP and SDNN with CRP, and IL-6 and WBC. DFA had and inverse association with IL-6 and CRP, and HRT slope to WBC and IL-6. This was observed both for daytime HRV and 24-h HRV (Kop et al. 2010).

It can now be concluded that there is clear evidence for a negative correlation between increased inflammatory parameters such as TNF-alpha, CRP, and IL-6 and decreased heart rate variability. Interestingly, this negative correlation did not attain for classical "parasympathetic" parameters like pNN50, rMSSD, or HF, but rather for more general or "sympathetic" parameters like SDNN, SDANN, TP, VLF, and LF (Haensel et al. 2008) (Fig. 6.1).

Glucose Metabolism

Two different pathways mediate normal insulin signaling in cardiovascular tissues: one that is predominant in metabolic tissues (the phosphatidylinositol-3-OH kinase pathway) and a growth factor-like pathway (mediated by mitogen-activated protein kinase). In cardiovascular tissues, insulin resistance leads to inhibition of the

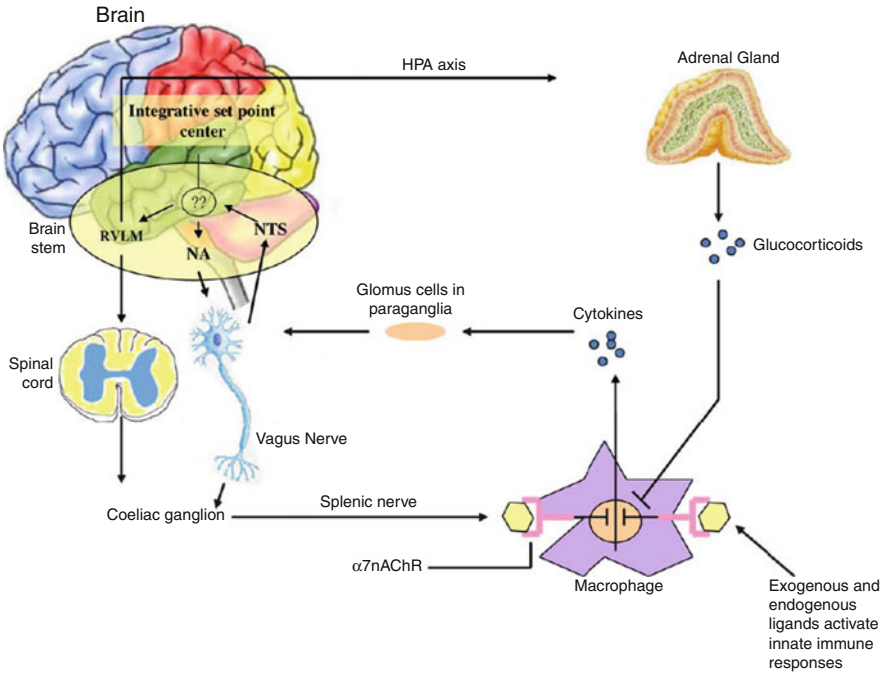

Fig. 6.1 The HPA axis in brain and its influence on the immune system (From Vinik (2012), with permission)

metabolic pathway and to overstimulation of the growth factor-like pathway (Nigro et al. 2006) and might lead to a decrease in glucose uptake, possibly hampering normal cardiac function (van Gaal et al. 2006; Ferrannini and Iozzo 2006).

Ectopic fat storage in the heart, blood vessels, and kidneys can impair their function, contributing to the increased risk in obesity. Besides the cardiac alterations that result from hemodynamic changes and hypertension, excessive lipid accumulation in the myocardium induced by weight gain might be directly cardiotoxic. Accumulation of large amounts of myolipids may result in apoptosis and systolic dysfunction. In peripheral vessels, high amounts of perivascular fat cells could contribute mechanically to the increased vascular stiffness seen in obesity. Periadventitional adipose tissue in particular may regulate the arterial tone of mesenteric arteries, with increased arterial stiffness as consequence. In addition, increased adipose paracrine secretion may lead to vascular smooth muscle cell (VSMC) growth induced by growth factors (van Gaal et al. 2006).

The prothrombotic state in the atherosclerotic process encompasses platelet hyperaggregability, hypercoagulability, and hypofibrinolysis. In obesity and metabolic syndromes, fibrinogen, von Willebrand factor (vWF), and PAI-1 have been studied as markers of the hemostatic and fibrinolytic system and as possible predictors for cardiovascular disease. So far, only PAI-1 levels are increased in obese patients. PAI-1 is expressed in visceral adipose tissue and especially visceral tissue

seems to have up to five times more PAI-1 compared to subcutaneous adipose tissue (van Gaal et al. 2006).

Obesity induces several cytokines and inflammatory markers that might contribute to the cardiovascular outcome in overweight and obese people. It is also associated with increased levels of endothelial cell products such as intercellular adhesion molecule-1 (ICAM-1) (Pontiroli et al. 2004).

The extensive innervation of islets with insulin-producing beta-cells by both parasympathetic and sympathetic neurons and the intimate involvement of the central nervous system in the regulation of metabolism suggest that the CNS might also have an important role in the functional adaptation to changes in insulin sensitivity. Increased insulin release is observed immediately after experimental lesioning of the ventromedial hypothalamus (VMH), and this effect is mediated by increased vagal activity, which can be blocked by vagotomy (Berthoud and Jeanrenaud 1979). Parasympathetic stimulation of insulin release occurs through activation by acetylcholine of the M2 muscarinic receptor on the beta-cell surface. The sympathetic nervous system is also important, with increased activity of the α2-adrenergic component associated with decreased insulin release, whereas increased β-adrenergic activity enhances insulin output (Ahren et al. 1986; Kahn et al. 2006).

Psychological Functioning, Cardiac Health, and HRV

Any challenging circumstances in life can lead to stress. Stress is not unequivocally negative and can lead to both positive and negative physiological consequences. Stress can be defined as any disruption of homeostasis (Miller and O'Callagan 2002), and in the terminology of computational biology, it is also possible to call it perturbations of a system. The main two systems involved in stress reactions in the body are the hypothalamic–pituitary–adrenal axis (HPA) and the sympathetic nervous system (SNS). The HPA axis meets the demands of stress primarily through the synthesis and release of 3 key hormones, corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and a species-specific glucocorticoid, either cortisol (COR) (human, nonhuman primate, swine and dog) or corticosterone (CORT) (rodents). The key organs involved are the hypothalamus, the hippocampus, the anterior pituitary, and the adrenal gland. The HPA axis is a negative feedback system where the end product, cortisol, the transmitter substance of the SNS, noradrenaline and GABA, inhibits the production of the initiating substances (Mathe 2000).

CRH-producing neurons of the hypothalamus are concentrated in the paraventricular nucleus (PVN, about 50–90 % of all neurons) and synthesize CRH due to internal and external stimuli. Interestingly, many of the CRH-containing neurons of the PVN also produce vasopressin. Vasopressin release is thus also under control of plasma cortisol. Vasopressin can also elevate ACTH levels through a distinct receptor system. During chronic stress, CRH and vasopressin release is regulated differentially, and novel stressors can lead to increased ACTH release through vasopressin

even if CRH response is suppressed due to earlier stressors (Aguilera 1998). CRH-containing neurons have also been identified in the hippocampus, amygdale, and cortex (Miller and O'Callagan 2002). The main effect of CRH is in the anterior pituitary, where it induces the release of ACTH and β-endorphin through a common precursor protein, pre-opiomelanocortin. ACTH also exerts a negative feedback control on CRH. ACTH again induces release of cortisol, which is produced from the precursor cholesterol in the zona fasciculata/reticularis zone of the adrenal cortex (Rosol et al. 2001). Apart from the systemic release, glucocorticoids are also released to the medullary area of the adrenal, where they regulate the level of the rate-limiting enzyme responsible for the conversion of noradrenaline to adrenaline (Miller and O'Callagan 2002). The sympathetic nervous system reacts to stress with a release of catecholamines, and the degree of sympathetic activity can predict the cortisol response engendered by the same stressor, even in healthy individuals. Subjects showing the greatest sympathetic response to a laboratory stressor also show the highest stress-related plasma cortisol level (Cacioppo et al. 1995).

Troubling life problems and the failure to resolve negative emotional states such as depression may generate continual physiological stimulation, frequently invoking a chronic physiological stress response. The continual stimulation of the sympathetic nervous system and the hypothalamic–pituitary–adrenal (HPA) axis that results from such chronic stress can produce a cascade of negative pathophysiological consequences (Rozanski and Kubzansky 2005).

Normally, elevations of cortisol that are associated with acute stress serve to downregulate HPA function through the negative feedback mechanism. However, under chronic stress, cortisol binds to central nervous system receptors, resulting, paradoxically, in a continued secretion of cortisol (Dallman et al. 2004). This hypercortisolemia is associated with a loss in the normal physiological plasticity of the HPA, as manifested by reduced variability in cortisol secretion measurements and diminution in the normal sensitivity of the HPA axis to exogenous suppression using dexamethasone. The enhanced SNS activation that is evoked under conditions of chronic stress may also lead to elevated resting heart rates and autonomic nervous system imbalance, which might be reflected by HRV changes. In addition, impaired function of the parasympathetic nervous system is known to cause reduced recovery in resting heart rates after exercise, and although the pathophysiological mechanisms remain to be clarified, slow recovery of resting heart rate and blood pressure has been noted in the presence of both acute and chronic forms of psychological stress as well (Rozanski and Kubzansky 2005; Rozanski et al. 2005).

Chronic stress also appears to produce an intrinsic increase in cardiovascular reactivity (i.e., heightened heart rate and blood pressure responsivity to acute physiological stimuli) that has been linked to the activation of an anatomical chronic stress network, involving several specific brain centers (Bathnagar and Dallman 1998). This pathophysiological change may be particularly important in light of recent studies that link heightened cardiovascular reactivity to a greater presence or progression of subclinical atherosclerosis (Barnett 1997; Mathews et al. 1998). Physiological hyperreactivity to acute stressors appears to be characteristic among various states (Rozanski and Kubzansky 2005; Rozanski et al. 2005). Among

cognitive states, job-related worry has been linked to higher cortisol levels on workdays (Schlotz et al. 2004), and preliminary studies suggest that laboratory-induced state rumination may prolong recovery of heart rate and blood pressure after physiological stimulation (Glynn et al. 2002). Similarly, among emotional disorders, both depressed objects (Carney 2005) and those with hostility (Suarez et al. 1998) show heightened neuroendocrine responses in the laboratory compared with normal subjects. Among life situations, chronic job strain as characterized by high job demand but low job latitude (Karasek et al. 1981) has also been linked to prolonged heart rate and blood pressure elevations after work, which, in the case of blood pressure, may last for days at a time (Vrijkotte et al. 2000); to higher cortisol levels while at work (Schlotz et al. 2004); and to both enhanced blood pressure responsivity to pharmacological challenge [phenylephrine] and decreased baroreflex sensitivity (Thomas et al. 2004). The accompanying feeling of being unable to relax after work (Suadicani et al. 1993) may present a clinical mirror of reduced physiological plasticity. Lack of adequate sleep may also result in neuroendocrine activation (Spiegel et al. 1999). Similarly, low social–economic status has been linked to physiological hyperreactivity (Steptoe et al. 2003). The heightened output from the HPA and SNS associated with chronic stress serves to produce a variety of other changes that have been strongly linked to CAD, including signs of increased inflammation, central obesity, hyperinsulinemia, diabetes, hypertension, and endothelial dysfunction (Rozanski and Kubzansky 2005; Rozanski et al. 2005). A significant observation in this field is that different consequences on brief stress stimuli can vary between subjects. Some may show rather big differences in HRV values before and during stress tasks, whereas others have rather small changes. “This result would have been missed entirely had this research been limited to description and discussion of group mean differences in responsitivity to stressors” (Cacioppo et al. 1995).

Visceral fat is possibly a yet underestimated but active element in chronic stress response. Visceral fat is much more endocrinological active than subcutaneous fat tissue. It contains cortisol receptors; increased cortisol production in Cushing’s syndrome leads to increases in abdominal fat. Abdominal obesity has thus been considered a “functional hypercortisolism” (Pasquali and Vicennati 2000).

Cognitive performance is associated with the autonomic function. Increased cognitive activity leads to reductions in heart rate variability (Althaus et al. 1998; van Roon et al. 1995), which reflect vagal withdrawal (Berntson et al. 1997; Denver et al. 2007). In some studies, increased cardiovascular reagibility and cognitive performance was predicted by lower parasympathetic activity shown with decreased HF (DeGangi et al. 1991). The MF band is sensitive to the amount of mental workload (Boucsein and Backs 2000). In fact, MF is more closely related to attentional processing than HF (Althaus et al. 1998). MF reductions have also been shown in complex, more naturalistic attentional tasks like flight simulation or car steering (Mulders et al. 1982; Veltman and Gaillard 1993, 1998). Reduced cardiac inhibition is of particular importance for the establishment of a physiological condition optimal for the mental process required by attentional tasks (Duschek et al. 2009).

HRV and Complexity: Revisited

Even if heart rate variability can be recognized as a complex system, this explanation needs to include more detailed concepts. It has been shown repeatedly that human HRV has a 1/f global scaling behavior independently of behavior. It has been postulated that HRV is a system in a critical state (Struzik et al. 2004), which prevents by antagonistic control mode locking through a permanent far-from-equilibrium-like critical state and thus enhances error tolerance of the system (West 1990; Struzik et al. 2004). Thus, the theory of phase transitions and critical phenomena in nonequilibrium systems should be useful to elucidate the mechanisms of complex heart rate dynamics. Characteristic features at a critical point of a second-order phase transition are the divergence of the relaxation time with strongly correlated fluctuations and the scale invariance in the statistical properties. This has been confirmed in a series of healthy human heart rates (Ivanov et al. 1999; Aoyagi et al. 2003; Kiyono et al. 2004). In addition it has been shown that a healthy human heart rate can exhibit transition-like dynamics between different behavioral states. Strongly correlated fluctuations as typical property of criticality have been observed in heart rate during usual daily activity, but not in sleep or under stress (Kiyono et al. 2005).

Conclusions

Any number of factors may influence the variability of heart rate. Some of these factors have been described and offer a partial explanation. Nevertheless, it is obvious that it is not simply the vegetative nervous system that is reflected in linear (or nonlinear) measures of heart rate variability.

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Part II
Clinical Studies and Applications

Chapter 7
General Mortality

Aging causes a range of physiological changes in the body. Some of them are well known; some of them were recently discovered. For instance, nerve conduction velocity decreases with age (Munsat 1984), hearing is impaired (Mader 1984), and the forced expiratory volume is reduced (Tobin 1981). The interaction between different factors is still insufficiently understood. It is generally agreed that decreased function of different systems is not crucial. Instead of that it is the interplay between the components that causes significant function loss. Function level is often preserved in normal situations, but adaptation to stress – in systems theory termed perturbation – is strongly reduced. There are some subsystems, however, for which variability increases with age (Vaillancourt and Newell 2002). General mortality in a (Western) population is caused mainly by cardiovascular diseases (around 40 %) and cancer (around 25 %), followed by far more seldom diseases like respiratory syndromes, gastroenterological syndromes (all under 10 and 5 %, respectively) (Gaber 2011).

A general idea has been proposed linking higher HRV to better health, not only in association with cardiologic diseases. Weber concluded after an experimental study: "We, hence, posit that low resting HRV may identify healthy subjects at risk for future disease, be it cardiovascular (in the first place), (auto-) immune or other stress-related condition" (Weber et al. 2010).

In one of the early observational studies using nonlinear algorithms, short-term HRV of younger (21–35 years) and older subjects (62–90 years) with quiet and paced respiration in two different positions was compared. Elderly persons showed a reduction in approximate complexity compared to the younger persons (Kaplan et al. 1991). Such changes have been observed in literally all studies independent of illnesses (e.g., Pikkujämsä et al. 1999).

If HRV would be a general surrogate marker for a risk of increased mortality in individual patients, it would be an extreme valuable tool in daily clinical practice. I evaluate existing evidence for and against this notion in this chapter.

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HRV as General Risk Factor in Population Samples

Tsuji investigated the mortality rate of 736 elderly men and women with a mean age of 72 and followed those over 4 years. Seventy-four persons died in this period, most of them not surprisingly because of cardiovascular diseases and cancer. Time- and frequency-domain indices obtained over the first 2 h of a Holter ECG showed an association between mortality and VLF, HF, LF as well as SDNN. Besides HRV parameters, the stepwise multivariable proportional hazards analysis used included age, sex, history of myocardial infarction or congestive heart failure, systolic and diastolic blood pressures, use of diuretics and beta-blockers, diabetes, cigarette smoking, alcohol consumption, the presence of complex or frequent ventricular arrhythmia, and the presence of supraventricular premature beats. LF was the only predictive parameter with hazard ratios (per 1 SD decrement) of 1.70–1.87. A standard deviation change in natural log-transformed low-frequency power was associated with an increase of 70 % in the hazard for all-cause mortality, adjusting for age, sex, and clinical risk factors. LF lower than 218.9 ms^2 was associated with the highest risk (Tsuji et al. 1994). One possible explanation for this was found shortly afterwards of van der Borne. In patients with severe heart failure, the LF pattern can be virtually absent in muscle sympathetic nerve activity, which correlates again closely to HRV LF (van de Borne et al. 1997).

In a study with a 10-year follow-up, 347 subjects >65 were examined at baseline with HRV (Holter monitoring, frequency domain, SDNN, and power slope). Different indices for mortality were found (among them, smoking, prior heart diseases, increased glucose, decreased cholesterol (sic)). SDNN, VLF, and LF were associated with mortality, which was not the case for HF. The slope was the best univariate predictor with a cutoff value of 1.5. In a multivariate regression model, a steep slope of the power-law regression line and congestive heart failure were the only independent predictors, with a relative risk of 2.01 and 1.85, respectively. None of the measures of HRV had a univariate association with cancer death or other nonvascular reasons for death (Huikuri et al. 1998) (Fig. 7.1).

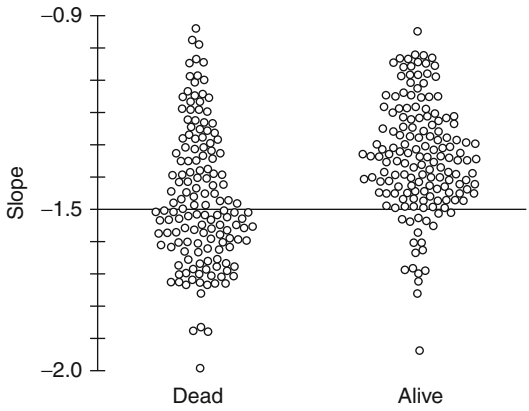

Fig. 7.1 Individual values of the slope of power-law regression of persons who were alive or died during a 10-year follow-up (Huikuri et al. (1998), reproduced with permission of Wolters Kluwer Health)

A particular interesting study in relation to mortality was presented by de Bruyne et al. (1999). The authors examined the association between heart rate variability on a standard 10-s electrocardiogram and cardiac and all-cause mortality in the Rotterdam Study, a population-based cohort study of men and women aged around 55 years, using data collected between 1990 and 1996 (mean follow-up = 4 years). Subjects with arrhythmia or fewer than six normal RR intervals were excluded. SDNN was categorized into quartiles, with 25th, 50th, and 75th percentile values of 9.6, 15.2, and 25.9 ms, respectively, on the whole rather very low values compared to other studies. In all 5,272 men and women participated. Subjects in the lowest quartile of SDNN relative to those in the third quartile had an 80 % age- and sex-adjusted increased risk for cardiac mortality (hazard ratio = 1.8/1.0–3.2). Interestingly, for subjects in the highest quartile of SDNN, an even more pronounced risk for cardiac mortality was present (hazard ratio = 2.3; 95 % confidence interval: 1.3, 4.0). The authors conclude that a 10-s HRV might be feasible to identify older patients with an increased risk for cardiac mortality, but that increased HRV in this study was an even stronger indicator of cardiac mortality than decreased heart rate variability (De Bruyne et al. 1999).

A case-cohort study (the ARIC study) was conducted within a longitudinal study of 15,792 middle-aged men and women. A sample of 900 subjects without prevalent coronary heart disease in baseline was drawn and compared to all subjects with CHD and all subjects who died before follow-up. HRV was determined by a 2-min rhythm strip; RR-distances were measured half-automatized. In addition plasma levels for cholesterol, HDL, LDL, triglycerides, serum insulin, and glucose were determined and diabetes was diagnosed according to the fasting blood glucose levels. Blood pressure, waist and hip circumferences, and carotid intima-media thickness were assessed. Four measures of HRV were determined: SDNN, rMSSD, SDSD, and pNN50, but no frequency-domain measures. Generally, low HRV was associated with an adverse cardiovascular risk profile and elevated risk of death from all causes, including cancer, and of incident CHD. The age-, sex-, and race-adjusted relative risks of cardiovascular mortality in the lowest (< 23.9) compared with the intermediary tertile of SDNN was 2.10 (95 % CI 1.21–3.64). The elevated risk could not be attributed to other risk factors. Relative risk of low SDNN was lower than from the other parameters. The authors conclude that low HRV possibly precedes different manifested diseases (Dekker et al. 2000).

In the Hoorn study, 605 persons between 50 and 75 years were followed over 9 years. 101 individuals died, 43 from cardiovascular causes. HRV indices were based on 3-min measurements while spontaneous breathing, SDNN, LF, Hf, and LF/HF was used. In diabetic subjects, but not in nondiabetic subjects, impaired HRV was consistently associated with an approximately doubled risk of mortality. Cutoff points for impaired autonomic function, taken from the lowest 25th percentile in the NGT group, were 25.7 ms for SDNN, 125 ms^2 for low-frequency LF, and 93 ms^2 for HF. Although significant, the indices of survivors and non-survivors were quite similar, for instance in SDNN, where survivors had 33.2 (18.8–56.5) and non-survivors 27.7 (13.7–55.8) (Gerritsen et al. 2001).

The variability of day-by-day blood pressure and HRV over 26 days was used in a volunteer sample ($n = 2{,}455$) aged between 35 and 96 years. Four hundred and sixty-two deaths occurred over a median of 11.9 years (168 cardiovascular, of them 83 stroke, 85 cardiac, rest noncardiac). In a regression analysis, the following factors were additionally included: sex, age, obesity, current smoking and drinking habits, history of cardiovascular disease, diabetes mellitus, hyperlipidemia, and treatment with antihypertensive drugs. An increase in systolic blood pressure variability was associated with increased hazard ratios for cardiovascular and stroke mortality, but not for cardiac mortality alone. Decreased HRV was associated with cardiovascular and cardiac mortality, but not stroke mortality. The increased hazard ratios were moderate (up to 1.41) (Kikuya et al. 2008).

Kop evaluated participants in the Cardiovascular Health Study, 907 persons with an average age of 71 years and without clinical symptoms of CVD. They used a wide spectre of measures including time domain, frequency domain, DFA, and heart rate turbulence (Holter monitoring) and analyzed it together with inflammation parameters like C reactive protein, IL-6, fibrinogen, and white blood cell count. Participants were followed for up to 15 years. Importantly, ANS reductions correlating with depression and CVD mortality were largely explained with CVD alone. Increased VLF, LF, TP (but not HF), SDNN (<120 ms), DFA, HRT onset, and slope were associated with increased mortality. The predictive value had the two HRT parameters (Kop et al. 2010).

A recent high-quality meta-analysis summarizes much of the existing knowledge. They used a wide search strategy (among others including non-English articles) and retrieved at first 3,613 studies. After different usual quality measures, eight studies remained, including in all 21,988 participants without cardiac disease in baseline and followed-up in cohort studies. Loss of follow-up in all studies was extraordinary low (about 5 %). Studies using indices not used in at least two other studies were excluded resulting in studies on time-domain and frequency-domain measures, but not nonlinear indices. The main finding of the meta-analysis is a robust association between decreased variability and later cardiovascular events. For SDNN a pooled RR of 1.35 was identified, and the authors mention a higher RR for Holter monitoring than for 2 min short-term HRV. Decreased LF was associated with a RR of 1.45 and decreased HF with a RR of 1.32. In addition they performed a meta-regression indicating "that an increase in SDNN of 1 % results in an about 1 % lower risk of the development of fatal or nonfatal CVD." They summarize that individuals with low HRV have about 40 % increased risk of fatal or nonfatal CVD compared with individuals with high HRV (Hillebrand et al. 2013) (Figs. 7.2 and 7.3).

Conclusion

Studies of general mortality display some particular features. Several used extreme short-term measurements, most extreme de Bruyne's study with 10-s stripes. Most evidence points to HRV as a predictor of CVD mortality, but some studies also

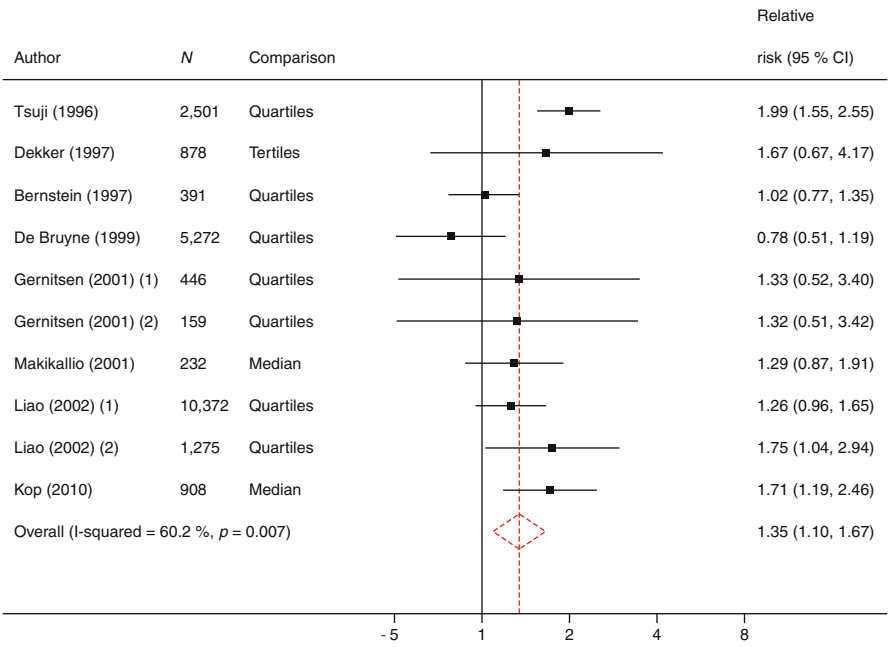

Fig. 7.2 Meta-analysis comparing risk of fatal and nonfatal cardiovascular disease in low versus high heart rate variability measured as standard deviation of NN intervals. Gerritsen and Liao report two cohorts (Reproduced with permission of Oxford University Press from Hillebrand et al. (2013))

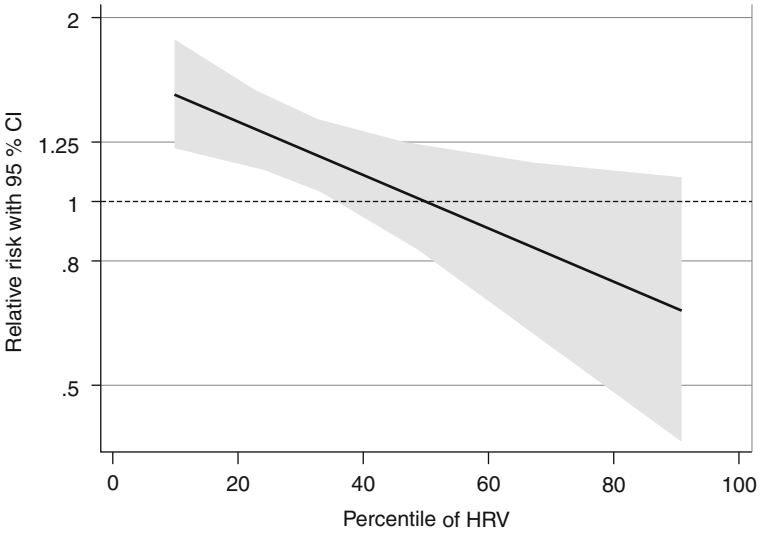

Fig. 7.3 Dose–response meta-regression for the association between heart rate variability measured as standard deviation of NN intervals and fatal and nonfatal cardiovascular disease (Reproduced with permission of Oxford University Press from Hillebrand et al. (2013))

found associations between cancer mortality and HRV. Cutoff values were quite different. The most convincing ones, from probably the best study, are from Kop et al. (2010). They found (among others) a VLF < 1,000, a LF < 340, an SDNN < 120, and a DFA < 1 of significance. Tsuji et al. (1994) found a LF < 218.9, which is quite similar.

Can we recommend using HRV in general population, e.g., by a general practitioner? It depends. As any screening method, HRV has not a high predictive value: many false positive (and false negative) results can be expected. A low HRV should not result in high diagnostic activity or prescription of drugs otherwise not indicated. A high HRV should not lead to a feeling of apparent safety. It is very important not to scare patients. On the other hand, it is probably advisable if low HRV is used to motivate patients to undertake preventive measures and HRV is used to follow patients on the way. In such a context, HRV could be an interesting preventive tool. This would not have negative impact in false positive patients. There is quite clear evidence that preventive measures will result in increasing HRV, which again can be used to motivate patients even more. Taking this into consideration, HRV can be a worthwhile addition for GPs and other medical staff working preventively.

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Chapter 8
Cardiology

Introduction

Heart disease causes more than one-third of all fatalities in humans. This has provoked huge efforts to understand heart physiology and pathophysiology. After decades of research, better diagnostic and treatment options are now available. Several factors have contributed to an enormous rise in life expectancy in the last 20 years. One such factor is certainly the progress in cardiology, in diagnosing, risk stratifying, and treating heart disease.

For scientists (and physicians) interested in HRV, heart diseases offer several interesting characteristics. The heart is obviously a crucial part in the system producing HRV. Using HRV on the heart is the classical approach. But there is also a technical advantage. Fatal arrhythmias can lead to sudden cardiac death. Thus, Holter monitoring techniques have been developed to identify highly pathologic arrhythmias. This has produced an enormous amount of time series, which also have been used for HRV analysis.

There are important caveats. A large number of studies are discussed here, but only few of them are primary HRV studies. Many bigger studies are intervention studies, introducing new medicaments. Only one of several parts in these studies is Holter monitoring. In addition, studies usually investigate several interesting parameters such as LVEF investigated by echocardiography and laboratory results. Many results published as HRV studies are in principle post hoc analysis. That means the research protocol often did not include a hypothesis regarding HRV. Generally, if studies included an HRV hypothesis, this was a minor one next to the larger hypotheses of the given study. Another large group of studies intended to do risk analysis. Consistently, many kinds of parameters were included, often analyzed in rigorous and good statistical models. But again, these studies were not focused primarily on HRV. Another problem is the lack of intervention studies. One would like to find randomized studies that would actually use HRV to stratify patients in the treatment group, to give different treatments according to the assessed risk, whereas the control group would receive state of the art therapy. The various

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studies contribute with virtually hundred thousands of patients, but they do not provide as much scientific insight on HRV as the fewer studies designed specifically around HRV.

In heart failure and after myocardial infarction (MI), complex changes in autonomic function are typical. There is an increase in sympathetic outflow to the heart and to the peripheral vasculature and a reduction in cardiac vagal outflow to the heart. These changes are typically associated with increased plasma noradrenaline, partially because of increased release, partially because of decreased clearance as consequence of the reduced cardiac output (Frenneaux 2004). Other known disturbances include a reduced response of RR intervals to a change in blood pressure (reduced cardiac baroreflex sensitivity (BRS) (Frenneaux 2004). In some studies, far-reaching interpretations about the state of the vagal system are drawn, which probably do not take into account the complexity of ANS changes in heart disease.

Coronary Heart Disease and Myocardial Infarction

The World Health Organization (WHO) (Task Force 1979) defines myocardial infarction as a combination of at least two of the following three characteristics:

- Typical features like chest pain or discomfort
- A rise in cardiac enzymes
- ECG patterns involving Q waves

There is some debate about this definition. Introduction of new more sensitive cardiac biomarkers and imaging technologies might change the definition profoundly, particularly extending it to patients who normally would not fall under this definition although they have ischemic conditions in the heart muscle. Already in the year 2000, the Joint European Society of Cardiology and the American College of Cardiology Committee (Alpert et al. 2000) proposed a new definition for an acute, evolving, or recent MI if at least one of the following conditions is fulfilled:

- Ischemic symptoms
- Development of pathologic Q waves on ECG
- ECG changes indicative of ischemia (e.g., ST changes)
- Percutaneous coronary intervention

Coronary heart disease leads to myocardial ischemia, first in conditions with increased myocardial oxygen demand, in advanced disease also in rest. Myocardial ischemia is often described as an imbalance between myocardial oxygen requirement and myocardial perfusion. Other definitions have been proposed like a mismatch between myocardial perfusion and contractile performance. According to this, in pathological conditions, increased heart rate reduces subendocardial flow and impairs contraction (Fox and Ferrari 2011). Strong clinical evidence exists for the relation between increased heart rate and ischemic episodes, for instance, in one study showing that 89 % of ischemic periods were preceded by increased heart rate of at least 10 beats/min (Panza et al. 1992). Therefore, observed correlations between minimum heart rate in Holter monitoring and SDNN are of interest

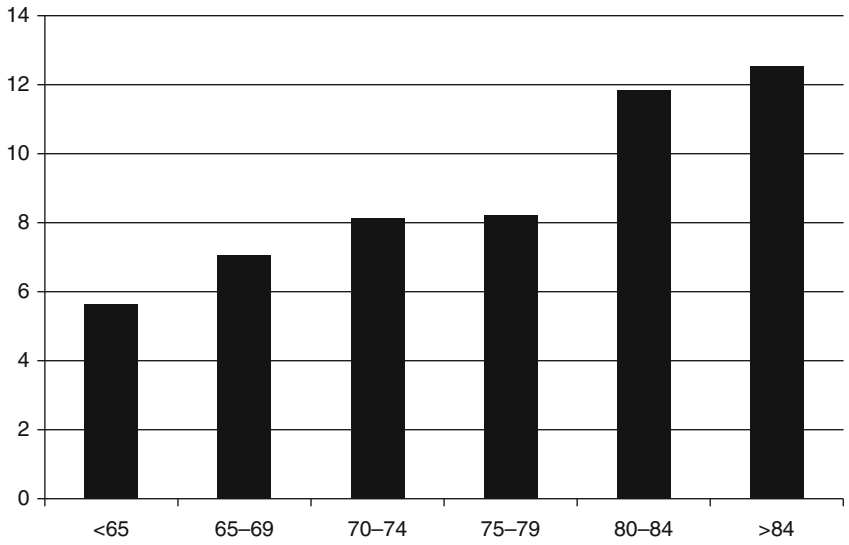

Fig. 8.1 Association between basal heart rate and mortality in patients with coronary artery disease, ejection fraction of less than 40 %, and end-diastolic short-axis internal dimension larger than 56 mm (Modified after Fox et al. (2008), with permission of Elsevier)

(Burr et al. 2006). Classical results have been published of 5,438 participants with coronary artery disease, left ventricular ejection fraction of less than 40 %, and end-diastolic short-axis internal dimension larger than 56 mm, identified by echocardiography. There was a clear relationship between basal heart rate at the beginning of the study and mortality after a mean follow-up of 14.7 years (Fig. 8.1).

HRV and General Prognosis After MI

In a landmark study of HRV and its association to CVD, Kleiger and colleagues analyzed Holter tapes of 808 patients who survived AMI using SDNN. Mean follow-up time was 31 months. Of all Holter variables measured, HR variability had the strongest univariate correlation with mortality. The relative risk of mortality was 5.3 times higher in the group with HR variability (SDNN) of less than 50 ms than the group with HR variability of more than 100 ms (Kleiger et al. 1987). This study was the first to use HRV for this purpose. Several studies were conducted thereafter. In the following section, the focus is mainly on studies made after the Task Force published its recommendations.

In the ATRAMI study, 1,248 patients with a recent (<28 days) MI underwent Holter monitoring with time-domain indices and BRS with phenylephrine technique (arterial cannulation). Patients were in a relatively low-risk group (LVEF 49 % in mean). SDNN <70 ms was an univariate predictor of cardiac 1 and 2-year

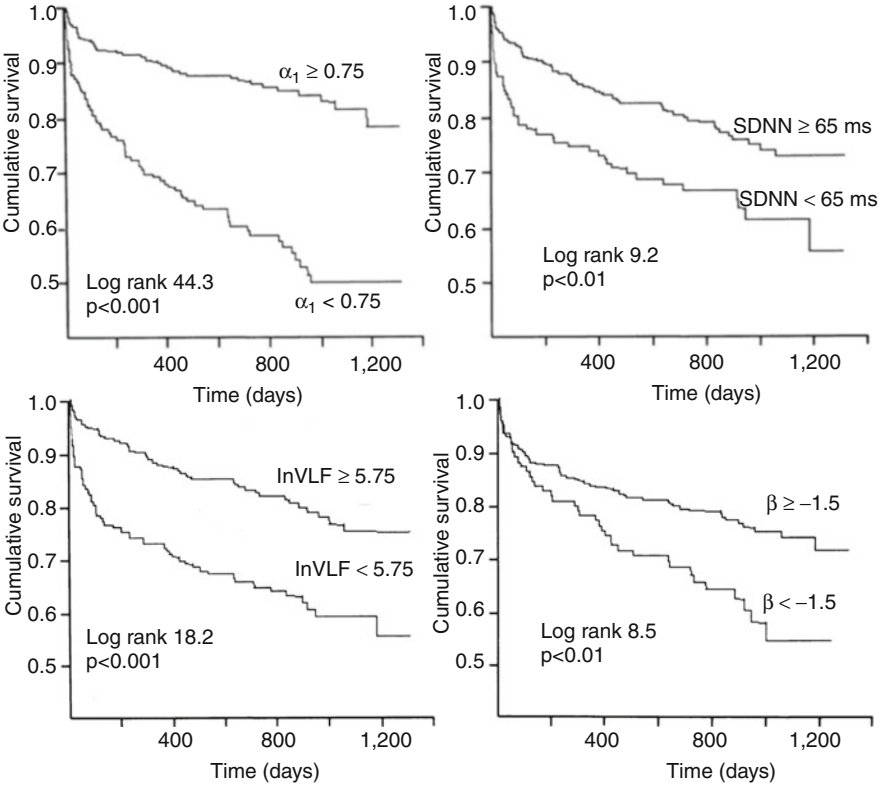

Fig. 8.2 Kaplan–Meier survival curves of patients with cutoff values of α1, SDNN, ln VLF, and β (Huikuri et al. (2000), with permission of Wolters Kluwer Health)

mortality. In a multivariate model, BRS <3 ms/mmHg RR was 2.8 and for SDNN <70 ms 3.2. In combination with an LVEF <35 %, the RR was 11.5 and 5.9, respectively (La Rovere et al. 1988) (Fig. 8.2).

One study observed 64 patients with a first acute myocardial infarction and 31 control subjects. HRV was calculated, and LV systolic and diastolic function was characterized by echocardiography. HRV indices were significantly reduced in patients with restrictive LV filling, whereas ejection fraction correlated only weakly with long-term HRV indices. Restrictive LV filling pattern was the strongest predictor of adverse outcome, independent of HRV and EF but restrictive LV filling pattern correlated with HRV (Poulsen et al. 2001).

Depressed patients with a recent MI ($n=307$) and MI patients without depression ($n=366$) were compared using Holter ECGs. After adjustment for other medical and demographic factors, lnULF (8.52 ± 0.05 vs. 8.66 ± 0.05), lnVLF (6.32 ± 0.06 vs. 6.59 ± 0.065), and lnLF (5.09 ± 5.34 vs. 5.34 ± 0.08) were significantly lower in depressed patients, whereas HF did not differ. There was no difference between patients with minor or major depression, lnULF correlated slightly with lnULF (Carney et al. 2001).

Molnar and colleagues studied 14 SHD survivors, 14 patients matched to the data of the first group and 14 healthy subjects. The mean QTc was significantly longer in control patients and was less in the survivor group. Of the HRV indices, only SDANN and SDNN were significantly lower in the survivor group. Reduced circadian variation was shown in the survivor group. In conclusion, the more advanced time- and frequency-domain measures were not suitable for characterizing survivors as compared to the other two groups (Molnar et al. 2002).

On univariate analysis, patients with HRT category 2 (i.e., TO $\geq$ 0 % and TS $\leq$ 2.5 ms/R-R interval) had a 4.4- to 11.3-fold risk of subsequent death within 2 years compared with patients with normal HRT. The risk of subsequent deaths associated with HRT category 2 was consistently as high as in patients with left ventricular dysfunction. HRT as prognostic factor was independent of HRV, LVEF, or arrhythmias (Bauer et al. 2008). Persistent impairment of HRT after percutaneous coronary intervention in patients with incomplete reperfusion implies prolonged baroreflex impairment and is consistent with poor prognosis (Sade et al. 2003).

HRT has been used in several large postinfarction studies and is discussed as a strong electrocardiographic risk factor. With a modified HRV algorithm (heart rate turbulence, which analyzes changes in heart rhythm after premature beats), it was possible to identify risk populations (Barthel et al. 2003).

Three thousand seven-hundred and seventeen post-MI patients were enrolled for an intervention study with azimilide. Placebo patients with low HRV had a significantly higher 1 year's mortality than patients with higher HRV. HRV was determined with the HRV triangular index. HRV <20 was regarded as high risk, > 20 as low risk (Camm et al. 2004).

In 463 post-MI patients, Holter monitoring with analysis of SDNN, rMSSD, LF, HF, and TP revealed an association to both overall survival and sudden death. Variables indicating a bad prognosis were SDNN <50 ms, rMSSD <20 ms, Lf/HF >2, non-sustained ventricular tachycardia, and left ventricular ejection fraction <40 %. Patients after successful revascularization had higher indices. LF/HF >2 and SDNN <50 ms had the same relative risk as LVEF (Balanescu et al. 2004).

In another study, patients 70–120 days after MI were invited to an intervention with antiarrhythmic treatment with a follow-up of 362 $\pm$ 241 days. Seventy-nine patients died during this period. Holter monitoring with time-domain, frequency-domain, and nonlinear measures (alfa1, DFA, and Poincaré dimension SD12) was used. Increased daytime SD12 had the strongest association with mortality. In multivariate analysis, increased SD12, decreased ULF, a history of prior MI, or congestive heart failure had the strongest associations in the model. The authors conclude that decreased long-term HRV and increased randomness of heart rate are each independent risk factors for mortality after MI (Stein et al. 2005).

In a trial comparing depressed patients with CHD and a recent MI and a nondepressed group of cardiac patients with similar conditions (inclusion criteria to the ENRICHD study), Holter ECG were taken; lnVLF was lower in the depressed group. Depressed patients had a higher mortality (hazard ratio 2.8), which dropped to 2.1 when low lnVLF was included into the model. This was interpreted to mean that low HRV partially mediates the effect of depression on survival (Carney et al. 2005).

Table 8.1 HRV and general mortality after MI

N	Observation	Method	Cutoff	RR	Source
808	31 months	SDNN	<50 ms	5.3	Kleiger et al. (1987)
715		Frequency domain		2–4	Bigger et al. (1993)
1248	1, 2 years	SDNN	<70 ms	3.2 (1.42–7.36)	La Rovere et al. (1998)
463		SDNN, RMSSD, LF/HF	<50 ms		Balanescu et al. (2004)
			<20 ms		
			>2		

In a cohort study after myocardial infarction, a Holter ECG approach was used to measure traditional HRV values and deceleration capacity. Deceleration capacity was superior to LVEF and SDNN (Bauer et al. 2006).

In a population-based study including 4,263 individuals followed up for 10 years, there was a significant association between HRV indices and CHD deaths. Adjusted for age, gender, race, education, smoking, diabetes, prevalent CHD, treated hypertension, and body mass index, the following significant associations with relative risk (hazard) of CHD death were found: increased short-term SDNN: 1.1 % lower risk ($p=0.06$); increased VLF: 4.8 % lower risk ($p=0.003$); decreased Poincaré ratio: 5.9 % lower risk ($p=0.003$); and increased DFA1: 8.4 % lower risk ($p<0.001$) (Mozaffarian et al. 2008).

A study focused on the association of fibrinogen, a known risk factor for coronary heart disease, and indices of 24-h HRV. Included were 559 employees of an airplane manufacturing plant between 17 and 63 years, mostly men. The study calculated nighttime RMSSD and correlated it with fibrinogen. Night-time RMSSD explained 1.7 % of the variance of fibrinogen ($p<0.001$), with a stronger correlation in women (Von Känel et al. 2009).

Hayano introduced a new nonlinear index, non-Gaussianity index (λ), and used it in a study including 570 post-AMI patients following them up for 2 years. The unadjusted Cox hazards regression analysis revealed that decreases in SDNN and DC were associated with an increased risk of recurrent nonfatal AMI, while DFA α1, HRT, and λ25 s had no predictive power for the recurrence. All HRV indices, with exception of λ25 s and abnormal HRT, predicted increased risk of both cardiac and noncardiac death, while increased λ25 s predicted increased risk of only cardiac death but not noncardiac death (Hayano et al. 2011) (Table 8.1).

Angina Pectoris

Twenty-five patients with stable angina pectoris without previous MI were analyzed with Holter ECG using nonlinear measures. They were compared with 20 healthy controls. A filter was used to eliminate noise, artifacts, and premature beats. The group used the fractal dimension with Hurst exponent and DFA. The short-term, but not the long-term, fractal scaling exponent of DFA (α1) was significantly lower in the patient group. AP patients had a higher fractal dimension (Krstacic et al. 2001).

Six-hundred and forty-one patients with stable angina pectoris were analyzed with the help of HRV spectra. In the follow-up period (mean 40 months), 27 died of cardiovascular events and 26 developed nonfatal MIs. HRV spectra did not predict nonfatal MI, but cardiovascular mortality (total power, HF, LF, VLF) LF/HF ratio was not related to prognosis. Use of metoprolol increased HRV (Forslund et al. 2002).

In a study including 531 patients with unstable angina pectoris, the patients were grouped in quartiles according to their CRP levels. The upper CRP quartile had significantly lower HRV values. Especially VLF and SDNN were significant predictors. The authors conclude on a significant relationship between inflammation and HRV parameters (Lanza et al. 2006).

In a recent study, 809 patients with AP were followed 9 years. Inclusion criteria were age below 70 and a typical history of stable angina pectoris. Twenty-four-hour ambulatory long-term electrocardiographic registrations including analyses of ST segment depression, arrhythmias, and heart rate variability within the time and frequency domains and by the differential index were performed. Independent predictive variables were among others age, female gender, fasting blood glucose, serum creatinine, and leukocyte counts but not HRV (Kahan et al. 2013). This is a very important negative study regarding HRV. The publication fails to provide some details regarding data acquisition and processing and does not contain the exact HRV data. Regarding the diagnostic prediction in this patient group, HRV is disappointing, but this might be because these patients had already low HRV indices at inclusion time.

Chronic Heart Failure

Introduction

Heat failure is a disease with increasing incidence and prevalence. Thought to be incurable earlier on, new treatment approaches have appeared more recently and have partially changed its trajectory from a fatal to a chronic disease. Treatment up to now was focused on hemodynamics in acute situations, but newer treatments focus on the chronic disease. Increased understanding of pathophysiological mechanisms offers new treatment options, including direct targeting of intracellular proteins, delivering genes to repair enzyme abnormalities, replacing cell populations, or implanting microprocessors. Many of these advances come from insights into the intracellular signaling pathways that control cardiac hypertrophy and dilation, myocardial energetics, cellular calcium signaling, and the contractile machinery itself (Mudd and Kass 2008).

Heart failure develops when the heart can no longer provide adequate blood flow and/or pressure to meet the body's demands. This failure triggers countermeasures, including the retention of salt and water by the kidneys, the stimulation of the body's organs by neurohormones, and the activation of intracellular signaling cascades in

the heart and vasculature that alter cellular and organ morphology and function (Mudd and Kass 2008). These counterbalancing effects may initially stabilize the situation, but they contribute in a longer run to deterioration and fatal outcome. About 50 % of patients end up in cardiac dilation with contractile failure (also called systolic heart failure), the other half ending up often with an hypertrophied heart and in a normal contraction but nevertheless diminished cardiac output (also called diastolic failure).

As in most diseases, intervention will be more efficacious if it is done early. Traditional approaches for the early identification of pathophysiological changes are not sufficient (Gerszten and Wang 2008). At the same time it is well known that heart failure results in a variety of heart rhythm abnormalities. Many of them are well known, but others might be less obvious. Heart rate variability has been shown to contribute in this challenging diagnostic area.

There is considerable uncertainty as to whether or not HRV can show real changes of SNS in heart failure. The sinus node has changed responsiveness on adrenergic inputs. HRV interpretations regarding SNS activity in chronic heart failure should therefore be interpreted with caution (Piccirillo et al. 2009; Shen et al. 2012).

Pathophysiology and Phenomenology

Heart failure is as mentioned, a clinical symptom resulting from complex interactions between initial myocardial insults and reactive, compensatory processes. Patients progress often from a clinically silent state, in which changes in the heart muscle already occur while cardiac output is preserved. This includes changes in cellular function to normalize ventricular wall stress, e.g., by hypertrophy. Heart failure leads to a chronic activation of barosensitive sympathetic efferents and consecutive increased (real) SNA. Because of decreased effect of the myocardium, this does not lead to hypertension (Guyenet 2006). In response to pressure-overloaded conditions, the heart reacts with remodelling and ventricular hypertrophy due to addition of myofibril units, which leads to a lateral expansion of the myocytes. Volume overload causes ventricular enlargement without changes in wall thickness. CAD and MI lead to ventricular expansion because the infracted segment stretches. This causes in turn disruption of the normal architecture of the ventricular wall including loss of myocytes.

Chronic systolic failure is most common and is synonymous to low-output failure. The stretched myocytes are unable to eject an adequate stroke volume. First, adaptive remodelling leads to changes in wall geometry and cavity size. Eventually the possibility for adaptation is exhausted and the volume overload ventricle will decompensate. Contractility decreases and filling pressure in the ventricle increases. This again leads to increased oxygen demand in myocytes and to a delivery problem, causing more cell deaths. The shape of the ventricle changes, cardiomegaly occurs, and the patient reaches then end-stage CHF.

Diastolic failure, unlike systolic failure, is caused by a filling problem during diastole. Relaxation of the ventricle is impaired due to a loss of ventricular compliance, most often caused by pathological conditions like left ventricle hypertrophy, coronary artery disease, or, simply, by aging. Often systolic and diastolic dysfunction exists together. In absence of a systolic dysfunction, pulmonary venous congestion develops. Three main mechanisms are involved in diastolic failure: impaired ventricular wall relaxation, increased ventricular stiffness, and increased collagen deposition in the ventricular walls.

A number of neurohumoral alterations develop during the course of heart failure. The sympathetic activation in chronic heart failure is well established with increased MSNA (Ferguson et al. 1990) being paralleled by increased total body, real, cardiac, and central nervous system noradrenaline spill over (Hasking et al. 1986; Meredith et al. 1993; Kaye et al. 1994; Rundqvist et al. 1997). Patients do not have symptoms because increased neurohumoral activity compensates the situation by increasing heart rate and contractility. But this compensation has its prize, again through an increased oxygen demand of myocytes, causing a mismatch between oxygen delivery, which is reduced due to increased wall pressure and heart rate, and the increased demand.

In addition, the activated SNS, releasing high doses of noradrenaline, may cause myocarditis, myocardial necrosis, and cardiomyopathy. Beta-1 receptors density is downregulated parallel to increasing ventricular dysfunction. Elevated plasma noradrenaline is a predictor of mortality in heart failure patients. In addition to direct effects on the myocytes, increased catecholamine concentrations can cause serious arrhythmias, one of the main reasons for sudden cardiac death.

The renin–angiotensin–aldosterone system is also activated in heart failure. When cardiac output decreases, the baroreceptor stimulation in the carotid and aortic sinuses is reduced. This triggers a reflex increase in sympathetic outflow and decrease of the vagal stimulation. Though less rapidly, this also causes increases in plasma rennin, arginine, vasopressin, aldosterone, and endothelin, combined cause for sodium and water retention and vasoconstriction. The response on atrial natriuretic peptide is reduced, peripheral dilatation, diereses, and natriuresis decreased, eventually resulting in general vasoconstrictor and volume overload conditions that contribute to the degradation of the heart function.

In summary, heart failure can be discussed as a series of adaptive and maladaptive processes after pathological events, causing vicious circles. CHF again has ring actions on other parts of the body, e.g., the kidneys, the gastrointestinal tract, the lung, including its gas exchange capacity.

Heart Failure and HRV

Already early research groups observed marked differences in HRV between patients with CHF and healthy controls. Casolo tested 20 patients with CHF characterized by less than 30 % LVEF (Holter monitoring) and observed markedly reduced SDNN (97.5 ± 41 vs. 233.2 ± 26 ms) (Casolo et al. 1989).

In a study comparing seven patients with chronic heart failure (NYHA II–IV) to eight age-matched healthy men, short-time HRV, MSNA, and plasma norepinephrine were obtained. Atropine was given in low dosage (assumed to increase central vagal–cardiac motoneurons). At rest, patients with heart failure had increased sympathetic and decreased parasympathetic indices. It was shown that the heart failure patients had respiratory modulation of sympathetic, but not parasympathetic, indices. Atropine did not lead to changes in HRV or MSNA in heart failure patients, but 10 μg/kg led to a reduction of SDNN in the control group (Porter et al. 1990).

In a study, 24 healthy volunteers and 24 patients with heart failure were compared. Twenty-four-hour Holter EKG were used to calculate usual HRV measures (RR intervals, standard deviations) and Poincaré plots, using each R-R interval plotted against the subsequent R-R interval. All healthy subjects showed a comet-shaped plot, whereas the patients showed three different patterns (torpedo shaped, fan shaped, complex) that could not be perceived from standard deviation information (Woo et al. 1992).

Binder followed patients with CHF awaiting heart transplantation and compared survivors with non-survivors: in non-survivors, SDNN was extremely low (18 ± 11 vs. 47 ± 24); the most sensitive parameter for survival was SDANN (Binder et al. 1992).[1]

Guzzetti introduced spectral measures in CHF patients, showing markedly reduced LF and VLF and increased HF in association with NYHA classes II–V (Guzzetti et al. 1995).

Time-domain analysis of 24-h HRV was performed in 64 patients with dilated cardiomyopathy (DCM) and 33 healthy control subjects. Indices of HRV were reduced in patients with DCM compared with controls. Measures of HRV were lower in DCM patients in whom progressive heart failure developed during a follow-up of 24 months. Reduced HRV was associated with NYHA functional class, left ventricular end-diastolic dimension, reduced left ventricular ejection fraction, and peak exercise oxygen consumption in all patients. DCM patients with SDNN <50 ms had a significantly lower survival rate free of progressive heart failure than those with SDNN >50 ms. Stepwise multiple regression analysis showed that SDNN <50 ms was an independent predictor for developing progressive heart failure (Yi et al. 1997).

Ponikowski included 102 patients with moderate to severe CHF due to different causes. Non-survivors had lower SDNN, SDANN, and LF. In multivariate analysis, HRV parameters (SDNN, SDANN, LF) were found to predict survival independently of NYHA functional class, EF, peak oxygen consumption, and ventricular tachycardia on Holter monitoring. The Kaplan–Meier survival curves revealed SDNN <100 ms to be a useful risk indicator: 1 year survival in patients with SDNN <100 ms was 78 % when compared with 95 % in those with SDNN >100 ms (Ponikowski et al. 1997).

[1] Note that in the abstract SDANN is described incorrectly as "The standard deviation of five consecutive RR intervals (SDANN)," but in the article correctly as "SDANN – Standard deviation of 5-minute mean RR intervals"

Nolan recruited 433 outpatients with CHF (NYHA functional class I to III; mean ejection fraction, 0.41 ± 0.17). The annual mortality rate for the study population in SDNN subgroups was 5.5 % for >100 ms, 12.7 % for 50–100 ms, and 51.4 % for <50 ms. HRV did not predict SCD, but it did predict death due to progressive heart failure (Nolan et al. 1998).

Time- and frequency-domain analysis of heart rate variability obtained by Holter monitoring was assessed in 116 patients with idiopathic dilated cardiomyopathy. Mean follow-up was 53 months. Using multivariate analysis, only SDNN and ventricular tachycardia during 24-h ECG recording predicted sudden death or arrhythmic events. For SDNN, a cutoff level of 100 ms seemed most adequate for risk stratification (Fauchier et al. 1999).

Galinier enrolled 190 patients with chronic heart failure. Time- and frequency-domain measures of heart rate variability were obtained from 24-h Holter ECG recordings; spectral measures were averaged for calculation of daytime (1000–1900 h) and nighttime (2300–0600 h) values. SDNN <67 ms and daytime low-frequency power <3.3 ln were predictors for non-survivors (Galinier et al. 2000).

In chronic heart failure, it has been shown that increased neuronal norepinephrine release and decreased efficiency of norepinephrine reuptake exist simultaneously (Eisenhofer et al. 1996). Cardiac noradrenaline spillover is a good predictor of mortality in advanced cardiac failure but requires an invasive catheterization laboratory for its determination (Kaye et al. 1995). An alternative to assess sympathetic outflow, such as HRV, would be highly relevant for this patient population (Notarius and Floras 2001). In this context it is worth noting that differences in age, gender, and ethnic background disappear in congestive heart failure (Stein et al. 1997).

Boveda included 190 patients with CHF. Time-domain measures of heart rate variability were obtained from 24-h Holter ECG recordings. In multivariate analysis, SDNN <67 ms was an independent predictor for all-cause mortality (Boveda et al. 2001). In an independent publication most probably of the same patient group, lower daytime LF is discussed as predictor for sudden cardiac death (Galinier et al. 2000).

Bilchick performed a retrospective analysis of electrocardiographic data from 127 patients in the Veterans Affairs' Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure in order to determine if HRV (using only SDNN) would be feasible as a predictor of overall mortality and sudden death. SDNN <65.3 ms was the sole independent factor predictive of survival in a multivariate model. A Cox proportional hazards model revealed that each increase of 10 ms in SDNN conferred a 20 % decrease in risk of mortality. Furthermore, patients with SDNN <65.3 ms had a significantly increased risk of sudden death ($p = 0.016$) (Bilchick et al. 2002).

In contrast to animal studies, the low-frequency component is virtually abolished in severe heart failure in humans and is associated with worsening clinical status and prognosis (van de Borne et al. 1997). This occurs paradoxically at a time when sympathetic activity as measured simultaneously by cardiac noradrenaline spillover and other methods is extremely high (Kingwell et al. 1994; Rundqvist et al. 1997; Notarius and Floras 2001).

SDNN, HR variability index, frequency-domain indexes, and the short-term fractal scaling exponent of RR intervals were studied from 24-h Holter recordings in 499 patients with CHF and left ventricular ejection fraction ≤35 % during a mean follow-up of 665 ± 374 days. Conventional and fractal HR variability indexes predicted mortality by univariate analysis. SDNN for people who died during the study period was 112 ± 54, for survivors it was 130 ± 91. Here there were no differences in spectral measures with exception of (a small) difference in VLF. After adjusting for age, functional class, medication, and left ventricular ejection fraction in the multivariate proportional hazards analysis, the reduced short-term fractal exponent remained the independent predictor of mortality. All HR variability indexes were more significant univariate predictors of mortality in functional class II than in class III or IV (Mäkikallio et al. 2001).

In 64 patients with decompensated congestive heart failure (NYHA III and IV), time- and frequency-domain HRV were obtained from 24-h Holter ECGs. Plasma renin, aldosterone, noradrenaline, and endothelin I levels were assessed. ET-1 correlated negatively with SDNN, SDANN, Tp, and ULF but not with LF/HF (Aronson et al. 2001a). TNF-α did not correlate with HRV variable, but IL6 correlated negatively with SDNN, SDANN, TP, and ULF (Aronson et al. 2001b).

Five hundred and fifty-three outpatients with chronic heart failure and left ventricular dysfunction (EF < 45 %) were examined. After 2,365 patient–years follow-up, 201 patients died, 76 due to progressive heart failure. Independent predictors using the Cox hazards model were identified: SDNN, lower serum sodium, higher creatinine, higher cardiothoracic ratio, non-sustained ventricular tachycardia, higher left ventricular end-systolic diameter, left ventricular hypertrophy, and increasing age. The hazard ratio for a 10 % decrease in SDNN was 1.06 (1.01−1.12) (Kearney et al. 2002).

In 29 patients with class I to class IIIa heart failure (and consecutive lower EFs) and ten healthy subjects, TNF levels increased and HRV decreased in correlation with heart failure. TNF levels and HRV were inversely correlated, showing statistically robustness using log linear and nonparametric tests. In a multiple linear regression analysis, only TNF and noradrenaline levels contributed significantly to the variation observed in HRV, where TNF was a stronger independent predictor (Malave et al. 2003).

An interesting point was made by Arora, who studied CHF patients with predominant systolic or diastolic failure. He compared 19 patients with diastolic heart failure, 9 patients with systolic heart failure, and 9 healthy volunteers. Time- and frequency-domain indices were reduced in both groups compared to normal controls. Patients with diastolic function had relatively higher values of HRV variables, compared to those with systolic dysfunction (SDNN, Total power, ULF power). Patients with diastolic dysfunction had generally reduced HRV, but values for HRV were not as profoundly reduced as in patients with systolic dysfunction. SDNN values for patients with systolic heart failure, diastolic heart failure, and controls were 94.4 ± 33, 121.9 ± 31 and 137.8 ± 32.9, respectively (Arora et al. 2004).

Fifty-four consecutive CHF patients with exacerbation of pulmonary congestion were included in a study using Holter monitoring. In univariate analysis, diabetes mellitus (DM), BNP, and New York Heart Association (NYHA) functional class were significant as risk factors for cardiac events. VLF power, LF power, and TP

were strong predictors for cardiac events in HRV. In multivariate analysis, VLF power predicted cardiac events independently of LF power, TP, DM, BNP, and NYHA functional class (Hadase et al. 2004).

A study with a group of patients with chronic heart failure (with a LVEF <45 % and without atrial fibrillation, paced rhythms, or >10 % arrhythmias time domain) used a control group of 15 healthy persons. Twenty-four-hour HRV analysis was performed, and venous blood samples were screened for soluble TNF-α receptors sTNF-RI and sTNF-RII and IL6 using ELISA. In the CHF group, SDNN, SDANN, and SDNNI were lower, whereas rMSSD and pNN50 were not different than controls. There was a significant negative correlation between sTNF-RII and SDNN ($r=-0.26$ and between SDNN, SDANN, and IL6 ($r=-0.25$, $r=-0.28$, respectively). These correlations were found both in the patient and the control group (Straburzynska-Migaj et al. 2005).

In 330 CHF patients, time domain, spectral domain, and fractal analyses of Holter monitoring were obtained. Data from clinical assessment, echocardiography, right heart catheterization, exercise test, blood biochemical examination, and arrhythmia pattern were included, and patients were followed up for 3 years. Lower nighttime normalized (≤509), high pulmonary wedge pressure (PWP ≥ 18 mmHg), and low left ventricular ejection fraction (LVEF ≤ 24 %) were independently related to death for progressive pump failure, while LF ≤ 20 and increased left ventricular end-systolic diameter (LVESD ≥ 61 mm) were linked to sudden mortality (Guzzetti et al. 2005) (Fig. 8.3).

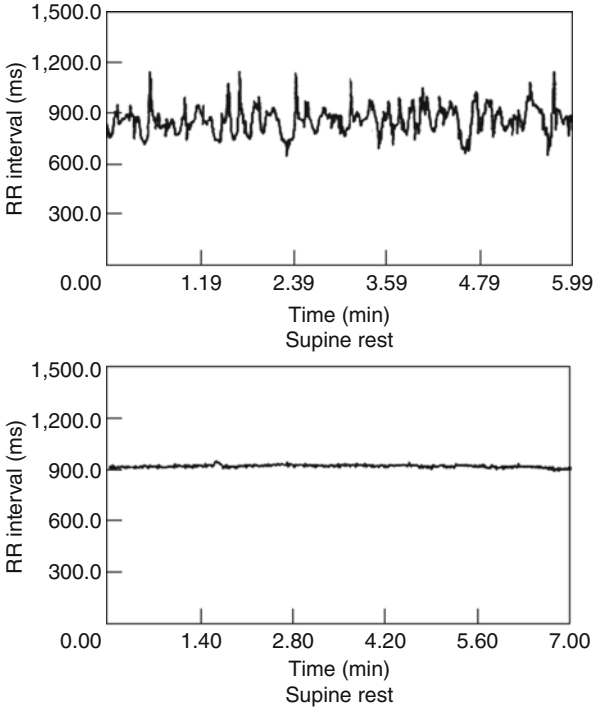

Fig. 8.3 HRV in mild (*upper graph*) and severe (*lower graph*) congestive heart failure (From Notarius and Floras (2001), with permission of Oxford University Press)

Table 8.2 Nonlinear indexes tested in the Maestri study

1VP	One variation pattern	Symbolic dynamics
2UVP	Two unlike variations pattern	Symbolic dynamics
BNI	Binary nonrandomness index	Symbolic dynamics
BLZC	Binary Lempel Ziv complexity	Entropy
DELTA	Long-range memory in RR time series	Entropy
SampEn	Sample entropy	Entropy
DFA	Short-term detrended fluctuation analysis	Fractality, multifractality
HFD	Higuchi fractal dimension	Fractality, multifractality
1/*f* slope	Slope of the power-law regression line	Fractality, multifractality
SMFSr	Ratio between the width of the singularity multifractal spectrum and the same quantity after phase randomization	Fractality, multifractality
UPI	Non-normalized unpredictability index	Predictability
UPIn	Normalized unpredictability index	Predictability
IMAI1	Ratio between the power associated with the mode with frequency closest to 0.1 Hz(LF1) and the power of modes with frequencies higher than LF1	Empirical mode decomposition
IMAI2	Ratio between the power associated with the first mode with frequency <LF1 and the modes with frequencies higher than LF1 (see IMAI1)	Empirical mode decomposition
pLF2	Power associated with the first mode with frequency <LF1 (see IMAI1)	Empirical mode decomposition
LEN	Length of the bidimensional Poincaré plots	Poincaré plots
SD12	Ratio between the axis of the ellipse fitting bidimensional Poincaré plots	Poincaré plots
RAD X	Radius of the semiellipse of inertia along the *X* axis of the 3-dimensional Poincaré plot	Poincaré plots
RAD Y	Radius of the semiellipse of inertia along the *Y* axis of the 3-dimensional Poincaré plot	Poincaré plots
RAD Z	Radius of the semiellipse of inertia along the *Z* axis of the 3-dimensional Poincaré plot	Poincaré plots

Maestri et al. 2007

In normal subjects, a curvilinear association exits between lag and Poincaré plot indices (SD1, SD2, SDLD, and SD1/SD2 ratio even for a small sequence of 50 beats). This curvilinearity was lost in a group of patients with CHF even in sequences with 50.000 R-R intervals (secondary data analysis with data from Physionet) (Thakre and Smith 2006).

Maestri used a very interesting approach. Twenty nonlinear HRV indices, representative of symbolic dynamics, entropy, fractality–multifractality, predictability, empirical mode decomposition, and Poincaré plot families, were obtained from 24-h Holter recordings in 200 stable CHF patients (see Table 8.2). End point for survival analysis (Cox model) was cardiac death or urgent transplantation. Homogeneous variables were grouped by cluster analysis, and in each cluster redundant variables were discarded. A prognostic model including only known clinical and functional risk factors was built and the ability of each selected HRV variable to add prognostic information to this model assessed. Bootstrap resampling was used to test the models

stability. Four nonlinear variables showed a correlation >0.90 with classical linear ones and were discarded (LEN, RAD Z, UPI, pLF2). Correlations >0.80 were found between several nonlinear variables. Twelve clusters were obtained, and from each cluster a candidate predictor was selected. Only two variables (IMAI2 and 1VP, from empirical mode decomposition and symbolic dynamics families) added prognostic information to the clinical model (Maestri et al. 2007) (Table 8.2).

In a small pilot study, use of losartan, spironolactone, or a combination led to an improvement of HRV indices in eight patients 18 weeks after baseline (Shehab et al. 2008).

In 294 patients with LVEF < 35 %, Holter monitoring was used to calculate heart rate variability, heart rate turbulence, and repolarization dynamics (QT/RR). If two of three parameters were significantly changed (beyond that SDNN < 86 ms), it predicted risk of death (30 % 3-year mortality rate) and sudden death (12 %) similar to LVEF < 35 % as risk factor (Cygankiewicz et al. 2009).

Five hundred and sixty-nine patients after AMI but with no initial history of CHF were followed over 8 years, and patients in need for hospitalization due to CHF were compared with the rest. SDNN (79 ± 28 vs. 100 ± 32), short-term scaling exponent α1 (1.07 ± 0.30 vs. 1.26 ± 0.22), HRT (TS (ms/NN) 2.53 ± 2.77 vs. 6.17 ± 6.14), baroreflex sensitivity, and heart rate were significantly different in comparison. In the ROC curve analysis, BNP and the ratio of BNP to SDNN were the most accurate of the studied parameters in predicting HF hospitalization (Perkiömäki et al. 2010).

In 110 patients with CHF, HRV, and HRT was assessed from 24-h Holter recordings. TO ≥ 0 %, TS ≤ 2.5 ms/RR, and TT > 10 were considered as pathological. End point was development of end-stage CHF requiring heart transplantation (OHT) or mortality during the follow-up of 6 years. Patients with at least one relatively preserved HRT parameter (TO, TS, or TT) ($n = 98$) had 5-year event-free rate of 83 % compared to 33 % of those in whom all three parameters were abnormal (only 12 patients). In multivariate analysis, the most powerful predictor of end point events was heart rate variability (SDNN < 70 ms, hazard ratio (HR) 9.41, $p < 0.001$), followed by LVEF ≤ 35 % (HR 6.23), TT ≥ 10 (HR 3.14), and TO ≥ 0 (HR 2.54, $p < 0.05$) (Sredniawa et al. 2010).

Ho used multiscale entropy in 40 patients followed up 684 ± 441 days. Among all parameters, Area5, Area6–20, and LF were significantly lower in the mortality group (Ho et al. 2011) (Tables 8.3 and 8.4).

There are several open questions. One was assessed by Stein, looking at possible cumulative effects of CHF and diabetes on HRV. She found some cumulative effects on NYHA class 2 patients but little effect on NYHA class 3 (Stein and Deedwania 2010).

Conclusion

It can be presumed that the idea of decreased HRV in patients with CHF is now established. It has been shown repeatedly that different HRV indices have a predictive value, both for deterioration and mortality. Best established is SDNN. In some studies, the cutoff point was 100 ms, in some around 60–70 ms, and in a few 50 ms.

Table 8.3 Cutoff points for SDNN in risk stratifications in some selected studies

Cutoff point	Observed differences	Reference
50	Lower in DCM patients in whom progressive heart failure developed during a follow-up of 24 months	Yi et al. (1997)
100	1-year survival in patients with SDNN <100 ms was 78 % when compared with 95 % in those with SDNN >100 ms	Ponikowski et al. (1997)
100	DCM, follow-up 53 months	Fauchier et al. (1999)
67		Galinier et al. (2000)
65.3	Each increase of 10 ms in SDNN conferred a 20 % decrease in risk of mortality	Bilchick et al. (2002)
67	Survivors: 91.3 ± 33, non-survivors 69.3 ± 31.7	Boveda et al. (2001)
70	SDNN <70 predictive in univariate but not multivariate analysis	Mäkikallio et al. (2005)
86	≥2 abnormal risk markers (SDNN; HRT, QT end/RR >0.21)were at risk of death (30 % 3-year mortality rate) and sudden death (12 %)	Cygankiewicz et al. (2009)
70	Most powerful predictor compared with LVEF and HRT	Sredniawa et al. (2010)

Table 8.4 CHF and SDNN in selected studies

Number of patients	Method	SDNN patients and control group	Reference
20	Holter monitoring	97.5 ± 41 versus 233.2 ± 26 ms	Casolo et al. (1989)
9	Holter monitoring	94.4 ± 33 versus 137.8 ± 32.9	Arora et al. (2004)
433	Holter monitoring	Annual mortality 5.5 % for >100 ms, 12.7 % for 50 to 100 ms, and 51.4 % for <50 ms	Nolan et al. (1998)
64	Holter monitoring	57 ± 30 in deteriorating patients, 121 ± 41 in stable patients, 144 ± 35 in controls	Yi et al. (1997)
242	Short term (8 min)	21 ± 19, patients with moderate to severe CHF	La Rovere et al. (2003)
499	Holter monitoring	SDNN for non-survivors 112 ± 54, for survivors 130 ± 91	Mäkikallio et al. (2001)

This can be used as diagnostic parameter together with other clinical data to stratify patients for interventions and clinical follow-up. If we put this together with data from rehabilitation studies, CHF patients can be followed, and a restoration of HRV might be a prognostic positive sign, but evidence for this is still lacking.

Risk Prediction for Sudden Cardiac Death

Sudden cardiac death (SCD) outside of the hospital is clinically very important. It causes more than 60 % of all deaths due to cardiovascular disease, which in turn is the leading cause of deaths generally. Even worse, the large majority of SCD

happen in individuals without known cardiovascular disease and without high-risk criteria for it (Adabag et al. 2010). The majority of SCD are not witnessed. This is also the reason for a rather wide definition (unexpected death that occurs within 1 h from the start of symptoms when death is witnessed and within 24 h of being seen alive and well when it is not witnessed) (Myerburg et al. 2007). In relation to HRV annual incidences of SCD are of particular importance. Fifty-three deaths per 100,000 were reported by one American study (Chugh et al. 2004) and 100 deaths per 100,000 by a Dutch study (de Vreede-Swagemakers et al. 1997). Data from China and Ireland have a similar order of magnitude (Hua et al. 2009; Byrne et al. 2008). In a recent study 3,276 patients were enrolled at the time of acute MI with or without diabetes, with a follow-up of 5 years. The incidence of SCD among diabetic patients was 5.9 %, in nondiabetic patients 1.7 % (Junttila et al. 2010). In most cases SDC is thought to be the consequence of ventricular tachycardia degenerating to ventricular fibrillation and subsequent asystole (Adabag et al. 2010). Most but not all people dying of SCD have coronary heart disease. Therefore SCD shares the same risk factors as CHD. These risk factors can be used on population level but are not sufficient on the individual level because of relatively low absolute risk (Adabag et al. 2010). Multivariable risk algorithms have been developed (e.g., Buxton 2009), but they have their limitations.

Many studies with HRV focus on prediction of sudden cardiac death. The prediction of SCD is of interest because there is a possible intervention, the implantation of an automatic defibrillator. This is an effective measure in risk groups, but the effectiveness clearly depends on the criteria for patient selection. In addition, this treatment is not inexpensive. For the prediction of SCD, several methods have been used (reviewed in Huikuri et al. 2003). Most of them are ECG based and have certain drawbacks. HRV with different methods has been tested extensively in the last few years.

In 715 patients, power spectral measures both from Holter monitoring and shorter 2–15 min series were used. Short-term and long-term values were similar (most correlations >0.75). Lower indices were correlated with increased risk for mortality (RR 2–4) (Bigger et al. 1993).

Bigger compared 274 healthy persons with 684 patients within 2 weeks after a myocardial infarction and 278 patients 1 year after myocardial infarctions. The study used Holter ECG recordings with frequency- and time-domain measures. All HRV measures were lower in patients with coronary heart disease. The HRV values 2 weeks after MI were lower than 1 year after MI. ULF was the best univariate separator between healthy persons and persons with cardiac disease. Values that are strong predictors of premature death in cardiac patients were only found in about 1 % of the healthy population, indicating a high specificity (Bigger et al. 1995).

Seven hundred and fifteen patients with recent myocardial infarction, 274 healthy persons, and 19 patients after heart transplantation were compared and followed up 3 years. Using frequency-domain values and power-law slopes, the MI group showed a steeper negative slope of –1.15, whereas the transplant group showed a slope of –2.08, whereas the healthy group had a slope of –1.08. In a Cox hazard ratio model, the slope was a far better predictor for all-cause mortality (Bigger et al. 1996).

Table 8.5 Sensitivity, specificity, and predictive accuracy in prediction of mortality of MI patients

	Sensitivity, %	Specificity, %	Positive predictive accuracy, %	Negative predictive accuracy, %	Overall accuracy, %
$\alpha_1 < 0.75$ ($n=168$)	62	73	46	84	65
α_1 (edited) < 0.85 ($n=117$)	48	80	43	81	62
$\beta < -15$ ($n=112$)	36	77	38	76	57
Mean R-R interval <750 ms ($n=147$)	44	63	30	76	53
SDNN < 65 ms ($n=131$)	39	75	34	78	56
HRVI < 16 ($n=108$)	35	79	37	78	57
ULF (ln) < 8.1 ($n=210$)	36	55	29	78	53
VLF (ln) < 5.75 ($n=168$)	54	67	38	79	58
LF (ln) < 5.5 ($n=228$)	58	60	36	79	58
LF/HF ratio < 1.6 ($n=205$)	58	59	35	79	56

Huikuri et al. (2000)

The positive effect of exercise on survival after myocardial infarction is well known. Exercise leading to the increase of more than 1.5 METS (metabolic equivalents) leads to a significant increase in SDNN, SDANN index, SDNN index, pNN50, TP, and HF (Pardo et al. 2000).

In a multicenter substudy in 37 coronary care units, 645 patients 5–10 days after MI were included, and 24-h Holter ECGs were obtained. Besides the usual HRV values, Poincaré plot analysis, Power-Law scaling analysis and Detrended Fluctuation analysis were used. During the follow-up period of 685 ± 360 days, 114 patients died, 28 of them classified as non-arrhythmic cardiac deaths. All power spectral components, except HF (!) differed between the groups, as did the nonlinear values. Some Kaplan–Meier curves are shown in Figure 2.2. The group calculated sensitivity and specificity for the different values. Nonlinear values had generally a higher accuracy than frequency- or time-domain values. For all-cause deaths, the highest adjusted relative risk was 2.0 for the DFA value α_1 (Huikuri et al. 2000) (Table 8.5).

Patients with SDNN <65.3 ms had a significantly increased risk of sudden death in a retrospective study (Bilchick et al. 2002).

With a standardized HRV study (fixed respiration rate 12–15 over 5 min) and using LF (0.040.15 Hz), HF (0.15–0.45 Hz), and LF/HF ratio and echocardiography, stable patients without atrial fibrillation were categorized to predict sudden death risk. HRV has an independent prognostic value identifying 38 % of patients with a mortality risk of 23 % over 3 years and more importantly a large population with a 3-year mortality less than 3 %. The author recommends use of HRV for risk stratification (La Rovere et al. 2003).

A multivariate survival model for the identification of sudden (presumably arrhythmic) death was developed with data from 202 consecutive patients with moderate to severe CHF using time- and frequency-domain HRV parameters obtained by 8 min spontaneous breathing and 8 min paced breathing. This model was then validated in 242 consecutive patients. In the derivation sample, sudden death was independently predicted by a model that included low-frequency power (LFP) of HRV during controlled breathing ≤ 13 ms^2 and left ventricular end-diastolic diameter ≥ 77 mm (La Rovere et al. 2003).

An LF < 20 was predictive for SCD in a 3-year longitudinal study in 330 patients (Guzzetti et al. 2005). Pathological HRT has also been associated with SCD in one study (Cygankiewicz et al. 2008a, b).

Arsenos reported in a letter a study assessing whether or not multiresolution wavelet analysis (MWA) of heart rate variability (HRV) has relevant prognostic information independently from other well-established predictive variables in the field of sudden cardiac death (SCD) prediction. He included 231 patients with CHF. In the multiresolution wavelet analysis (MWA), Haar wavelet was used, and the final index σ_{wav} was extracted as the standard deviation of the detailed coefficients of scale 8. The σ_{wav} index outperformed the conventional SDNN in SCD prediction. It is difficult to draw conclusions based on this study since at the moment it is only published as letter, and not all relevant details are known (Arsenos et al. 2012).

SCD Summarized

A recent review comes to the conclusion: "(…) these specialized markers have a high negative predictive value and a low positive predictive value. Thus, SCD risk is low with a negative test, but indeterminate with a positive test" (Adabag et al. 2012). In conclusion, different linear and nonlinear HRV measures have been used for risk stratification of sudden cardiac death, and good evidence has been established. HRV seems to be feasible at bedside to distinguish between groups at risk and not at risk. Used alone as a marker, HRV has a low sensitivity and specificity. Combinations of HRV variables alone or in combination with other parameters (e.g., baroreflex sensitivity, left ventricular ejection fraction, periodically non-sustained ventricular tachycardia) can increase sensitivity, specificity, and calculation of the relative risk significantly (Sztajzel 2004). There is a lack of interventional studies based on HRV risk stratification.

SCD in Heart Failure Patients

Nolan did not find HRV indices predicting SCD in CHF in a prospective study with 433 patients (Nolan et al. 1998). Galinier enrolled 190 patients with chronic heart

failure. Time- and frequency-domain measures of heart rate variability were obtained from 24-h Holter ECG recordings, spectral measures were averaged for calculation of daytime (1000–1900 h) and nighttime (2300–0600 h) values. Daytime low-frequency power <3.3 ln was an independent predictor for SCD (Galinier et al. 2000).

In patients with idiopathic dilated cardiomyopathy, HRV time-domain variables and baroreflex sensitivity correlated only weakly. HRV variables seemed feasible prognostic parameters, but results of prospective studies are warranted (Hoffmann et al. 2000).

Wessel and collaborators studied ICD data before the onset of 131 VT episodes and 74 control intervals in 63 ICD patients with severe congestive heart failure. They used standard time and frequency-domain algorithms and nonlinear concepts. They used the recurrence quantification analysis returning recurrence rate, determinism, averaged length of diagonal structures, (Shannon-) entropy, and trend and found significant differences between the groups. Increased short laminar phases with low variability preceded the onset of VT. The onset of slow VT was characterized by a significant increase in heart rate and an increase in laminarity. The fast arrhythmias were preceded by decreased heart rates and a low degree of laminarity. (Wessel et al. 2001).

In the Marburg Cardiomyopathy Study including 343 patients with a mortality of 13 patients after 5 years, HRV parameters (SDNN, baroreflex sensitivity) did not predict sudden cardiac death. The only relevant parameter was LVEF, with a relative risk of 2.3 per 10 % decrease of EF (Grimm et al. 2003). In 54 patients with deterioration of congestive heart failure coming to an emergency department, HRV power spectra (VLF, LF) predicted cardiac events in the follow-up period (Hadase et al. 2004).

In a study with patients with congestive heart failure, 199 patients were followed 312 ± 150 days. Forty patients (21 %) died. All patients underwent a 24-h Holter HRV analysis. In a multivariate model, SDNN (RR2.2), SDANN (RR2.1), TP (RR 2.2), and ULF (RR 2.6) in the lower tertiale were predictive factors for mortality after hospital discharge (Aronson et al. 2004).

In a longitudinal study, 330 CHF patients (with sinus rhythm) were tested with help of Holter monitoring (using time domain, frequency domain, and fractal analysis with the 1/f slope), echocardiography, right heart catheterization, exercise tests, blood biochemical examination, and arrhythmia patterns. Patients were followed 3 years with the goal of finding prognostic models for different forms of cardiac death (pump failure vs. sudden cardiac death). Depressed power of nighttime VLF (<509 ms^2), high pulmonary wedge pressure (>18 mmHg), and low ventricular ejection fraction (LVEF > 24 %) were independently related to death for progressive pump failure, while power reduction between 0.04 and 0.15 Hz (LF, <20 ms^2) at nighttime and increased left ventricular end- systolic diameter (LVESD > 61 mm) were linked to sudden mortality. The relative risk for pump failure with a low VLF was 2.3 (PWP 2.0, LVEF 1.9) and for sudden cardiac death for LF < 20 ms^2 2.7, for HF < 60 ms^2 2.2, and for LVESD > 60 mm 2.6, but in multivariate analysis only LF remained significant. Three-year mortality for patients with LF > 20 ms^2 was 8 %, for patients <20 ms^2 was 21 %. Cumulative mortality for patients with the identified

risk factors for pump failure was 7 % without risk factors, 20 % for patients with one risk factor, 32 % for patients with two, and 44 % for patients with three risk factors (Guzzetti et al. 2005).

One study included data of 397 patients with implanted cardiac resynchronization devices. HRV was measured as 5-min SDAAM. SDAAM <50 ms over 4 weeks was associated with increased mortality risk, SDAAM between 50 and 100 ms at intermediate risk. SDAAM decreased in a median of 16 days before a necessary hospitalization because of decompensation. Sensitivity for detecting a hospitalization was 70 % (Adamson et al. 2004; Adamson 2005).

One hundred and fourteen patients were included in a study failing to show associations between deterioration and autonomic markers. Correlations between the different autonomic markers were only modest. During a follow-up of 22 months, an end point event occurred in 15 patients. In univariate analysis, left ventricular ejection fraction and baroreflex sensitivity were significant predictors of arrhythmic events. In multivariate analysis, only baroreflex sensitivity remained an independent predictor (Klingenheben et al. 2008).

In 42 patients with diastolic heart failure, HRV was analyzed before and after compensation. HRV was more decreased in decompensation and in patients with more pronounced forms of diastolic failure (Tanindi et al. 2012).

Three hundred and eighty-eight patients with chronic heart failure were recruited for a Holter monitoring study and were followed over 4 years. VLF, LF, and turbulence slope (TS) improved predictive discrimination and risk classification when added to clinical variables (La Rovere et al. 2012).

Special Subgroups

Cachexia

A subgroup of chronic heart failure patients develops cachexia. In a cross-sectional study, 13 patients with cardiac cachexia (other reasons excluded), 26 noncachectic heart failure patients, and 11 healthy controls were observed (short-term HRV, BRS, hormonal measures). Cachectic patients had a significantly lower LF and depressed baroreflex sensitivity; furthermore, they presented elevated levels of catecholamines relative to noncachectic patients and controls (Ponikowski et al. 1999).

Hypertrophic Cardiomyopathy

Ambulatory Holter monitoring was performed in 106 HCM patients with sinus rhythm. No HRV parameters predicted fatal outcomes after 10 years (Kawasaki et al. 2012).

HRV Biofeedback Training in Heart Failure Patients

Biofeedback has been used in patients with heart failure before, but without HRV, employing skin temperature as parameter (Moser et al. 1997). Moravec and colleagues use a standardized approach with eight training sessions and (among others) SDNN as biofeedback parameter. Their preliminary data demonstrate regulation of heart rate variability in patients with lower ejection fractions. Unfortunately they do not offer details about how SDNN is processed to make it available for the patients, e.g., how many minutes are collected (McKee and Moravec 2010; Moravec and McKee 2011). The only published randomized study included 29 patients either receiving six sessions of breathing retraining, HRV biofeedback and daily practice, or quasi-false alpha-theta biofeedback and daily practice. The method used is described as follows: "Various colour screens were displayed, reflecting depth and frequency of respiration, HR, and HRV." Here, again, details of HRV processing are not provided. HRV biofeedback significantly increased exercise tolerance for the treatment group in the high LVEF category between baseline and follow-up, but there were no changes in SDNN ($p = .09$) or quality of life ($p = .08$), probably due to a low (and insufficient) number of participants (Swanson et al. 2009). More details on use of HRV biofeedback are provided in the chapter about therapeutic applications of HRV.

Chronic Heart Failure and Heart Rate Turbulence

There are only limited data for the prognostic value of HRT in patients with congestive heart failure. TO and TS might be strongly correlated with the extent of heart failure (Cygankiewicz et al. 2006). TS was an independent predictor of decompensation (Moore et al. 2006) and was a prognostic factor regarding sudden death in another study (Cygankiewicz et al. 2008a, b). Yet another study analyzed various risk parameters from Holter monitoring for 2,130 AMI patients. During a median follow-up of 3 years, cardiac mortality was 113/2,130, including 52 SCDs. All Holter variables predicted the occurrence of SCD, but only reduced postectopic turbulence slope (TS) (from HRT) and non-sustained ventricular tachycardia remained as marked SCD predictors after adjustment for age, diabetes, and ejection fraction (EF) (Mäkikallio et al. 2005). The prognostic value of HRT has been discussed in relation to the etiology (Bauer et al. 2008).

Other Newer Approaches

An emerging analysis is QT beat-to-beat variability. One study included heart failure patients. Increased QTVI because of depressed heart rate variability predicted cardiovascular mortality and non-SCD but not SCD or extracardiac mortality in

heart failure independently of left ventricular dysfunction. Abnormally augmented QTVI separated 97.5 % of healthy individuals from heart failure patients at risk (Tereshchenko et al. 2012). Another variant of HF, V_{index}, taken from 24-h Holter recordings was used on 590 post-AMI patients and was the most potent predictor of SCD (Kiviniemi et al. 2007).

Paroxysmal and Permanent Atrial Fibrillation

Introduction

Atrial fibrillation is the most common arrhythmia in adults in developed countries. It is a complex disease where it is possible to distinguish between trigger factors (pulmonary veins) (Haïssaguerre et al. 1998) and underlying pathological conditions. Once present, AF leads to remodelling of the electrical and structural properties of the atria, initiating a vicious circle. Many patients start with paroxysmal AF eventually going over to permanent AF (Shen et al. 2012). Most studies only use HRV if sinus rhythm is present. As a consequence most data are based on studies with patients with paroxysmal AF. There are, however, a few studies that use this technique in patients with permanent AF. Prediction of AF has been tried with different algorithms and methods (see overview in Poli et al. 2003).

Pathophysiology

Pulmonary veins and the pulmonary–left atrial junction are richly innervated by parasympathetic and sympathetic nerve fibers (Chen and Tan 2007). Enhanced activity is associated with increased (Patterson et al. 2005) ablation with reduced incidence of AF (Lu et al. 2009). Both increased sympathetic and parasympathetic tone are associated with increased vulnerability for AF (Shen et al. 2012). First reports describing ANS activity before onset of paroxysmal AF were published in 1978 (Coumel), already then both regarding PNS (in younger healthy adults) and SNS (in older patients with organic heart disease). After introduction of HRV in clinical research, several reports appeared, observing changes in ANS activity immediately before the onset of AF, something which was discussed in the first part of this book. These changes are nonspecific, all kinds of changes were observed (e.g., increased SNS activity, increased PNS activity, and mixed adrenergic and vagal activities) (de Vos et al. 2008). It would be desirable to observe ANS changes at the heart directly, but this and several other studies use short-term HRV changes as surrogate for ANS alterations and no local ANS data of the pulmonary vein/atrial junction. Therefore the results have been challenged (e.g., of (Shen et al. 2012)). In advanced heart failure, for instance, the response of the sinus node on SNS activity

is diminished, which again has consequences for HRV indices, probably not showing the real activity of SNS (Piccirillo et al. 2009). Also in other conditions where the sinus node is affected, HRV results can be biased. First direct recordings of SNS in animals were reported 2003 in renal SNS (Barrett et al. 2003), 2006 in stellatum neurons (Jung et al. 2006), confirming to some degree HRV measurements. Another line of evidence relies on ablation sympathetic connections to the heart, stopping all episodes of paroxysmal AF in animal models (Ogawa et al. 2007). Clinical studies, however, showed markedly lower response rates between 34 and 90 % (Shen et al. 2012). This might be based not only on different technical approaches for ablation but also on more complex patterns of ANS activity in these patients or advanced remodelling of the electrical atrial system.

Assessing the underlying ANS changes in permanent AF is more difficult for obvious reasons. Most authors base their approaches on direct nerve recordings, showing a substantial influence of the ANS on the AF frequency (Shen et al. 2011). These challenges are discussed in the last part of this subchapter.

HRV Changes Prior to the Onset of Paroxysmal AF

Twenty-minute heart rate intervals immediately before onset of atrial fibrillation were analyzed in 22 without structural heart disease. Traditional HRV variability indices showed no significant changes before onset of AF, but ApEN and α1 decreased progressively before onset (Vikman et al. 1999). In a similar study, 26 episodes of AF onset stored in pacemakers were analyzed with 2-min HRV directly before onset. SDNN of PP intervals and RMSSD of pp intervals increased the last 10 s before the onset of AF (Wiegand and Bonnemeier 2001).

In 77 unselected patients with paroxysmal AF, a linear decrease in the RR interval (925 ± 16 vs. 906 ± 16) was observed, at the same time as an increase in SDNN (65 ± 4 to 70 ± 4). HF increased, LF decreased, and LF/HF increased until 10 min before AF onset, followed by a sharp decrease immediately before onset. There were no differences between patients with idiopathic AF and patients with structural heart disease (Bettoni and Zimmermann 2002). A study by Dimmer did not show relevant changes of time-domain or frequency-domain indices. They included 27 patients with paroxysmal AF. Five minutes before onset of AF, SDNN changed; all other indices remained unchanged (Dimmer et al. 2003).

In patients with COPD, patients who developed arrhythmias, including AF, had unchanged nighttime HF and increased LF all day (Tükek et al. 2003). In 23 patients, HRV was analyzed 60, 20 min, and immediately before onset of AF. Fourteen patients had an AF episode at night, 9 during daytime. In the night group, AF was preceded by a gradual increase of HF and LF, which left LF/HF unchanged. In the daytime group, LF and LF/HF, but not HF, increased before AF onset (Tomita et al. 2003).

Holter monitoring in 18 patients with paroxysmal AF and 19 healthy controls and assessing heart rate dynamics with the help of the power-law spectral exponent (slope) revealed a steeper slope in AF patients even while having sinus rhythm,

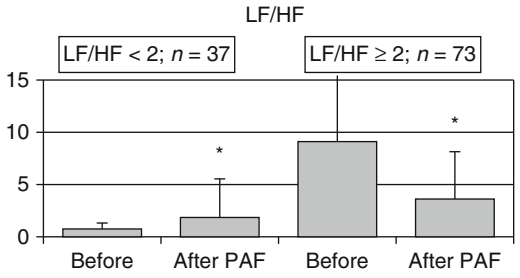

Fig. 8.4 Changes in LF/HF ratio directly before and after paroxysmal atrial fibrillation (Lombardi et al. (2004), with permission of Oxford University Press)

compared to the controls (Sato et al. 2003). In 269 patients with paroxysmal AF, a study showed a decline in TP, LF, and HF and an increase in LF/HF (Ivanov 2003)

An analysis of 110 paroxysmal atrial fibrillation episodes in 65 patients revealed in 37 cases a low LF/HF, in 73 cases a high LF/HF ratio as sign of autonomic imbalance before fibrillation; after fibrillation, the ratio showed more physiologic numbers (Lombardi et al. 2004) (Fig. 8.4).

Lombardi's results seem to be challenged by follow-up results from the Framingham study. One thousand four hundred and thirty-two women and 1,142 men around 54 were followed up for 12 years; in this time 132 of them developed persistent AF. A change of one SD in log LF/HF was associated with an increased risk of developing AF. This effect, however, disappeared after including confounding variables in the analysis. Thus the authors conclude that much of the apparent association between HRV and AF is mediated by traditional risk factors (Singh et al. 2004). This view is most probably right, but the idea wrong – HRV changes should not be a cause but a surrogate marker for other changes within the complex cardiopulmonary system.

In Holter ECGs from 32 healthy persons and 54 patients with PAF, time- and frequency-domain measures were lower in patients with cardiac diseases. Patients with idiopathic AF had higher HF values at nighttime (Tadzhieva et al. 2005).

Tuzcu et al. included HRV data of 25 patients prior to the onset of AF, using two records of 30 min each, one immediately preceding AF and one during a period distant to the onset. Sample entropy was significantly reduced prior to AF compared with the earlier period (0.45 ± 0.25 vs. 0.78 ± 0.46). The 30-min period before AF was divided in three 10-min periods; sample entropy was decreasing before AF (Tuzcu et al. 2006).

In an analysis of 105 Holter tapes, 44 PAFs were identified in 33 patients. Time- and frequency-domain variables showed no change before PAF. ApEN and SampEn decreased 60 min before onset of PAF with about 0.1–0.15 and similar 10 min before onset. Interestingly, the results are similar in edited and unedited measures (Shin et al. 2006).

The observations made by several groups discovering vegetative disturbances just before the onset of AF seem plausible and fit with pathophysiological considerations. But no unambiguous changes were observed. Results are contradictory (see, e.g., Ivanov 2003 vs. Tomita et al. 2003). Lombardi's study might give a hint: is it possible that we have here at least two different pathophysiological mechanisms,

probably even more? I find no major methodological problems in the studies as an alternative explanation. Probably we have a patient group in which no major changes occur before AF, one in which complexity generally increases, one with an isolated increase of LF and, in some cases, patients whose TP decreases.

HRV to Predict the Onset of AF After Thoracic Surgery

A special case is related to AF after thoracic surgery, a frequent situation that has led to a particular interest in studying this group of patients. In 102 patients, HRV was analyzed before CABG using 24-h Holter monitoring. Twenty-nine patients developed AF. Independent predictors were identified by logistic regression as age, vagal index <10 %, ectopic supraventricular beats, and episodes of non-sustained supraventricular tachycardia (Frost et al. 1995).

In 64 patients scheduled for elective coronary artery bypass grafting (CABG), HRV parameters were obtained with 96-h Holter tapes; 26 patients developed AF postoperatively. SDNN increased 15 min before onset of AF. LF/HF was lower 30 min before onset followed by an increase (mainly because of a decrease of HF) (Dimmer et al. 1998).

Hogue et al. observed higher or lower measures of HRV before AF after CABG. They obtained HRV data of three sequential 20-min intervals preceding the onset of AF and compared it with data of matched postoperative CABG patients without AF. Logistic regression revealed that increased heart rate and decreased ApEn were independently associated with AF. Other HRV parameters showed either increased or decreased variability (in time-domain values and quantitative Poincaré plot analysis) (Hogue et al. 1998).

Two hundred and ninety-seven patients undergoing cardiovascular surgery were studied prospectively, using myocardial perfusion scanning, HRV, and D-dimers. Impaired HRV (and a positive thallium scan) was an independent predictor of adverse events, including arrhythmias (Mamode et al. 2001).

Eighty patients with a history of PAF were evaluated by Holter monitoring and blood samples measuring neuropeptides and catecholamines pre- and postoperatively. 36.3 % of these patients developed AF postoperatively. They showed a significant lower circadian variation of HF and LF/HF ratio. HF decreased in both groups postoperatively. Neither neuropeptides nor catecholamines differed between the groups (Jideus et al. 2001).

Ninety-two patients with scheduled CABG were examined with a short-term HRV (power domain, time-domain indices), 30 patients developed postoperative HF. Logistic regression analysis revealed age and a higher BMI but not HRV parameter as risk factor for AF (Hakala and Hedman 2003). AF onset in 48 patients after thoracotomy was evaluated by 2-h Holter monitoring. SDNN, pNN50, RMSSD, LF, and HF were increased before onset of AF, compared to patients who did not develop AF (Amar et al. 2003). In a study with 86 CABG patients, a lower exponent α1 predicted the onset of AF and postoperative morbidity (Wu et al. 2005). In 88 patients scheduled for CABG,

13 developed AF. Ten-minute electrogram recordings were processed. Off-line and time-domain, frequency-domain, Poincaré, and point correlation analyses were calculated. Logistic regression analysis was used to detect associations. Only peak point correlation dimension and age were independent predictors (Chamchad et al. 2006).

Here, the situation is quite similar. An interesting result is related to decreased entropy before onset of AF (Hogue et al. 1998). Also here, the existence of several subgroups can be assumed.

HRV to Predict Recurrence After Cardioversion of Paroxysmal AF

One possible treatment, especially in newly developed AF, is electrical cardioversion. A relevant number of patients, however, will experience recurrence. Since cardioversion itself is not without risks, it is desirable to identify patients where cardioversion has no sustainable effects.

In 40 patients with AF, HRV was evaluated immediately after defibrillation by Holter monitoring. Patients with relapse within the first week had a significant higher LF/HF ratio (Michelucci et al. 2001). Twenty-seven patients after successful cardioversion in case of paroxysmal AF and 20 healthy controls were examined by Holter monitoring, using HRV indices with time-domain parameters. In 15 persons, recurrence was observed; all HRV parameters in these patients were lower than in patients maintaining sinus rhythm. All cardiac patients had generally lower HRV values (after cardioversion) compared to healthy controls (Akyürek et al. 2003).

Also the Huikuri group tested patients with paroxysmal AF after electrical cardioversion. They included 78 patients, 27 of them had recurrence of AF within a month. In contradiction to Akyürek's study, the patients with AF recurrence had higher SDNN (117 ± 34 vs. 100 ± 29), increased lnHF (5.7 ± 0.6 vs. 5.3 ± 0.7), lnLF (6.2 ± 0.8 vs. 5.6 ± 0.9), and lnVLF (7.1 ± 0.8 vs. 6.5 ± 0.8). Early AF recurrence was predicted best by lnHF, whereas lnVLF predicted best late recurrence. No clinical or echocardiographic parameters predicted recurrence (Vikman et al. 2003).

HRV in Persistent AF: A Challenge

Since most HRV studies were conducted in patients with sinus rhythm, patients with AF and heart failure are a challenge. Atrial fibrillation (AF) is markedly more prevalent in CHF patients than in the general population (Benjamin et al. 1994). In mild to moderate CHF, the prevalence of AF is estimated at 10–15 % while in patients with more advanced heart failure (in NYHA class IV), AF is present in up to 50 % of patients (Maisel and Stevenson 2003). Current AF management guidelines provide no treatment recommendations that take the various mechanisms and patterns of AF into account. It seems advisable to develop tests that quantify AF disease state and guide AF management (Bollmann et al. 2006).

Most HRV studies exclude patients with permanent AF. The possible significance of HRV is far from clear in this context. During AF, ventricular variability does not purely reflect sinus node modulation but is also dependent on AV nodal refractoriness as well as degree of concealed conduction (Hayano et al. 1998). Some of the approaches were discussed earlier, but the focus here is on newer studies.

Van den Berg analyzed 16 patients with chronic AF treated with digoxin or verapamil; 12 healthy men in sinus rhythm were used as controls. SDNN, RMSSD, LF, and HF were calculated after 500 recorded RR intervals at baseline, after administration of propranolol, and after administration of methylatropine. HRV at baseline and changes in HRV after methylatropine were then related to vagal tone (vagal–cardiac control), quantified as the decrease in mean RR after methylatropine. Baseline HRV was higher in the atrial fibrillation group than in the control group; after propranolol, HRV increased in both groups; and after methylatropine, HRV neared zero in the control group, whereas it returned to baseline values in the atrial fibrillation group. SD, RMSSD, LF, and HF at baseline were significantly correlated with vagal tone not only in the control group but also in the atrial fibrillation group (Van den Berg et al. 1997).

In persistent atrial fibrillation, lowered HRV correlated with increased left atrial dimensions (Friedman 2004). In a study testing a novel A1-receptor antagonist, Holter monitoring with time-domain indices was used to determine the effect. The test substance increased SDNN, pNN50, and rMSSD (Piot et al. 1998).

Stein and Lerman approached AF from the chaos theory paradigm. They developed an algorithm that, according to them, uses nonlinear predictive forecasting to search for evidence of sensitive dependence on initial conditions in a time series – a prerequisite to nonlinear deterministic systems. This algorithm seems to be based on strange attractor patterns in phase space. It was tested on simulated RR intervals and different constructed chaotic systems prior to its use on data of 16 patients with chronic AF due to heterogeneous reasons. They were able to discriminate linear, chaotic, and random types of ventricular behavior, measured as RR intervals. In AF, strictly chaos in a mathematical sense was not predominant. In a significant group of patients (but not all) the beat-to-beat ventricular response was not fully predictable (Stein et al. 1999).

Using time-domain and nonlinear measures at Holter monitoring data (ApENbb, ApENmm, Shannon entropy), the nonlinear indices predicted fatal outcomes in 107 patients with AF. When the patients were stratified with the 33rd and 67th percentile values of ApENbb (1.83 and 1.94, respectively), the 5-year cardiac mortality rates for the upper, middle, and lower percentiles were 0, 13, and 43 %, respectively (Yamada et al. 2000) (Fig. 8.5).

Another method of variability analysis in AF uses the RR interval histogram analysis. When constructing them from Holter recordings, uni-, bi-, or multimodal RR distribution patterns can be found (Bollmann et al. 2006). In about 55 % of patients, the bimodal pattern is predominant (Rokas et al. 2001), usually interpreted as conduction along two different atrio-nodal routes (Fig. 8.6).

Friedman used Holter monitoring in 38 patients with AF and used time-domain indices to characterize HRV. To stratify data and taking into account the strong rate dependence of HRV in AF, he conducted linear regressions for each HRV

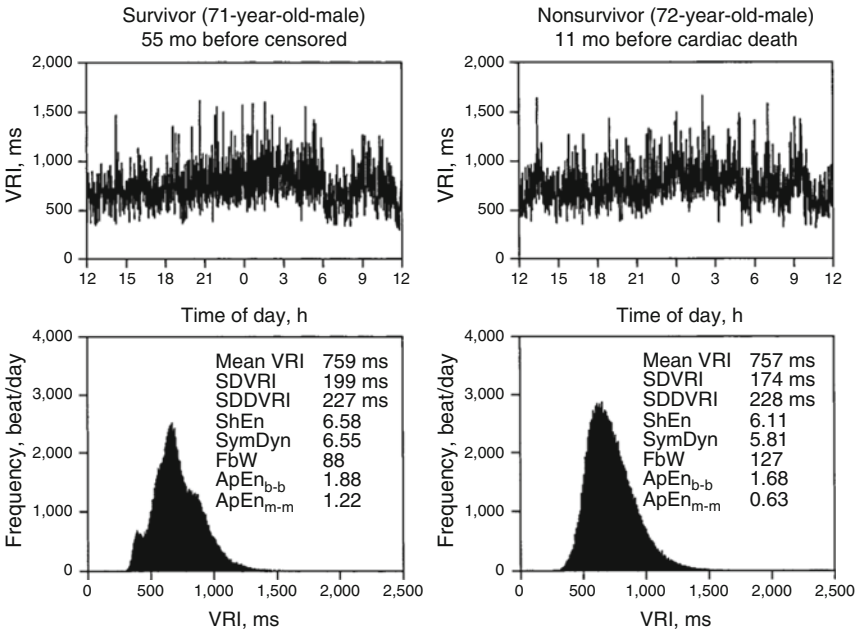

Fig. 8.5 Two examples from the Yamada study showing how subtle differences can be between two patients with difference course. Note the very similar time-domain curve but clear differences in ApEN m-m (Yamada et al. (2000), reproduced with permission from Lippincott, Williams & Wilkins)

measurement with the average RR interval as independent variable. From the regression equations, the expected HRV measurements predicted from average RR intervals were obtained for each patient. The differences between derived values and actual measurements were interpreted as an estimate of the HRV referenced to heart rate, with a negative difference denoting less HRV than expected with the data set. The HRV differences calculated this way correlated with left atrial size (Friedman 2004).

Khand used the minimal hourly RR interval, which he assumed to approximate the Av nodal functional refractory period (FRP) for that hour, and used it to examine changes during 24 h; in addition, Khand plotted RR interval histogram for each hour and calculated SDNN and SDANN. The study involved 40 patients with chronic AF. FRP correlated with SDANN and heart failure (Khand et al. 2006).

Corino analyzed BP variability rather than RR variability in 15 patients. He found a stable LF component partially independent of very irregular RR series (Corino et al. 2008).

Sosnowski analyzed Holter monitoring data of 197 patients with permanent AF and used HRVF, an index based on numerical processing of a Poincaré plot. The researchers divided the patients between subjects with HRVF under 5th percentile, respectively, under 35 % and above. In addition they calculated SDNN, SDANN, RMSSD, and pNN50. Patients with reduced HRVF were more likely to have

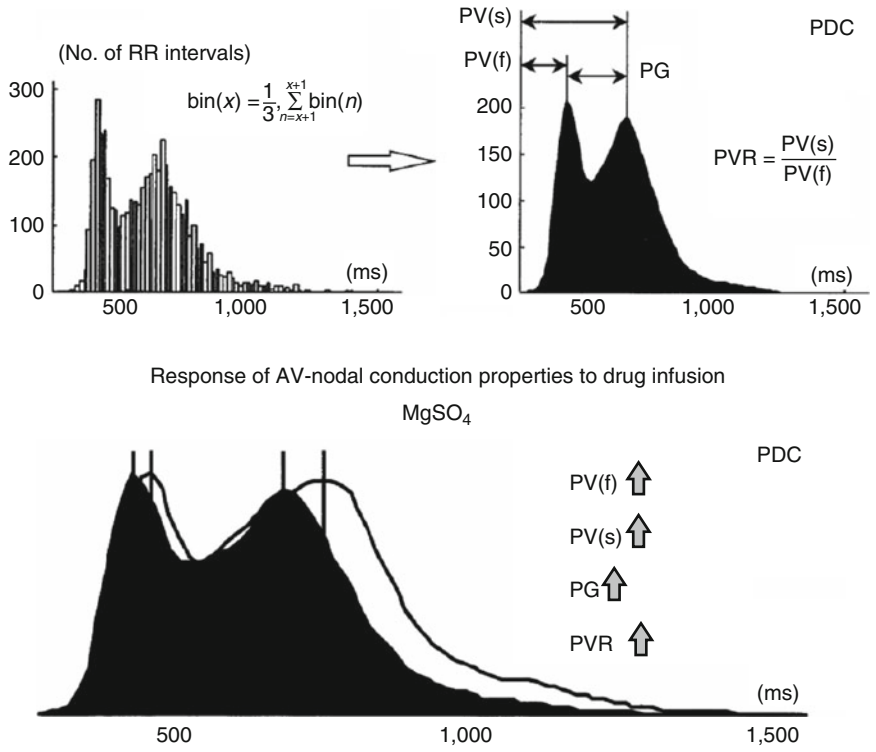

Fig. 8.6 Illustration of the RR interval histogram analysis. RR intervals with the same average heart rate are pooled into the same histogram. In this example, the effects of $MgSO_4$ infusions are shown (From Bollmann et al. (2006), reproduced with permission from Oxford University Press)

diseases like diabetes, previous MI, and coronary revascularization procedures; about one-third had an EF < 30 %. All traditional HRV parameters were significantly lower as in healthy persons. The authors use HRVF to determine global heart rate variability. They discuss the similarity of HRVF reduction with age compared with sinus rhythm (Sosnowski et al. 2011).

HRV does not necessarily deteriorate in CHF but can increase in case of physical activity. Sixty-six participants aged 69 ± 5 years with HF were randomly assigned to 16 weeks of supervised exercise training or attention control. SDNN and RMSSD were measured at baseline and after completion of the study. The exercise group had a significantly greater increase in both SDNN and RMSSD (Murad et al. 2012).

Corino used RR distances to calculate HRV in permanent AF at 127 patients and used time series of 15 min to calculate usual and rather unusual time-domain parameters (the latter pNN20 and pNN80 in addition to pNN50), as nonlinear indices ApEn and regularity index. Main findings were significant positive correlations between atrial fibrillation rate (AFR) and indices of RR irregularity and the presence of significant correlations between AFR and time-domain measures of HR

Table 8.6 Some HRV methods in permanent AF in different studies

Method	References
HRV indices compared before and after application of atropine	Van den Berg et al. (1997)
Minimal hourly RR interval (=minimal functional refractory period)	Khand et al. (2006)
HRVF	Sosnowski et al. (2011)
RR as base of HRV	Corino et al. (2013)

variability during AF in patients not treated with rate- or rhythm-control drugs (Corino et al. 2013) (Table 8.6).

As shown in this short overview, there is probably no reason to neglect HRV measurements in chronic AF. Several groups tried new approaches, but also normal linear and introduced nonlinear indices might be interesting. Often, the reason for not using HRV in AF might be that the traditional interpretation in SNS or PNS dominance is questionable. On the other hand, some intervention studies showed effects on traditional HRV parameters. In addition it has been shown in an animal model that SDNN in pigs with AF increases during vagal activation, indicating that HRV measures can at least indicate the state of parasympathetic activity (Kneip et al. 2010). HRV researchers should in the future not ignore AF patients, but rather study them separately. It is well possible that this group as well might show associations between HRV and survival or the general course of the disease.

Effects of the Maze Procedure on HRV

The maze procedure is a surgical procedure that cures atrial fibrillation by interrupting the electrical impulses that cause abnormal heart rhythm. The surgery involves the placement of incisions in both atria. When the incisions heal, scar tissue forms and prevents the abnormal electrical impulses from passing through the heart. Simple in concept, the maze procedure works essentially by creating blocks that the electrical impulses cannot cross. In so doing, it corrects all the major problems associated with atrial fibrillation: it stops the atrial arrhythmia, it restores normal rhythm between the atria and the ventricles, and it preserves the ability of the atria to contract on its own.

Kamata analyzed with the help of Holter monitoring 12 patients 1, 6, and 12 months after maze interventions (ablation) and 7 patients without, using RR intervals and computing time-domain (SDRR) and frequency-domain (HF, LF, TP) values. The circadian variation 1 month after surgery was significantly disturbed but restored after six and 12 months, possibly due to vegetative reinnervation of the sinus node (Kamata et al. 1997).

In 17 patients undergoing maze III, Holter monitoring was conducted preoperatively, 2 months and 7 months postoperatively. Two months after the operation, all HRV values were markedly reduced, 5 months later, only TP increased (Lönnerholm et al. 2003).

Discussion and Conclusion

In conclusion, the role of HRV in predicting paroxysmal or permanent AF is still unclear. Its predictive value has been challenged in predicting AF after coronary artery bypass crafting (Hakala and Hedman 2003). Another review states good results in terms of sensitivity and specificity but a lack of reliability (Poli et al. 2003). Its value in hypertension-generated AF is also unclear (Yildirir et al. 2002). Most studies and reviews use HRV to consider the vagal tone, not with a complexity paradigm.

Hypertension

Introduction

Elevated arterial pressure is one of the most important public health problems in developed countries and an increasing issue in non-industrialized countries as well. It is common, often asymptomatic, readily detectable, often easy treatable, and frequently leads to lethal complications if untreated.

Patients with arterial hypertension and no definable cause are said to have primary or essential hypertension. Secondary hypertension can occur due to renal pathology or endocrine abnormalities. More than 90 % of patients with hypertension have the primary form. Hypertension has profound effects on the body over time. It causes concentric left ventricle hypertrophy and consecutively congestive heart failure. Angina pectoris might also occur because of the combination of accelerated coronary disease and increased myocardial mass. Hypertension causes or contributes to general arteriosclerosis, leading eventually to kidney failure and/or cerebral arteriosclerosis with consecutive increased risk for stroke.

Hypertension has been early associated with dysfunction of the CNS, namely, the ANS. Before the development of effective medication, a number of operations on the sympathetic nervous system were devised in an attempt to lower blood pressure. Notable among these was radical lumbodorsal splanchnicectomy, developed in 1938 by Smithwick, which lowered blood pressure and reduced mortality but at the cost of often incapacitating side effects (Parati and Esler 2012). Antihypertensive medication eventually developed mostly affected ANS, such as central sympathetic inhibitors methyldopa and clonidine, sympathetic neuronal blockers, such as guanethidine, and alpha- and beta-adrenergic blockers. For the past three decades, the major focus in high blood pressure research has been the renin–angiotensin system. The proven value of antihypertensive drugs that block this system has led to a neglect of other blood pressure-raising systems, including the sympathetic nervous system (Parati and Esler 2012).

HRV has been used both in individuals with risk factors for, but not established hypertension, patients with hypertension, and to check the effects of antihypertensive treatment. Relevant studies are presented and their results discussed.

A Short Description of the Pathophysiology of Hypertension

It is generally recognized that the renin–angiotensin system (RAS) plays an important role in the regulation of blood pressure and renal function. In the kidney, the key role of RAS in the regulation of sodium and extracellular fluid homeostasis has been studied extensively (Kopkan et al. 2009). The relationship between fluid volume, sodium, and endogenous RAS activity is critical for maintenance of normal blood pressure level. An enhanced activity of RAS can alter this relationship leading to the development of hypertension. Angiotensin II (ANG II), as a major vasoactive agent, is responsible for physiological as well as pathophysiological effects of RAS (Navar 2004).

RAS was discovered over a century ago, but its significance in the pathogenesis of hypertension and renal disorders has gained wide acceptance only during the past several decades, largely due to the development of specific pharmacological agents designed to block the system. Renin is a protease mainly produced by the juxtaglomerular cells of the kidney and catalyzes the first step in the activation pathway of angiotensinogen to angiotensin I. Angiotensinogen is a precursor of angiotensin and is mainly produced by the liver and found in the α2-globulin fraction of plasma. ACE (angiotensin I-converting enzyme), mainly produced by the lungs and kidneys, plays a pivotal role by hydrolyzing angiotensin I into angiotensin II. This product interacts with angiotensin II receptors, leading to potent vasoconstriction, release of aldosterone by the adrenal cortex, ADH (antidiuretic hormone) secretion by the pituitary gland, renal sodium and fluid retention, sympathetic overdrive, and thirst. There are two distinct subtypes of cell surface receptors, angiotensin receptors types 1 and 2 (AT1 and AT2). AT1 seems to mediate the major cardiovascular effects of angiotensin II. In pathologic conditions, RAS is hyperactive, leading to hypertension and kidney lesions in a "vicious cycle" (Santos et al. 2012).

Another system that plays an important role in the regulation of blood pressure and renal function is a group of enzymes producing NO (called NO synthases; NOS) (Kopkan 2009). NO is characterized as a major vasodilator agent regulating basal vascular tone. It also inhibits renal tubular transport of sodium. Any pathological changes in NO function have consequences for blood pressure (Fig. 8.7).

The metabolic syndrome plays a major role in hypertension. Roughly 80 % of essential hypertension in men and 65 % in women can be directly attributed to obesity. There is a clear association between body mass index and arterial pressure even in non-obese, lean people (Mendizábal et al. 2013). There are three conditions typical of metabolic syndrome that may cause an exacerbation of sympathetic tone: hyperinsulinemia, hyperleptinemia, and hyperlipidemia. The insulin hypothesis of hypertension proposes that the compensatory hyperinsulinemia that occurs with insulin resistance increases sodium reabsorption and sympathetic activity, which combine to cause elevated arterial pressure (Mendizábal et al. 2013). Another newly researched pathophysiological player are adipocytes, which release so-called adipokine-like leptin, adiponectin, adipocyte-derived prostaglandins, endothelin-1, angiotensin II, and cytokine-like TNF-α. Also inflammatory influences are under discussion. Inflammatory processes might induce changes in cardiac function,

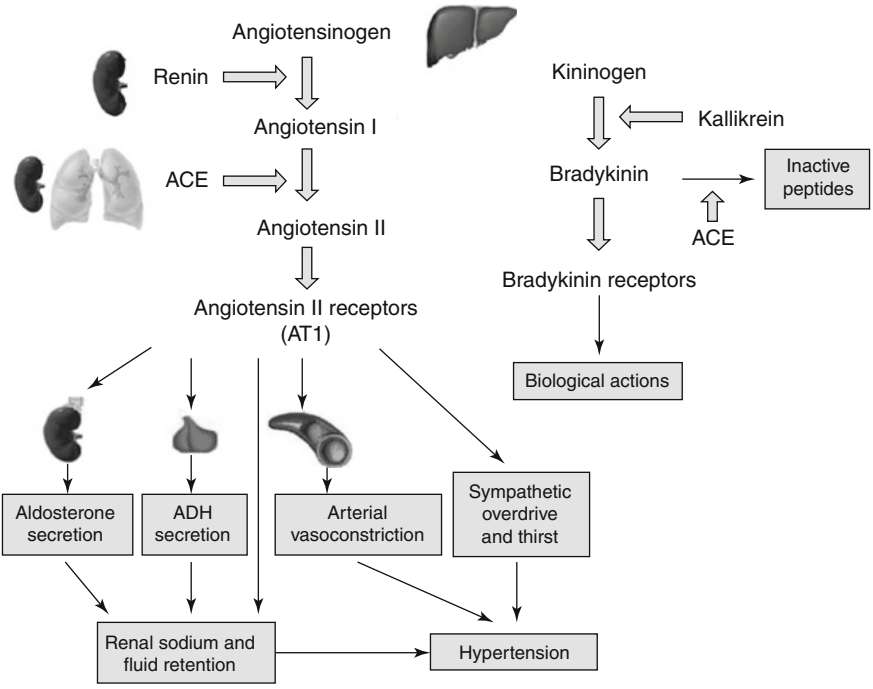

Fig. 8.7 Renin–angiotensin system and bradykinin pathways modified from (Santos et al. (2012), with permission)

peripheral vascular resistance, and renal control mechanisms of plasma electrolytes and volume. Furthermore, renal and vascular inflammation might increase oxidative stress and endothelial dysfunction, thus favoring atherogenesis (Montecucco 2011).

Renal sympathetic nerves are pivotal in the pathogenesis of experimental and essential hypertension through influences on renin release, glomerular filtration rate, and renal tubular reabsorption of sodium (DiBona 2002, DiBona and Esler 2010). With respect to the beginning of hypertensive disease, arguments have been made about a "high renin essential hypertension" (Parati and Esler 2012), where renal sympathetic activity is sufficiently elevated to increase renal secretion of renin but not to reduce renal blood flow. On the other hand, in treatment-resistant hypertension, renal sympathetic activity might play a major role as hypertension diminishes after radiofrequency ablation (Symplicity HTN-2 Investigators 2010). Other studies have highlighted the role of the kidneys. As discussed below, in end-stage renal disease, sympathetic nervous activation is at a very high level, higher than in essential hypertension and equal to or exceeding that seen in cardiac failure (Converse et al. 1992). Renal injury studies used injection of phenol into the renal parenchyma to cause renal damage. They showed increased activity of renal afferent inputs to the hypothalamus, which again caused increased CNS sympathetic outflow and hypertension (Converse et al. 1992). Our group has recently shown that sympathetic nervous activity during mental arithmetic predicts blood pressure 18 years later, indicating a possible causal factor in the

development of essential hypertension independent of the initial blood pressure (Flaa et al. 2008). Resting blood pressure is related to sympathetic activity in young men who are unaware of their blood pressure status in high, normal, and low ranges and reflects both variation in resting arterial catecholamines and variation in cardiovascular and sympathetic responses specifically to mental stress (Flaa et al. 2006).

The pathophysiology of metabolic syndrome and its relation to vascular function have become a very complex subject. Besides the sympathetic system, other pathophysiological aspects that affect vascular function include insulin, endothelium, perivascular fat, and adipokines (Mendizábal et al. 2013). One element involved in hypertension are, for instance, serotonin (5-HT) and serotonin receptors, although "it is fair to say that the effects of 5-HT within the cardiovascular system are not well understood and integrated compared with the well-established actions of 5-HT in the gastrointestinal system, and the plethora of knowledge regarding the actions of 5-HT in the central nervous system" (Watts et al. 2012). Various 5-HT receptors are known that contribute to cardiovascular regulation. In humans and in animals, 5-HT predominantly causes direct arterial constriction. The effects of 5-HT in the vasculature become less clear, however, when the subject are more complicated models and systems than an isolated vessel, probably because 5-HT is now known to possess the ability to stimulate multiple receptors within multiple tissue types that might act in seemingly contradictory fashion (Watts et al. 2012). In addition, 5-HT has multiple effects on the central and peripheral nervous system that can lead to a modification of sympathetic activity (Fig. 8.8).

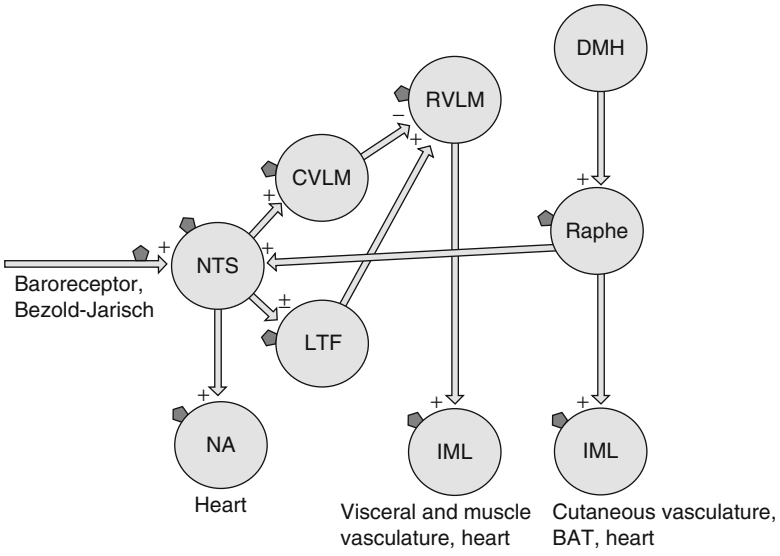

Fig. 8.8 Central autonomic circuits and potential central sites of action of systemically administered serotonin. The excitatory (+), inhibitory (−), or mixed (±) connections are shown. Solid pentagon symbols show locations of 5-HT receptors. *BAT* brown adipose tissue, *CVLM* caudal ventrolateral medulla, *DMH* dorsomedial hypothalamus, *LTF* lateral tegmental field, *NA* nucleus ambiguous, *NTS* nucleus of the tractus solitarius (From Watts et al. 2012, with permission)

HRV in Normotensive Individuals Developing Hypertension

Singh used first 2 h of ambulatory ECG recordings obtained from 2,042 persons included into the Framingham Heart Study and used SDNN, pNN50, rMSSD, TP, HF, LF, VLF, and LF/HF. HRV was significantly lower in already hypertensive men and women. Among 1,434 participants normotensive at baseline, 246 persons were newly hypertensive at follow-up 4 years later. After adjustments, multiple logistic regression analysis revealed an association between LF and incident hypertension in men but not in women. SDNN, HF, and LF/HF were not associated with hypertension in either sex (Singh et al. 1998).

A stratified random sample of 2,061 examinees from the biracial Atherosclerosis Risk in Communities (ARIC) cohort was used in this analysis. From this sample, 650 hypertensive persons were identified. Of the other normotensive persons at baseline, 64 participants developed hypertension during 3 years of follow-up. A graded inverse association between baseline HF and the risk of incident hypertension was observed. No clear association was observed for LF. An association for LF/HF and SDNN and incident hypertension was also found (Liao et al. 1996). These results were followed up 7 years later (Schroeder et al. 2003).

Schroeder and collaborators investigated the temporal sequence linking hypertension, blood pressure, and heart rate variability in a population-based cohort of 11,061 individuals aged 45–54 years at baseline. HRV was assessed by 2-min initially and 6-min beat-to-beat heart rate recordings approximately 9 years apart, focusing on SDNN and RMSSD. SDNN, rMSSD, and R-R interval were lower among hypertensives compared with normotensives, and this difference persisted after adjustment for age, sex, race, study center, diabetes, smoking, education, and BMI. Treated hypertensives had a higher rMSSD but no difference for SDNN. In general, those using β-blockers had HRV equal to or greater than that in untreated hypertensives, whereas those using diuretics or ACE inhibitors had a lower HRV. Higher blood pressure was associated with markedly lower HRV in the entire cohort. After adjustment for age, sex, race, study center, smoking, education, and BMI, researchers observed an inverse relation between HRV at baseline and development of hypertension. Twenty ms lower SDNN were associated with a 1.12 higher risk for hypertension at the follow-up. The authors concluded that individuals with low HRV at baseline were at an increased risk of developing hypertension over 9 years of follow-up, thus indicating that decreased HRV often precedes the development of hypertension (Schroeder et al. 2003).

One thousand six hundred and thirty-eight subjects were included in a study that included a short-term HRV (5 min). Nine hundred and ninety-two non-hypertensive participants completed the follow-up 7 years later, and 959 participants were included for the final analysis. Incident hypertension was determined by blood pressure status at follow-up. In a multivariate model LF/HF ratio and HF were independently associated with incident hypertension (Wu et al. 2013).

HRV in Hypertensive Compared to Normotensive Persons

Clear differences in HRV between hypertensive and normotensive persons have been shown in many studies, both prospective and cross-sectional ones (Chakko et al. 1993; Fagard 2001; Guzzetti et al. 1988; Huikuri et al. 1996a, b; Langewitz et al. 1994; Liao et al. 1996; Mussalo et al. 2001; Petretta et al. 1995; Prakash et al. 2005; Radaelli et al. 1994; Schroeder et al. 2003; Siché et al. 1995; Singh et al. 1998; Virtanen et al. 2003; Wu et al. 2008).

A typical study was presented by Huikuri. Time- and frequency-domain measures of HR variability were compared in randomly selected, age-matched populations of 188 normotensive and 168 hypertensive males. SDNN was lower in the hypertensive subjects than in the normotensive ones (52 ± 19 vs. 59 ± 20). VLF analyzed as absolute unit was reduced in the hypertensive patients relative to the normotensive controls. Multiple regression analysis showed that SDNN was predicted most strongly by systolic blood pressure, both in the patients with hypertension and in the normotensive subjects (Huikuri et al. 1996a, b). These differences were also shown in studies using short-term HRV. In 34 patients with severe hypertension, 29 patients with mild hypertension and healthy control subjects were studied using 10-min recordings with frequency-domain values. In the group with severe hypertension, SDNN, rMSSD, TP, LF, and HF were significantly lower than in the healthy control group and the group with mild hypertension (with exception of rMSSD), whereas there was no relevant difference between the group with mild hypertension and the control group (Mussalo et al. 2001).

A Holter monitoring was established in 215 patients with untreated hypertension. Nine percent showed a corrected QT (QTc) >440 ms, which is a risk factor for ischemic heart disease in persons with essential hypertension. Time-domain indices (SDNN, RMSSD, pNN50) were reduced in this group, compared to patients with normal QTc (Maule et al. 2008).

Younger women have a higher LF and lower HF ($n = 1{,}780$) (Koskinen et al. 2009). Women with a new diagnosed essential hypertension had a lower SDNN, LF, and a generally lower HRV during paced breathing (Pavithran et al. 2008).

Most cross-sectional studies show convincingly reduced time-domain indices in relation to untreated hypertension. These differences decrease under effective treatment and also probably as an effect of aging (Schroeder et al. 2003), when the lower time-domain indices of hypertensive persons and the initially higher indices of healthy persons converge.

Frequency-domain measures are more difficult to interpret in this context. In some studies, LF is higher in hypertensive participants (e.g., Guzzetti et al. 1995; Prakash et al. 2005; Pavithran et al. 2008 or Wu et al. 2008); in other LF is rather low (e.g., Liao et al. 1996, Sevre and Rostrup 2001; Singh et al. 1998). This might be due to the heterogeneity of hypertension and to difficulties of finding groups with isolated hypertension without any other syndromes. Most participants in studies are necessarily in antihypertensive treatment. Given the confounding effects of different kinds of medication, it is not surprising that HRV indices can differ. But even

looking at patients with one identical treatment approach can reveal different effects in diverse studies. Persons taking beta-adrenergic blocker have in some studies increased (Schroeder et al. 2003) and in other studies decreased (Chiladakis et al. 2004) HRV.

Conclusion

Autonomic system abnormality, clinically manifested as a hyperkinetic circulation characterized by elevations in heart rate, blood pressure, plasma noradrenaline levels, and cardiac output, has been repeatedly demonstrated in hypertension. A transition from the early hyperkinetic state to a high resistance, established hypertension has been documented in longitudinal studies. High blood pressure induces vascular hypertrophy, which in turn leads to increased vascular resistance. Cardiac output returns from elevated to normal values as beta-adrenergic receptors are downregulated and stroke volume decreases. In parallel with the hemodynamic transition, the sympathetic tone is reset in the course of hypertension (Palatini and Julius 2009). We know that all this is associated with a moderate reduction of some HRV indices before clinical onset of hypertension. In manifest hypertension, HRV is reduced, which again might be a predictor of later cardiovascular pathology. Antihypertensive drugs increase different HRV indices often but not always. This should not be confused with an established proof for their effectivity in preventing hypertension-associated deterioration or prolongation of life expectancy.

Other Cardiologic Diseases and Problems

Power spectrum analysis of HRV in cardiac transplant recipients showed a reduced HRV, which fits with the hypotheses that HRV is influenced by autonomic nerve tone. Furthermore, rejection reactions showed increased HRV (Sands et al. 1989). This has been reproduced in pediatric transplantation patients. In addition, in some patients 4 years posttransplantation increasing sympathetic influence can be shown by HRV changes (Pozza et al. 2006).

Twenty-three high-risk noncardiac patients were continuously monitored from the evening before surgery up to 80 h during the postoperative period. Nine of them demonstrated postoperative ventricular dysfunction, 14 had an uncomplicated postoperative course. All but two patients had high ApEN (>0.7). Postoperative ApEn < 0.55 had a sensitivity of 88 % and a specificity of 71 % to be associated with postoperative ventricular dysfunction, two times ApEn < 0.7 % with 8-h timeframe between had a specificity of 79 % (Fleisher et al. 1993).

There is a phenomenon of *sudden cardiac death* in *epilepsy* patients. The risk of this might be attenuated through successful surgery. Twenty-one patients before and after temporal lobe epilepsy surgery were studied. The patients with poor outcome

after surgery (remaining attacks) had lower TP, SDNN, VLF, and LF than matched healthy controls; the patients with favorable outcome did not differ from the controls. There were no postoperative changes in HRV compared with preoperative results. The present lower HRV in patients with bad surgical outcome was already in place before operation (Persson et al. 2006). Reduced heart rate variability has been observed in patients with refractory epilepsy and can be induced in animal models; its role in sudden unexplained death in epilepsy (SUDEP) is not known (So 2008).

Ninety-six patients with *viral myocarditis* were followed over 6 months. All time- and frequency-domain measures were significantly reduced in the early stage of the disease but improved after 6 months (Gao et al. 2008).

HRV has been tested to distinguish between patients after syncope in emergency departments. Thirty-two patients were recruited, and HRV parameters were compared with existing syncope risk guidelines of the department. No HRV parameter showed a statistical difference in relation to risk assignments (Bonney et al. 2009).

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Chapter 9
Perioperative Care

Introduction

For anesthesiologists preparing patients for operations, perioperative care involves inducing a reversible state of loss of responsiveness, amnesia, analgesia, decreased stress response, and possibly unconsciousness (depending on the kind of operation), maintaining homeostasis under operations, and any treatment after operations to support the initial phase in the patient's recovery. Most anesthesiologic and surgical procedures can have profound effects on homeostasis, including fluid balance, the cardiovascular system, and the autonomic nervous system. The fact that one-third of all postoperative complications and 50 % of postoperative mortality are due to cardiac events underlines the importance of risk estimation (Laitio et al. 2007). But not only cardiac events are of interest. Simple methods like score or bedside investigations, which do not depend on advanced qualifications and experience (e.g., echocardiography) to detect fluid imbalances, beginning SIRS or other circumstances that can have consequences for the planning and execution of anesthesia are needed. In this context, anesthetists have been well aware for decades now of the association of pathological changes in ANS and worse outcome, for instance, in diabetic patients with advanced autonomous neuropathy (Burgos et al. 1989).

Not surprisingly, heart rate variability has been used to predict instability, to monitor anesthesia, and to guide perioperative treatments. It is, however, far from being an established tool for anesthetists. HRV has been recently proposed as "helpful, non-invasive, bedside, low-cost monitoring tool to evaluate the perioperative risk in patients with suspected autonomic dysfunction, to select individuals who need further cardiac testing and to optimize preoperative status" (Mazzeo et al. 2011).

Perioperative problems have been associated with ANS dysfunction (e.g., Mazzeo et al. 2011), but there is no clear evidence for this, as discussed in Chap. 4. This is not an issue in this chapter. The question itself is a very interesting research question for anesthetists, but our main focus here is on the associations between alterations of HRV and perioperative morbidity and mortality.

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Induction and Maintenance of General Anesthesia

General anesthesia is a pharmacologically induced and reversible state of amnesia, analgesia, loss of responsiveness, loss of skeletal muscle reflexes, and decreased stress response. Anesthetic agents are intravenous drugs or inhalation agents. All anesthetic agents have more or less profound effects on the cardiac and circulatory system. Most volatile agents are potent vasodilators and reduce systemic vascular resistance. They can increase heart rate due to reduced blood pressure but also independently of blood pressure. At least some volatile agents have a direct influence on SNS and PNS. They depress baroreceptor function and cause a decrease in stroke volume, which results in reduced cardiac output. All volatile agents sensitize the myocardium to adrenaline. In addition, anesthetic agents depress CNS function. All these elements are also part of the system that causes HRV; thus, one should expect any form of anesthesia to affect HRV.

Prediction of Hypotension

Nearly all forms of anesthesia cause hypotension, but some patients develop higher falls in blood pressure than others. Preoperative low blood volume is a frequent cause for low blood pressure after induction of anesthesia. In healthy patients, compensatory mechanisms blunt the effect of blood loss or dehydration. At the moment when anesthetic agents diminish cardiocirculatory reflex responses, blood pressure goes down. One issue in HRV research is therefore to identify patients at risk for a more pronounced blood pressure fall. Another issue is rhythm disturbances like brady- or tachycardia during or after the induction phase.

In an early study, low HF (then described as RF) predicted bradycardia in 80 % of included patients (Estafanous et al. 1992). Huang studied 46 patients with and 87 patients without diabetes, all of them ASA II or III undergoing elective surgery. They obtained 5 min HRV measurements under paced breathing immediately before anesthesia. TP, LF, and HF were lower in participants with hypotension (defined as decrease of greater than 30 % or a systolic BP under 85). Interestingly enough, in contradiction to results in association of spinal anesthesia presented later in this chapter, LF/HF showed no association. Unfortunately, Huang does not present mean and standard deviation of the HRV measures (Huang et al. 2006). In diabetic patients, HRV has been recommended as standard test, meant to give additional crucial information in preventing hypotensive episodes in diabetic patients with diabetic autonomic neuropathy (Oakley and Emond 2011).

Prediction of Cardiac Events

In a study, Mamode included 297 patients undergoing elective peripheral arterial surgery and used a plethora of blood samples, myocardial perfusion scanning, and heart rate variability (Holter monitoring) preoperatively. Patients were screened for

myocardial infarction the first three postoperative days with ECG and cardiac isoenzymes (CK-MB). Primary end point of the study was the occurrence of myocardial infarction or cardiac death within 30 days postoperatively. Twenty-one patients reached this end point (14 death, 7 myocardial infarction). Clinical risk factors were poor predictors. High predictive value had increased age, ECG evidence for previous myocardial infarction, prior aortic surgery, positive thallium scan, and impaired HRV (triangular index). For the interpretation of the study, it is of major significance that several different HRV measures had no predictive value, so SDNN, SDANN, pNN50. They did not apply frequency-domain algorithms, neither nonlinear measures. Their combined model showed a sensitivity and specificity of 84 and 80 %, respectively, for perioperative cardiac events (Mamode et al. 2001).

For measuring preoperative HRV on 32 patients >60 years of age undergoing operations for traumatic hip fractures, Holter ECG recordings were made using short-term fractal scaling exponent. In stepwise multivariate logistic regression, this variable was the only independent predictor of postoperative prolonged ischemia, showing an odds ratio of 7.7 (Laitio et al. 2004).

One hundred patients ASA 3–4 scheduled for major vascular or abdominal surgery were examined with a 24-h Holter monitoring, and the revised cardiac risk index was calculated; patients were only included with a score of three or more. Intraoperative hypotension was defined as a fall of MAP to 60 % of preoperative MAP, bradycardia as a decrease of heart rate to 60 % of baseline or lower than 50 beats per minute. The first 50 patients were analyzed retrospectively, the second 50 prospectively. A cutoff for TP of 500 ms^2 was chosen after the retrospective part to distinguish low-risk and high-risk patients, lower TP indicating possibly unstable patients. TP < 500 did predict bradycardia, hypotension, and use of vasopressors but not atropine (Hanss et al. 2008).

Mazzeo proposes HRV to guide premedication with beta-blockers. According to this idea, HRV with low variability should give a relative indication for perioperative use of beta-blockers. This has not been studied yet, but Mazzeo quotes an intervention study for myocardial infarction (Lampert 2003). This patient population consists of postmyocardial infarction patients. HF was a predictor for outcome. HF was more increased in patients treated with propranolol than in patients with placebo. The conclusion that beta-blockers should be considered for patients with low HF (or generally low HRV) is not backed by this evidence, but it is a good indication for a well-controlled study.

Effects of Anesthesia on HRV

Inducing anesthesia with propofol and maintaining it with isoflurane/nitrous oxide led initially to reduction of HF and increase of LF, but HF returned subsequently under isoflurane/nitrous oxide, while LF remained depressed (Galletly et al. 1992).

Thiopental has a bigger effect on HRV frequency domain than etomidate (Latson et al. 1992; Scheffer et al. 1993). Inhalation of 30 % N_2O in healthy subjects led to

reduction in HF and to a rise in LF/HF ratio. The authors discussed the effect as consistent with an enhanced sympathetic balance of sinoatrial control through reduced parasympathetic tone (Galletly et al. 1993). No difference has been observed between isoflurane 1.5 % and halothane 0.75 % (Galletly et al. 1994a).

Induction of anesthesia with propofol in ten women undergoing laparoscopy led to reduction of TP, LF, and HF, maintenance with propofol in further reductions of TP and LF but not HF. Placement of the laparoscopic trocar led to an increase in HF. This was interpreted to mean that propofol had less of an effect on the parasympathetic tone than on the sympathetic tone, which makes the patients more sensitive to bradycardia-inducing events (Deutschman et al. 1994). In another study, LF, MF, and HF was decreased, but LF reduction was less than MF and HF reduction (Galletly et al. 1994b).

Induction with thiopental alone caused a higher blood pressure increase than a thiopental/midazolam induction. After induction with thiopental alone, HF increased under intubation conditions, whereas in the thiopental/midazolam group, HF continued to decrease (Nishiyama et al. 2002).

In a study comparing propofol and sevoflurane anesthesia, propofol had no effects on LF but induced a decrease in HF. Sevoflurane decreased LF but had no effect on HF. LF/HF ratio was not changed in either group (Kanaya et al. 2003).

Premedication with temazepam before induction with propofol or thiopental led to a higher HF, LF, and TP as without premedication but not in the LF/HF ratio. The induction itself induced reductions in TP and HF and an increase in LF/HF ratio (Howell et al. 1995).

Thirty-eight patients undergoing lung resection for cancer were randomized to thoracic-epidural treatment or general anesthesia followed by patient-controlled analgesia (PCA) as postoperative pain treatment. After operation there were no differences in regard to pain but lower incidence of hypertensive or tachycardia periods in patients with epidural. HRV data were collected four times, preoperatively, 4 h after the operation and at the first and second postoperative day. Frequency-domain measures were used. HRV values decreased generally after operation and remained low in both groups until the second postoperative day. However, in the epidural group, HRV increased day one and two. LF/HF remained unchanged in the PCA group all the time, whereas it was reduced during the whole observation period after use of epidurals. This was discussed as a shift in sympathovagal balance toward vagal predominance (Licker et al. 2003).

In a randomized study, propofol or propofol/midazolam inductions were compared and their effects on short-term HRV post-induction. Propofol was administered at 2.5 mg/kg in the propofol group and midazolam at 0.1 mg/kg followed by propofol at 1.5 mg/kg in the midazolam–propofol group. The midazolam–propofol combination had an increased LF/HF ratio the first minutes after induction, which was interpreted as compensated modulatory effects on the cardiovascular system (Win et al. 2007).

In summary, there is good evidence that anesthesia changes HRV parameters. In most studies LF increases and/or HF decreases, leading to a changed LF/HF ratio. No nonlinear factors have been tested, probably due to the necessary use of short-term HRV of less than 10 min.

Spinal Anesthesia

In spinal anesthesia, a small amount of local anesthetics is injected intrathecally on the level of L3 or L4, where damage to the spinal cord is unlikely. Depending on the amount, spinal anesthesia can anesthetize the legs or bigger parts of the body up to the Th4 level. The physiological effects of spinal anesthesia depend on the level. The effects depend also on the concentration of the agent, the speed of injection, the specific gravity of the solution, the position of the patient, the presence of increased intra-abdominal pressure, and other factors. The SNS is blocked in proportion to the height of the anesthesia level obtained. Total sympathetic block can be expected from high spinal anesthesia exceeding Th2. This produces a 15–20 % decrease in mean arterial pressure, central venous pressure, and total peripheral resistance. Cardiac output, stroke volume, and heart rate are not substantially affected but can change due the decreased resistance. Hypotension is a well-known side effect of spinal anesthesia and can be profound. In some departments, either infusion of 1 l saline or use of catecholamines is used as preventive measure. Here too, it is of interest to identify patients with possible major blood pressure drop after induction.

In a retrospective study, short-term HRV was analyzed in 41 patients scheduled for elective cesarean delivery. They were grouped in three categories: mild decrease of systolic blood pressure (>100 mmHg); moderate decrease (80–100); and severe decrease (<80). LF/HF was increased in patients with moderate to severe BP decrease (2.8; 2.7 and 1.2, respectively). In a prospective study with 19 patients, this result was confirmed (Hanss et al. 2005). These results led to an intervention study in the same patient group: patients received vasopressors or preoperative colloid infusion if LF/HF was greater than 2.5. Hypotension did not occur in 17 of 20 patients with LF/HF > 2.5; in the control group, 20 of 23 patients with LF/HF > 2.5 developed hypotension (Hanss et al. 2006).

Fifty two Patients undergoing elective transurethral surgery were tested before and after onset of spinal anesthesia with HRV, using traditional indices and ultra short-term entropy (UsEn) as a nonlinear index. The patients were then assigned to two groups (Group LO and HI) according to preoperative UsEn. Spinal anesthesia decreased LF/HF but did not affect UsEn. The number of patients who developed hypotension was significantly higher in the group with lower UsEn (Fujiwara et al. 2007).

Short-term HRV of 80 ASA I–II patients scheduled for spinal anesthesia was obtained, and the predictive value for severe bradycardia after onstart (defined as <45 bpm) was analyzed. Nineteen of 80 patients developed bradycardia. HF in the bradycardia group was significantly higher (1,061 ± 1,301 vs. 696 ± 1,378). With the help of ROC analysis, a sensitivity and specificity of 65 % was detected; however, low baseline HF had a sensitivity and specificity of 74 % (Chatzimichali et al. 2011).

The studies by Hanss are one of the few examples that used HRV (successfully) to guide interventions.

Maintenance of Anesthesia

In 20 spontaneously breathing patients undergoing minor surgical procedures with a propofol/fentanyl anesthesia, the relationship between heartbeats and respiration was examined. There was evidence for phase coupling in whole number ratios. Phase coupling seemed to be unidirectional from the respiratory system to the sinus rhythm. Six different coupling patterns were observed (Galletly and Larsen 1997). Apnea during stable anesthesia leads to reduction of HF but not LF (Nakatsuka et al. 2002).

Using point correlation dimension (PD2), it was possible to predict hypotension accompanying spinal anesthesia for cesarean delivery in all 11 patients with a systolic blood pressure <75 % of baseline compared to 11 patients without hypotension (Chamchad et al. 2004). Short-term HRV was used to monitor the stress response during awake craniotomy. Specially LF/HF ratio yielded a stress/response pattern and could probably be used to monitor stress responses during anesthesia (Conte et al. 2009).

Postoperative Course

One hundred and six patients admitted in the ICU after abdominal aortic surgery were analyzed with the help of 24-h Holter ECGs. VLF was a rather strong predictor for length of stay at the ICU. Other predictors were increased age and insulin-dependent diabetes (Stein et al. 2001).

Eighty patients with a history of PAF were evaluated by Holter monitoring and blood samples measuring neuropeptides and catecholamines pre- and postoperatively. 36.3 % of patients developed AF postoperatively and showed a significant lower HF and LF/HF ratio. HF decreased in both groups postoperatively. Neither neuropeptides nor catecholamines differed between the groups (Jideus et al. 2001).

Between 1994 and 1996, Mamode examined 297 patients in terms of different risk factors for perioperative mortality undergoing peripheral arterial surgery (92 aortic, 47 carotid, 37 infrainguinal, 13 major amputation, and 108 miscellaneous procedures) and used Holter monitoring to obtain HRV (SDNN, SDANN5, triangular index, and pNN50). The primary end point of the study was the occurrence of myocardial infarction or cardiac death within 30 days of surgery. Twenty-one patients had myocardial infarction or died within 30 days. Independent end point predictors determined through a logistic regression analysis were increased age, ECG evidence of previous myocardial infarction, aortic surgery, impaired heart rate variability (triangular index), and positive thallium scan. The mean triangular index for patients with fatal events was 21.5 (±1.7), for patients without 26.6 (±0.6). The authors propose a cutoff value of <25 to identify high-risk patients. Interestingly, SDNN seemed not to be a significant factor in the statistical model, neither in univariate analysis; it is not mentioned in the results of the article (Mamode et al. 2001).

Laitio studied 32 patients over 60 who had been admitted to hospital for surgical repair of a traumatic hip fracture. He used preoperative Holter monitoring. Twelve patients experienced in all 384 ischemic episodes. Preoperative α1 was significantly lower (i.e., increased randomness in HRV) during nighttime compared with daytime in patients with postoperative myocardial ischemia. In stepwise multivariate logistic regression analysis, increased preoperative night/day difference of α1 was the only independent predictor of postoperative prolonged ischemia. LF in patients with no ischemia was 179 ± 63 compared with 278 ± 131 in patients with ischemic episodes, HF 127 ± 34 compared to 325 ± 176. SDNN was 28.9 ± 3.3 compared to 30.1 ± 4.8. Thus, although only α1 remained significant in this small study, it is not improbable that LF and HF can be relevant predictive factors if analyzed in a higher number of patients (Laitio et al. 2004).

With a prospective study, Filipovic showed that LF/HF ratio <2 analyzed only 6 min before induction of anesthesia was the best predictor for 2 year all-cause mortality in 167 patients (odds ratio 6.4, CI 1.9–21). This study included risk score established by Eagle et al. (2002) and Detsky et al. (1986) and the Revised Cardiac Risk Index (Lee et al. 1999). The only other main independent predictors were a history of congestive heart failure and age over 70 (Filipovic et al. 2005).

Our own preliminary results in hip fracture patients support the studies above. In a pilot study, we enrolled 22 consecutive patients with hip fracture scheduled for operation. Within 24 h after the event, we took a 10-min ECG analyzed for time and frequency domain, in addition ApEN. Perioperative complications were recorded, including pneumonia and cardiac events. Thirty percent of patients had some perioperative problems, such as stroke, MI, or pneumonia. We found significant univariate associations between perioperative problem and several HRV parameters. Heart rate, TP, normalized LF and HF, LF/HF, and VLF were significantly lower in patients developing postoperative problems. In multivariate analysis, LF/HF and VLF had the highest predictive value (Ernst G, 2011, unpublished results) (Fig. 9.1).

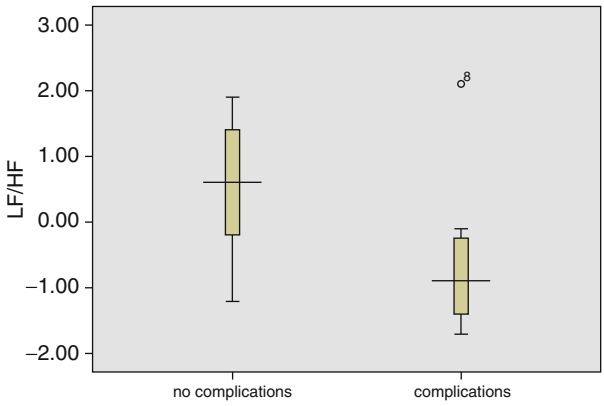

Fig. 9.1 LF/HF and perioperative complications

Conclusion

There is evidence that preoperative HRV measurement offers a feasible technique for stratifying perioperative risks and for estimating the need for further preoperative evaluation and optimization. Mazzeo concludes: "In an ideal setting, a preoperative HRV measurement should be performed to evaluate perioperative risk in patients with known ANS dysfunction or in patients with suspected dysautonomia undergoing high risk procedures." Mazzeo suggests that such an evaluation be performed at least 2 weeks before scheduled operation (Mazzeo et al. 2011). Different linear and nonlinear HRV measures have been used to identify patients at risk before surgical procedures and to predict successful outcome in therapeutic procedures. There have been some promising results, but HRV analysis in anesthesiology has not been used often. Thus, it is not possible to draw conclusions regarding clinical usefulness. Mazzeo et al. (2011) proposes to investigate patients with cardiac history or an existing risk for ANS imbalances at least 2 weeks before elective surgery and to use HRV beyond others to select patients who need further examination (e.g., by cardiologists) preoperatively. Existing studies offer strong evidence in this regard, but this conclusion seems premature. We need more efficacy studies that not only describe HRV abnormalities but also use the results within a preoperative algorithm.

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Chapter 10
Intensive Care and Trauma

Sepsis

Introduction

During the course of the twentieth century, impressive innovations were introduced that improved the treatment of critically ill persons. Such innovations include the identification of the entity "shock" and its treatment by fluid resuscitation in the 1930s, introduction of dialysis in the 1950s, modern respiratory therapy following the big polio epidemics of the 1950s, and improved treatment of respiratory failure in the 1960s. Probably because patients survived such ailments, in the 1970s increased awareness of conditions eventually led to the description of what we now call "multiple organ failure." The idea of sepsis is much older, but the concept has changed fundamentally over the last decades. Originally, sepsis was associated with the fatal effects of bacteria coming from a certain source and circulating in the blood. As early as in the 1970s, a concept arose which described the fatal effects of sepsis not as consequence of bacterial damage but as consequence of an overreacting immune system. Lewis Thomas wrote 1972 "the microorganisms that seem to have it in for us… turn out… to be rather more like bystanders… It is our response to their presence that makes the disease. Our arsenals for fighting off bacteria are so powerful… that we are more in danger from them than the invaders" (Thomas 1972). In the following years, animal models were developed that led to the description of immunological cascades involving different pro- (and anti-) inflammatory substances. Possible interventions were then outlined and tested on animals, albeit with disappointing results. Until now, only two non-antibiotic medicaments with effect on sepsis survival (see below) have been identified. The concepts did not arise from an increased pathophysiological understanding; rather, pathophysiological concepts changed with the evolution of clinical experience. Enormous evidence about sepsis as a complex syndrome with multiple circuits and feedback mechanisms has been published. Sepsis is perhaps one of the best-described pathological

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conditions, but there is no qualitative comprehensive model, not even a quantitative temporal model.[1]

Sepsis is today defined as an infection-induced syndrome with two or more of the following features of systemic inflammation: fever or hypothermia, leukocytosis or leucopenia, tachycardia and tachypnea, or supranormal minute ventilation. If proof for bacterial involvement is absent, it is called SIRS (systemic inflammatory response syndrome). When an organ system begins to fail because of sepsis, the sepsis is considered severe (Bone 1992). Each year, sepsis develops in more than 500,000 patients in the United States and only 55–65 % of them survive (Rangel-Frausto 1995). There have been considerable advances in the treatment of sepsis in the last years. Some landmark studies have focused on special treatment algorithms like low-dose steroids (Annane et al. 2004), tight glycemic control (van den Berghe et al. 2001), and active protein C (a coagulation factor) in special subgroups (Bernard et al. 2001). A landmark study changed focus on the early development of sepsis. Aggressive treatment of patients with fluids, blood concentrates, and vasoactive medicaments in addition to standard treatment was shown to have an effect if it was started within hours of the first symptoms, whereas similar interventions 6 h later failed to have an effect on the outcome (Rivers 2001). The first hours of sepsis have been termed the "golden hour" and "silver day" of early resuscitation (Rivers et al. 2005). Thus, early identification of sepsis has become more important than ever. But also identifying treatment responders and nonresponders is an important part of clinical work. For both parts, heart variability analysis with different algorithms has been advocated.

Pathophysiological Considerations

It is difficult to outline a general model of sepsis, but it is possible to draw a reasonable picture of the early biochemical events involved. A trigger such as a microbial toxin stimulates the production of cytokines such as tumor necrosis factor and interleukin-1, which in turn promotes endothelial cell-leukocyte adhesion, release of proteases, and arachidonate metabolites, and activation of clotting. Interleukin-1 and TNF are proinflammatory messenger molecules and have similar and synergistic properties. In animal models, inhibiting their effects had positive effects on the sepsis course, but in human patients their use had disappointing results. Interleukin-8, a neutrophil chemotaxin, may play an especially important role in perpetuating tissue inflammation. Interleukin-6 and interleukin-10, which perhaps are counterregulatory, inhibit the generation of tumor necrosis factor, augment the reaction of acute phase reactants and immunoglobulins, and inhibit T-lymphocyte and macrophage function.

[1] To focus on the complexity of illnesses in the intensive care unit, mathematicians, physicists, and clinicians recently founded a new society on complexity in acute illnesses. See www.scai-med.org.

Sepsis has been considered a failure of the immune system. In this context, T-lymphocyte anergy and apoptosis have been described (Hotchkiss and Karl 2003). The arachidonic acid metabolites thromboxane A_2 (a vasoconstrictor), prostacyclin (a vasodilator), and prostaglandin E2 participate in the generation of fever, tachycardia, tachypnea, ventilation/perfusion abnormalities, and lactic acidosis (Wheeler and Bernard 1999).

Over the course of sepsis, pulmonary dysfunction is frequent. Respiratory failure often progresses rapidly; a sustained respiratory rate that exceeds 30 breaths per minute is usually a sign of impending ventilatory collapse, even if arterial oxygen levels are normal. Timely intubation and mechanical ventilation reduce respiratory muscle-oxygen demand and the risk of aspiration.

Cardiovascular failure is part of any severe sepsis. Shock is caused by an inadequate supply or inappropriate use of metabolic substrates (especially oxygen), resulting in lactate acidosis and tissue damage. In a high percentage of patients, sepsis leads to acute heart failure with reduced contractility of the heart muscle. Frequently, a low systemic vascular resistance is observed and has to be treated. Real dysfunction due to hypotension, volume deficits, and circulating inflammatory agents can lead to renal failure. Hypoperfusion of bowels leads to atrophy of gut mucosal cells. This consecutively leads to aggravation of the immunologic barrier function of the gut and increased uptake of bacterial substances. Coagulopathy develops and is caused by deficiencies of the coagulation system proteins, including protein C, antithrombin III, tissue pathway inhibitor, and the kinin system. A temporal network of the genetic activation and deactivation patterns has been analyzed and described recently. It shows how different genes change their activity level dependent on their interaction within the first 24 h (Calvano et al. 2005).

Schmidt and Werdan offer one possible explanation for the attenuation of HRV as consequence of sepsis (Werdan et al. 2009). As discussed in other chapters, the efferent sympathetic and vagal signals to the heart use binding of the neurotransmitters norepinephrine to cardiac adrenoceptors and acetylcholine to muscarinic receptors. Receptor binding triggers signal transduction pathways in the cardiac pacemaker cells that finally result in a modulation of the pacemaker current. This pacemaker current is mainly conducted through the I_f current. It is the result of ion flux through the hyperpolarization-activated cyclic nucleotide-gated (HCN) channel. The channel is controlled by direct interaction with cyclic adenosine monophosphate and hence contributes to sympathetic and parasympathetic regulation of the heart rate. Schmidt and Werdan's in vitro experiments demonstrated both a direct inhibitory effect of endotoxin on I_f and a sensitizing of I_f to b_1-adrenergic catecholamines. These phenomena might trigger a narrowing of HRV and therefore might contribute to the autonomic cardiac dysfunction (reduced HRV) seen in patients with sepsis, SIRS, and MODS. Consequently, autonomic dysfunction is the result not only of an alteration of the autonomic nervous system but also of an impairment of the signal transduction pathways and ion channels mediating the autonomic nervous signals in the heart itself (Werdan et al. 2009).

Severe sepsis has been associated to a dysfunction of the HPA axis. It might be of significance that subgroups of test persons with high sympathetic (like) reaction on

acute stress have at the same time higher cortisone levels and test persons with lower sympathetic activation similarly lower levels (Uchino et al. 1995). This might be reflected in the circumstance that patients with a low LF/HF ratio have a worse prognosis and at the same time might have higher steroid levels than survivors. Inflammation in peripheral tissues alters neuronal signaling in the hypothalamus. This is a consequence of bidirectional communication between the immune and the nervous system. Neurons in the CNS can synthesize and express TNF and interleukin-1; cytokines can activate hypothalamic–pituitary release of glucocorticoids. In turn, glucocorticoids suppress further cytokine synthesis. Cells of the immune system can produce neuropeptides, acetylcholine, and other neurotransmitters. Glial cells in the CNS play an active role in this process (Tracey 2002). The parasympathetic system has been described as a cholinergic anti-inflammatory pathway. Direct electrical activation of the vagus nerve has inhibitory effects on the synthesis of TNF in liver, spleen, and heart (Borovikova et al. 2000). The vagus nerve probably also has a sensory function, which in turn can modulate vegetative nervous system circuits around NTS and RVLM (Tracey 2002, see the extended discussion in Chap. 5).

Clinical Studies

There exists evidence that decreasing complexity of different time series is correlated with negative outcome in critically ill children and adults (Overview: see Buchman et al. 2002). Sympathetic–parasympathetic balance may be altered in critically ill patients (Schmidt et al. 2001).

The first report about HRV changes in sepsis included 17 patients with sepsis who were studied in an ICU. A short-time ECG was taken. Acute and recovery data were obtained of 12 patients. HRV (TP) was significantly lower during sepsis, as were LF and LF/HF (1.34 ± 1.61 vs. 4.27 ± 7.06 in recovery) (Garrard 1993).

In an early study, 12 patients with sepsis were characterized by HRV analysis, photoplethysmography, respiration pattern, and arterial pressure. All measures were taken at the same time (9 a.m.) at least 40 min before any other manipulations on the patient. LF fluctuations were low or absent during sepsis, but increased under recovering, or stayed absent in two patients who died. The HF component was elevated in relative units (Hfnu) but much lower in absolute values (2.5 ± 0.3 ln ms^2) with respect to age-matched controls (5.9 ± 0.1 ln ms^2). HF results did not appear to be affected by the presence or absence of mechanical ventilation. LF and HF changes occurred seemingly independent of use of catecholamines (Piepoli et al. 1995).

Winchell conducted automated 5-min HRV measures every 6 h in 742 patients. Low TP and low LF/HF ratio (authors used HF/LF) were associated with increased mortality, a high LF/HF with increased survival. The authors concluded that monitoring HRV parameters has the potential to detect physiological deterioration or response to therapy (Winchell and Hoyt 1996). In a study focusing on patients with head injuries, the same approach was used to obtain HRV values simultaneously with intracranial pressure (ICP) and cranial perfusion

pressure (CPP). In all, 80 patients with a mortality of 29 % were included in the study. Low HRV values were associated with increased mortality with a relative risk of 7.7 and predicted 80 % of acute deaths. High LF/HF was associated with higher survival rates; there was no association between low LF/HF and mortality. Analysis of temporally matched ICP and CPP showed significant correlation between two types of abnormal HRV measurements (low TP and low LF/HF ratio) and pathologic changes in intracranial pressure relationships (high ICP or low CPP). High LF/HF was associated with apparent improvement in ICP and CPP (Winchell and Hoyt 1997).

Yien included in a study 65 consecutive patients of an ICU with noncardiac emergencies. Thirteen had to be excluded because of onset of AF, other forms of arrhythmias or implantation of a pacemaker. Mortality was around 50 %. The diagnosis of patients is mentioned and includes patients with advanced carcinoma and diverse bleeding conditions including in the brain, but the majority had variations of critical infections and sepsis. The study observed in survivors a progressive increase of both VLF and LF, progressive decreases of the same frequency components in the non-survivors (Yien et al. 1997).

Ten patients with sepsis syndrome for less than 48 h, ten patients in an early stage of septic shock, and six control subjects were analyzed using short-term measures of HRV via finger arterial blood pressure and pulse intervals. LFnu was lower in sepsis and septic shock than in controls, septic shock having the lowest values. LF/HF was 1.51 ± 0.32 for healthy persons, 4.58 ± 3.72 for patients with sepsis, and 1.36 ± 1.23 for septic shock. The authors used another coefficient "alpha," which was the square root of the ratio between LF and systolic blood pressure. This was lowest in septic shock and lower than in controls in sepsis alone. LF/HF correlated with plasma noradrenaline in septic shock patients (Annane et al. 1999).

A retrospective study analyzed 22 critically ill patients: 16 had a septic and 6 a non-septic MODS (distinguished by means of the APACHE II Score > 19 and a sepsis score > 11 or < 11). Six patients without MODS were used as controls. Twenty-four-hour ECG recordings from the ICU were used. Patients with MODS had reduced HRV values, but there was no difference between MODS with or without sepsis (Heinroth et al. 1999).

In a cohort study all patients of a medical ICU (no surgical patients) with an expected unit stay of 48 h or longer were included, very ill or only mildly ill patients excluded. Twenty-eight patients did not develop sepsis, 13 did. A 30-min recording in supine position was obtained between 8 a.m. and 12 p.m. A LF/HF ratio of <1.5 in HRV power spectrum was associated with sepsis (odds ratio 3.63). The likelihood ratio for a sepsis with an existing LF/HF <1.0 was 6.47 (Korach et al. 2001) (Tables 10.1 and 10.2).

Ellenby et al observed seven pediatric patients with the help of a computerized surveillance system that calculated HRV frequency-domain measures out of a time course of 128 s (sic, ?) every 6 h. Six of the seven patients had a favorable outcome. LF and LF/HF increased, HF decreased during the recovery process. The patient with fatal outcome showed a low LF/HF ratio that only increased for a short period

Table 10.1 Differences between survivors and non-survivors in frequency domain (Korach et al. 2001)

	Survivors (ms^2)	Non-survivors (ms^2)
TP	164, 093 ± 272,163	8,112 ± 12,644
VLF	1,179 ± 932	194 ± 124
LF	891 ± 815	130 ± 106
HF	627 ± 811	273 ± 225
LF/HF	1.789 ± 0.852	0.578 ± 0.544

Table 10.2 Diagnosing sepsis using LF/HF (Korach et al. 2001)

LF/HF category	Presence of sepsis	Absence of sepsis	Likelihood ratio
<1	9	3	6.47
1–1.9	3	9	0.72
>1.9	1	16	0.13
Total	13	28	

Table 10.3 Results of the retrospective study in MODS patients (Heinroth et al. 1999)

	MODS with sepsis ($n=16$)	MODS without sepsis ($n=6$)	Controls ($n=6$)
SDNN	30.9 ± 19.6	25.1 ± 10.5	75.2 ± 29.4
SDANN	24.2 ± 15.2	17.1 ± 6.9	48.1 ± 23.4
ASDNN	16.1 ± 12.8	15.8 ± 7.1	46.5 ± 15.0
rMSSD	18.6 ± 13.0	16.7 ± 8.9	34.3 ± 7.9
TP	4.8 ± 1.4	4.9 ± 1.5	5.6 ± 1.1
LF	2.8 ± 1.7	2.3 ± 2.3	6.5 ± 1.1
HF	3.5 ± 1.4	3.2 ± 1.2	4.9 ± 0.6
LF/HF	0.7 ± 0.6	0.9 ± 1.2	2.8 ± 2.3

in which he had a clinical improvement. Short-term HRV data were thus suitable for monitoring the course of critically ill patients (Ellenby et al. 2001).

LFnu (normalized low-frequency power) as assessment of the relative sympathetic contribution to the overall HRV was correlated with increased illness severity and accounted for 40–60 % of the variance in illness severity scores. LFnu and LF/HF ratio measured in a 5-min period apparently provided a noninvasive early marker of disease severity in 14 patients with SIRS criteria at the emergency department (Barnaby et al. 2002).

The cardiac output oscillations of 13 consecutive patients with sepsis and MODS were analyzed. Ten patients showed 18 episodes of ultra low-frequency periodic oscillations in the frequency range of 0.0028–0.000053 Hz (6–316 min). The authors proposed ULF-Co as possible prognostic marker (Seiver and Szaflarski 2003) (Table 10.3; Fig. 10.1).

Fifty pediatric patients with different grades of MODS were observed with the help of a 5-min recording under stable conditions. A power-law model was used, described through $r2$, slope, and x-intercept. Time domain, frequency domain, and DFA were also used. Loss of HRV with increasing number of organ failure could be

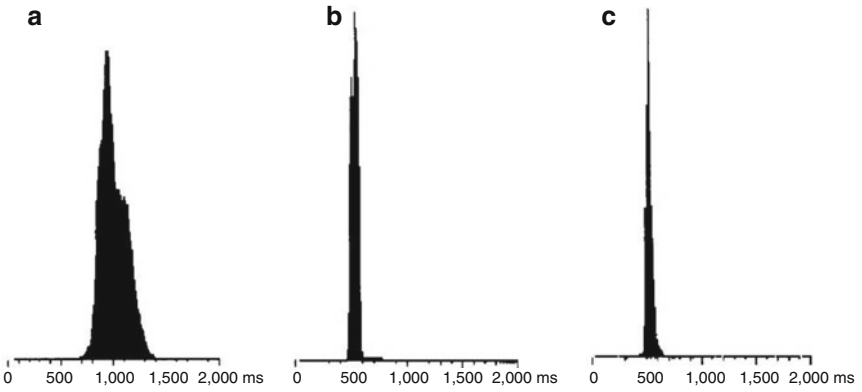

Fig. 10.1 Three typical patients with a non-septic MODS (**b**), a septic MODS (**c**), and a control (**a**) (Heinroth et al. (1999))

demonstrated for all measures, but only the power-law model was able to discriminate between the groups (Tibby et al. 2003).

In 29 patients with class I to class IIIa heart failure (and consecutive lower EFs) and ten healthy subjects, TNF levels increased and HRV decreased in correlation with heart failure. TNF levels and HRV were inversely correlated showing statistically robustness using log-linear and nonparametric tests. In a multiple linear regression analysis, only TNF and noradrenaline levels contributed significantly to the variation observed in HRV, where TNF was a stronger independent predictor (Malave et al. 2003).

In 39 septic patients, HRV analysis was used at admission to the ICU. Eleven patients developed MODS with a mortality of 63 %, 28 did not develop MODS (mortality 0 %). Patients who developed MODS had a significant lower HRV (LF, rMSSD). LF was the best predictor for MODS with a cutoff point of 18 ms (Pontet et al. 2003).

Zwiener compared the data of 14 patients with brain injuries or damages with the data of healthy subjects from a previous study by using an algorithm that analyzed the patterns of coherence between respiratory movements, heat rate fluctuations, and arterial blood pressure fluctuations. The patterns of coherence were almost the same, but there was a significantly reduced frequency of HRF patterns in patients. In patients with fatal outcome, the number of pattern incidence was significantly lower than in patients with a favorable outcome (Zwiener et al. 2003).

Sample asymmetry was used retrospectively to analyze 158 infants admitted consecutively to a neonatal intensive care unit. Fifty of them had in all 75 episodes of SIRS or sepsis. An ECG time series of 4,096 (approximately 20–30 min) was used. Three data sets were analyzed: before sepsis, immediately before sepsis, and after resolved sepsis. Sample asymmetry is an algorithm to analyze the asymmetry of the time domain of a time series. The sample asymmetry value increased gradually days before sepsis and decreased after a sepsis period (Kovatchev et al. 2003).

Table 10.4 HRV values of MODS patients

	MODS patients ($n=85$)	Normal values (Bigger et al. 1995)
SDNN	57.7 ± 30.7	141 ± 39
SDANN	51.2 ± 29.7	127 ± 35
pNN50	4.8 ± 8.4	9 ± 7
RMSSD	26.9 ± 26.6	27 ± 12
LF	129.3 ± 405.1	791 ± 563
HF	112.3 ± 267.3	229 ± 282
VLF	191.3 ± 661.1	1,782 ± 965
LF/HF	1.1 ± 0.9	4.61 ± 2.33

Modified from Schmidt et al. (2005)

In a prospective study, the hypothesis was tested that use of HRV in addition to standard laboratory tests is feasible to identify neonatal children with sepsis at the beginning of treatment. Six hundred and seventy-eight consecutive infants were monitored. One hundred and forty-nine episodes of sepsis (137 with positive blood cultures) were observed. HRC index was highly significant associated with sepsis; the order of magnitude was nearly the same as all other laboratory tests. If included in a model, the accuracy of diagnosis increased (Griffin et al. 2005a, b).

Schmidt followed for 28 days 90 consecutively admitted score-defined MODS patients in a mono-center study. He investigated the correlation between different HRV parameters and mortality. lnVLF predicted mortality best and was comparable to the predictive value of the APACHE II Score. The sedated patients showed no significant differences from the non-sedated patients in autonomic function, neither in a treatment with catecholamines. Attenuation of HRV values was similar in all age groups (Schmidt et al. 2005) (Table 10.4).

In a prospective trial, 2,088 trauma patients were tested with HRV. The results and other data (age, ISS, AISA Head Score, total transfusion requirements) were included in a multivariate analysis (logistic regression). 63.5 % of patients showed HRV deviations during their ICU stay. This was interpreted as uncoupling phenomena. There was a big difference between patients with "uncoupling phenomena" and others. The authors used an algorithm delivering the standard deviations of 5-min periods termed "short-term heart rate volatility," which seems to be similar to a trend analysis of SDANN, in other words a two-dimensional analysis of 288 5-min periods. The authors conclude that "uncoupling" is an independent predictor of death in trauma patients; it has a predictive window of 2–4 days and appears to increase in response to inflammation, infection, and multiorgan failure. It predicts death within 24 h with a sensitivity of 70 % and a specificity of 80 % (if age and injury severity score is incorporated) (Norris et al. 2006, probably partially published in Morris et al. 2006).

A retrospective study compared patients with MODS with and without beta-blockers. They included 157 patients, 69 of the with beta-blocker treatment, and took a 24-h ECG within the initial 48 h. Beta-blocker treatment was associated with

a higher survival, especially if ischemic conditions were detected. HRV was less reduced in patients receiving beta-blockers (Hennen et al. 2008).

One hundred and sixty-eight trauma patients with penetrating and blunt trauma were monitored using short-term HRV. Patients with blunt trauma had a mortality of 24 %, those with penetrating trauma 19 %. In the analysis, data from surviving and deceased patients were compared. LF of the survivors remained unchanged until at least the third day after emergency room admission, whereas LF of non-survivors increased after 12 and 24 h to nearly five times normal and then declined to similar values as the survivors after 48 h. Survivors HF patterns were higher than normal, but HF of non-survivors was significant higher than that of survivors. L/R was below normal for non-survivors, slightly higher for survivors (Colombo et al. 2008).

Ahmad og Seeley used a group of patients that frequently experience sepsis as therapy complication: bone marrow transplantation recipients. They monitored multiparameter HRV (continuous individualized multiorgan variability analysis, CIMVA) in average 12 days in 17 patients, 14 of them developing sepsis. Twelve of 14 patients showed a 25 % or higher reduction of HRV in SDNN, RMSSD, SampEn, MSE, FFT, DFA, and wavelet analysis. Wavelet HRV showed a drop already 35 h before clinical symptoms of sepsis appeared. The three noninfected patients showed no difference. Interesting in this study is the focus on relative change instead of comparing with controls or using standard values (Ahmad et al. 2009b). The same group conducted another study with this patient group, using a composite measure of HRV. This study used a windowed analysis (5-min window size) and sophisticated data reduction techniques based on Spearman correlation coefficient and analyzing change of the individual baseline (first 24 h after admission). With this method, they identified variability measures with the highest predictive value. In the end, they identified 11 variability measures (SDNN, coefficient of variation, power law *Y*-intercept, DFA, wavelet area under the curve, Shannon entropy, Plotkin–Swarm average energy, fuzzy entropy, global correlation dimension, cardiac vagal index, and the largest Lyapunov exponent), which then were used to construct the composite measure system. The system was able of properly identifying 15 out of 17 subjects, both those who did and those who did not develop sepsis (Bravi et al. 2012) (Fig. 10.2).

Bradley and colleagues included not only ECG but also respiratory rate variability (RRV, $etCO_2$-waveforms) in a pilot study with 34 patients (Apache II Score 22.8 ± 6.7). They reported very low HRV data loss (AF only 0.6 %) and were able to calculate continuous variability in 81 % of available ECG data (because of a conservative approach whereby in case of missing data a whole 5-min period is removed) (Bradley et al. 2012).

The decrease in HRV observed in sepsis and MODS patients is most likely due to a mitigated heart rate regulation either by the rate-increasing sympathetic activity, the rate-decreasing vagal activity, or both (Werdan et al. 2009). Of importance is that HRV is comparatively little attenuated by sedation or catecholamines (Schmidt et al. 2005).

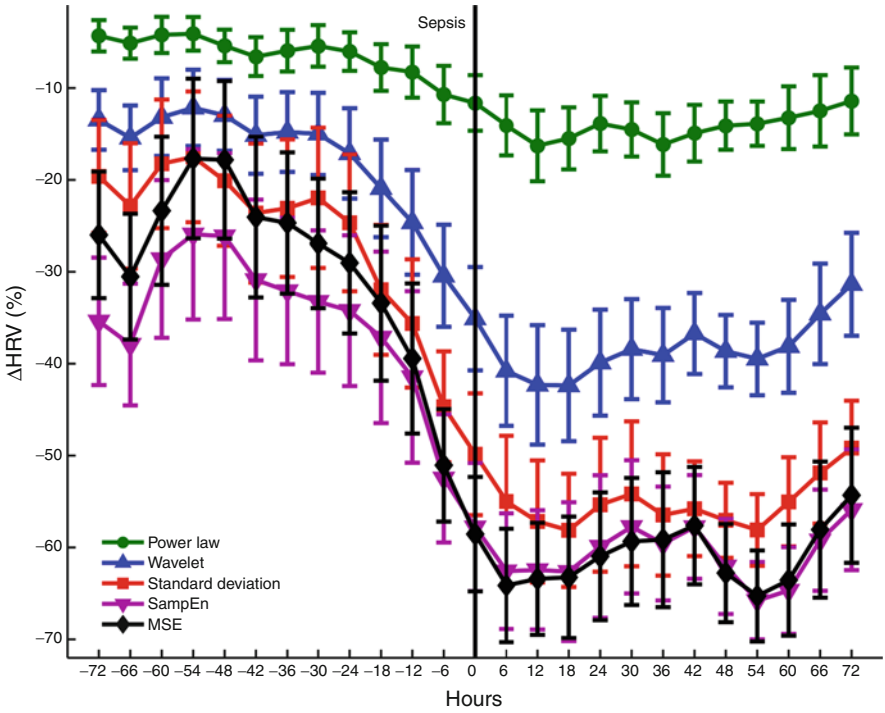

Fig. 10.2 Changes of different HRV parameters before onset of sepsis in 14 bone marrow transplant patients (Ahmad et al. (2009a, b), with permission)

Neonatal Sepsis

Many of the published studies on neonatal sepsis were done by one research group (Griffin, Moorman, and colleagues). They developed their own proprietary measure, "heart rate characteristics." In one of their studies, 30 pediatric patients with sepsis or septic shock were followed. Differences between shock and non-shock patients existed in LF (2.68 ± 0.24 vs. 3.37 ± 0.17), HF (2.18 ± 0.14 vs. 2.79 ± 0.23), and DFA (1.22 ± 0.06 vs. 1.00 ± 0.07). Recovery was associated with increases in LF and HF (Toweill et al. 2000). In 63 neonatal patients with sepsis or SIRS compared to 26 control patients, HRV analysis showed abnormal results up to 24 h before clinical deterioration (Griffin and Moorman 2001).

The same group monitored 1,022 infants at two tertiary care centers, using standard deviation, sample asymmetry, and sample entropy. In 1,022 patients, 223 episodes of sepsis, 108 of urinary tract infections, and 48 deaths occurred. The group was able to distinguish between a high-risk and a low- risk group. Infants with HRV parameters associated with high risk had a five- to sixfold risk of developing sepsis, UTI, or death, compared to the low-risk group (Griffin et al. 2005a, b).

As noted by Ahmad et al. (2009a, b), one major finding of these studies is that HRV measurement (at least the group's algorithm) independently complements information that is otherwise used to estimate the risk of a sepsis development. This is of special importance, because treatment of neonatal sepsis is possibly even more dependent on early antibiotics treatment. On the other hand, too generous use of antibiotics in patients who probably won't develop sepsis has its own well-known problems (like resistance and adverse effects). There are some caveats to the use of HRC alone since, as Griffin notes, not all abnormal readings in neonates predict pathological conditions.

The group around Griffin developed yet another algorithm integrated in HRC, "sample asymmetry analysis" (SAA). It is based on shape changes of frequency histograms of the RR intervals and its dependency on periodic decelerations and reduced variability. SAA increased significantly from its baseline as early as 4 days before clinical development of sepsis in a study including 158 infants. But it looks as if the variation between subjects might be even higher than for usual HRV indices, making it again difficult to use on the individual level (Kovatchev et al. 2003).

One problem is that heart rate signals in neonatals are basically non-stationary, and non-stationarity probably even increases when sepsis features appear (Cao 2004). This is a problem because nearly all HRV algorithms are based on the assumption of stationarity.

To meet this problem, sample entropy has been used in neonatals by the same research group. SampEn decreased already 24 h before onset of sepsis, which was clearly visible in subgroups that developed sepsis several times during the course of the study. Unfortunately, SampEn was particularly sensitive to artifacts and decreased due to noise in the signal without any association to a later sepsis (Lake et al. 2002).

In conclusion, different linear and nonlinear HRV measures have been used on a few groups of septic patients and seem feasible for risk stratification. There is reasonable theoretical background for this but only limited clinical data. It is possibly a promising bedside method for early identification of risk patients.

Trauma

Mechanical trauma can cause different injuries, again resulting in changes in HRV. Beyond the mechanisms, we find head trauma with brain injury, shock due to blood loss, pathological conditions in gas exchange, and more. Shock is here best defined as an abnormal physiological state in which oxygen delivery is inadequate to meet normal metabolic needs or metabolic needs in stress. HRV has been mostly used to estimate prognosis, interestingly in some studies also in the pre-hospital setting, while other studies have focused on the first 24 h after admission.

Grogan and collaborators included 1,316 trauma patients and calculated heart rate volatility by sampling 100–150 heart rate data per 5 min (a sample every 1–4 s). Out of this a standard deviation was calculated. This method has some similarities

to SDANN, but in SDANN every RR-distance is included, whereas in heart rate volatility, only a sample of all the RR-distances is included. Heart rate volatility was able to predict an unfavorable outcome as early as 24 h before death. The prediction accuracy in the prospective study had an area in the receiver operator curve of 0.816, and the sensitivity and specificity were 70.1 and 80 %, respectively (Grogan et al. 2004).

Heart rate data points were prospectively collected from 1,316 trauma ICU patients and linked to outcome data in another study. Here too a variant of SDANN was calculated (using a moving 1-h window approach, similar to Ahmad 2009b), and logistic regression identified ranges predictive of death. The study group was randomly divided, and the first group was used to establish the model, the second to validate it. SDANN predicted death at low (0.1–0.9 bpm) and survival at high (1.8–2.6 bpm) ranges, as early as 12 h (ROC = 0.67) (Norris et al. 2005).

Seventy-five patients with trauma requiring pre-hospital helicopter transport were assessed with short-term HRV. Pre-hospital SDNN predicted patients with base excess ≤ -6, those defined as seriously injured and benefiting from trauma center care, as well as patients requiring a lifesaving procedure in the operating room (with an accuracy of 76 % for predicting a lifesaving intervention in the operating room). SDNN was far better for prediction than pre-hospital trauma triage criteria and pre-hospital en route vital signs including Glasgow Coma Scale and paramedic judgement (King et al. 2009). A similar study was conducted on trauma patients without significant head injury requiring helicopter transport. These were identified from a retrospective research database. An equal number, unmatched sample of patients who lived, were compared with those who died ($n = 15$ per group), all patients having hemorrhagic shock but no brain damage. Age, sex, Glasgow Coma Scale score (GCS), blood pressure, pulse pressure, pulse, intubation rate, SpO_2, mechanism of injury, transport time, and time of death after admission were recorded. R-waves from the first available 2 min of usable data were detected from normal electrocardiograms, and heart rate variability was assessed. Non-survivors had lower normalized LFnu (42 ± 6 vs. 62 ± 4), higher HFnu (42 ± 3 vs. 32 ± 3), and higher HF/LF ratio (144 ± 30 vs. 62 ± 11) (Cooke et al. 2006).

An important prospective observational trial at a Level I Trauma Center was performed in 243 healthy student volunteers and 257 trauma patients, the latter receiving CT scans of the head at arrival. SDNN and RMSSD were obtained by a short-term HRV of 5 min. A head CT scan was considered as pathological if there were abnormalities in the parenchyma (diffuse axonal injury or contusion), vasculature (intraparenchymal, subdural, or epidural hemorrhage), and/or structural or bony components (fractures of the face or cranium). In volunteers, SDNN was 73 ± 15, CT-negative patients without sedation had 42 ± 22 (with sedation 31 ± 19). Patients with pathological CT founds had 28 ± 17 without sedation, 12 ± 8 with it. RMSSD differences were similar. For both SDNN5 and RMSSD5, in each category, there was a wide overlap in the range of values and strong inverse correlations with heart rate. Using multiple logistic regression in a subset with no missing data, an index was derived from ln(SDNN) adjusted for six confounding factors. With a negative predictive value held constant at 0.90, compared with ln(SDNN) alone, the

stepwise addition of heart rate, sedation, age, gender, and blood pressure progressively improved the specificity of the HRV index from 0.56 to 0.77, positive predictive value from 0.55 to 0.68, and efficiency from 0.68 to 0.80. This index was then normalized (0–100 scale) for ease of interpretation (Proctor et al. 2007).

All this studies look promising. Interesting is that 2–5 min HRV, partially with algorithms that can be used in difficult conditions, are able to provide additional information about the severity of trauma. HRV alone or in combination with established trauma scores might help clinicians to decide on the right priorities for individual trauma patients and could be used as one further instrument to anticipate complications.

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Chapter 11
Neurologic Disorders

Brain Damage

Any major brain injury can have consequences for brain control of ANS. A wide variety of changes in the ECG is seen in the context of neurological disease. Two major categories of change are regularly noted: arrhythmias and repolarization changes (Samuels 2007). The presence of altered HRV in patients with brain injury was reported as early as 1965 (Valbona et al. 1965). ANS control of the brain is impaired proportional to the damage itself (Goldstein et al. 1996). Increased intracranial pressure (ICP) >30 mmHg or decreased cerebral perfusion can be associated with autonomic dysfunction (Goldstein et al. 1996; Biswas et al. 2000), at least in children. Another early study tested the variability of heart rate in ten patients with neurologic deficits with acute onset. The variability decreased quickly if the intracranial pressure rose. The rate of recovery of the variability reflected the neurologic state better than a decreased ICP (Lowensohn et al. 1977). Another early study tested six ICU patients, four of them later with brain death, two in vegetative state, and described particular HRV patterns (Lacquaniti et al. 1993).

Winchell conducted a one-center study that included all patients with severe brain injury at admittance defined as Glasgow Coma Scale of 4 or 5 with a short-term HRV measurement of 5 min. They included also CPP and ICP data. The study focused on general low HRV (TP) and abnormalities of LF/HF (in both directions). Eighty trauma patients met the criteria and had feasible HRV measurements. Overall mortality was 29 %, most of it early and primarily caused by the brain injury. Low HRV (defined as being under the fifth or over the 95th percentile for age-matched and diagnosis-matched patients) was associated with a relative mortality risk of 7.7 and predicted 80 % of acute deaths. High HF/LF ratio was not associated with unfavorable outcome; low HF/LF however was associated with better outcome (Winchell and Hoyt 1997).

In 24 brain-injured patients, neurological recovery and survival was associated with low-frequency bands in power spectra whereas brain-dead patients showed decreased low-frequency heart rate power. This phenomenon was discussed as

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direct evidence for cardiovascular and autonomic uncoupling in case of acute brain injury and completes uncoupling in case of brain death (Goldstein et al. 1998a).

One hundred and thirty-five critically ill children were analyzed with the help of HRV and different pediatric scores. Lower LF and HF correlated significant with score systems and outcome (Goldstein et al. 1998a, b).

In 15 critically ill children and 4 controls, Holter ECGs were taken and frequency-domain values calculated. There was no linear correlation between LF/HF and ICP but a significant association if the ICP was >30 or the CPP >40 mmHg. GCS correlated with LF/HF. Patients who progressed to death had a markedly lower LF/HF with a significant decrease the first 4 h of hospitalization (Biswas et al. 2000).

Twenty-nine consecutive neurosurgical patients at an ICU with a Glasgow Coma Scale score <13 were investigated with help of a 60-min short-term HRV. Reductions in TP of those who subsequently died relative to those who survived were observed. This was also significant for VLF and LF but not HF. Blood pressure variability did not differ between groups (Haji-Michael et al. 2000).

In ten patients with a brain-death diagnosis, HRV was measured. BRS was estimated from the spontaneous fluctuations of the systolic blood pressure and the pulse interval. A dramatic reduction of the global spectral power (44.919 ± 31511 vs. 3.204 ± 1.469 ms^2) was observed (Baillard et al. 2002). In 11 patients BRS and HRV were obtained prior to and after brain death. VLF decreased significantly and the respiratory peak at 0.1 Hz dropped, which was interpreted as a damage of the baroreflex loop. BRS was nearly comparable with normal subjects before brain death but with highly dispersed values. After brain death, BRS disappeared nearly completely (Conci et al. 2001).

In 12 patients HRV was obtained 6 h prior and 6 h after brain death. TP began to decrease before brain death, and autonomic activity ceased after brain death. The authors concluded that HRV may be a very sensitive but less specific method to diagnose brain death (Rapenne et al. 2000).

Twenty patients with severe head trauma underwent 24-h Holter ECG 1 day after trauma and 48 h after withdrawal of sedative drugs. Both time-domain and frequency-domain values were calculated. Patients with fatal outcome were compared with survivors; survivors' data were analyzed regarding good or bad neurologic outcome. The six patients with fatal outcome had higher global HRV and sympathetic tone. During the awakening period, global HRV and the parasympathetic tone were significantly lower in the patients with worse neurologic outcome (Rapenne et al. 2001).

Baillard conducted a prospective, observational study with ten patients with a diagnosis of acute and irreversible brain injury but without brain death at the time of admission in the intensive care unit. Patients were intubated endotracheally and mechanically ventilated at a respiratory frequency of 12/min. They measured heart rate, arterial blood pressure, and heart rate variability in time- and frequency-domain method, which included calculation of the instant center frequency of spectrum. Brain death was associated with tachycardia, dramatic reduction of TP (from 44919 ± 31511 to 3204 ± 1469), and LF/HF (from 1.01 ± 0.01 to 0.14 ± 0.05) (Baillard et al. 2002) (Figs. 11.1 and 11.2).

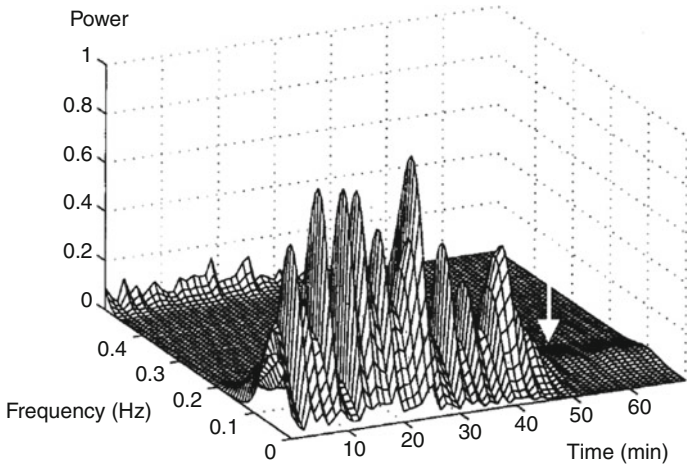

Fig. 11.1 Typical changes of spectral power during brain death (occurring at this patient at 45 min). LF disappears nearly completely and TP decreases dramatically (Baillard et al. 2002)

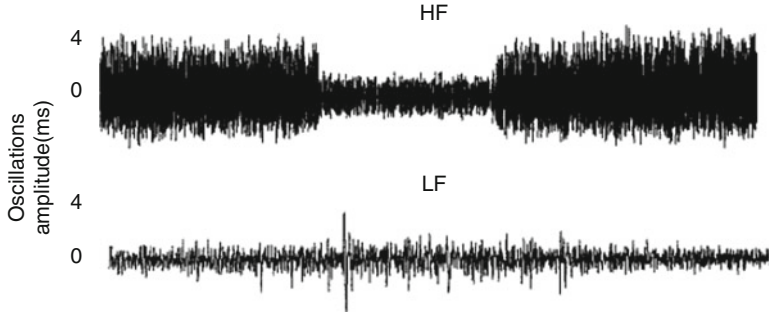

Fig. 11.2 Changes of HF during an apnea test of a typical patient. LF is already diminished, low HF from before (ventilator-treated patient with a RF of 12) is even more diminished (Baillard et al. (2002), with permission)

Rapenne included 20 patients with head trauma and GCS <9 at inclusion and took a 24-h ECG 1 day after trauma and 48 h after withdrawal of sedative drugs. HRV and HF of patients who later died were significantly higher (Rapenne et al. 2001). This fits pre-hospital data where Cooke observed lower LF, higher HF, and consecutively higher HF/LF ratio in patients who died later, but GCS differences had more significance in prediction as HRV abnormalities (Cooke et al. 2006).

Sixteen subjects after brain injury with or without dysautonomia and 16 age-matched controls were examined. In the traumatic brain injury group, subjects with and without dysautonomia showed HRV differences compared to controls. HRV of the disautonomic group showed evidence of uncoupling between heart and vegetative balance (Bagley 2006).

For their study, Morris and colleagues had to screen 4,116 trauma ICU admissions to find 1,871 patients with sufficient physiologic, laboratory, pharmacy, and demographic data for analysis, 75 of them failing corticotropin-stimulation testing, defined as adrenal insufficiency (AI). A variant of SDANN (short-term HR volatility) was used. HRV was different between patients with and without AI. It was similar in AI survivors and non-survivors before steroid treatment but increased substantially in survivors after steroid administration and did not increase in non-survivors unresponsive to steroids (Morris et al. 2007).

Mowery investigated 145 trauma patients with head injury having simultaneous HRV and ICP monitoring with a Camino monitor. ICP and heart rate (HR) data were matched and divided into 5-min intervals. In each interval, the median ICP and SDANN were calculated (note that this was not in accordance with usual SDANN, it differs from that used in traditional HRV analysis because precise instantaneous HR is not acquired at every beat). Cardiac uncoupling was defined as an interval with this modified SDANN approach, between 0.3 and 0.6 bpm. Cardiac uncoupling was compared between ICP categories using the Wilcoxon Rank-Sum test, and logistic regression was used to assess the continuous relationship between ICP and risk of uncoupling. Cardiac uncoupling increased as ICP increased with clear trend and seemed to precede increases in ICP, at least when long (24 h) time periods were considered (Mowery et al. 2008).

By now it has been clearly established that HRV- and HRV-related measures decrease or change with increasing brain damage. This can be interpreted as the consequence of a generalized autonomic storm, which occurs as a result of a life-threatening stressor, with both sympathetic and parasympathetic effects (Samuels 2007). The approach of Mowery et al. (2008) is interesting, because their system works automatically and generates data without manual interpretation. This should not discourage ICUs using short-term HRV. The patient group with traumatic brain damage is younger and frequently has no heart problems, which makes uptake and interpretation of HRV data problematic. It is obviously too early for clear recommendations, but there are many good arguments to use HRV as one prognostic tool among others in this patient group. I agree with Ryan et al. (2011) about challenges, but at least solutions for technological challenges are on their way, for example, multiple wireless vital signs monitoring technologies. More important are guidelines for the monitoring and assessment of trauma and head injury patients using HRV and the development of normal values and thresholds for treatment, similar to other areas of clinical HRV use.

Neurogenic Cardiomyopathy

Aneurysmal subarachnoid hemorrhage (SAH) is associated with many special, often interrelated systemic complications that impact on morbidity and mortality. Cardiopulmonary complications are common, but the most intriguing complication is the concomitant injury to the heart (Lee et al. 2006). Approximately 20–30 % of patients with SAH manifest a secondary cardiomyopathy and/or regional wall motion

abnormality, which is usually reversible in the absence of underlying obstructive CAD (Bybee and Prasad 2008). This entity has been referred to as neurocardiogenic stunning and "neurogenic stress cardiomyopathy" (NSC). Cardiac injury may be immediately evident or develop within hours after aneurysmal rupture. Some patients may have minor increases in cardiac enzymes and remain asymptomatic, whereas in others overt cardiac shock emerges. Approximately 10 % of patients develop pulmonary edema (Friedman et al. 2003). SAH-induced heart syndromes can be confused with MI and cause a delay in appropriate treatment. An intriguing syndrome that overlaps substantially with SAH-related cardiac dysfunction is takotsubo cardiomyopathy. This syndrome is characterized by transient LV dysfunction that produces a distinctive configuration during systole on the ventriculogram that resembles a Japanese octopus trap (Lee et al. 2006). There is clear evidence that cardiac lesions can be produced as the result of nervous system disease (Samuels 2007).

There have not been many studies looking at HRV changes in neurogenic cardiomyopathy. Kawahara studied 42 patients with SAH and 42 healthy controls, the patients on admission and 30 days or more after admission with Holter monitoring. Thirty-nine of the 42 patients (i.e., 93 %) with acute SAH showed ECG abnormalities, especially prolongation of QTc, presence of U wave, and ST depression. In the chronic phase, 16 of the 42 patients (38 %) had abnormalities. LF was significantly higher in the chronic phase than in the acute phase, also compared to the controls. HF was higher in the acute phase. LF/HF was significantly lower in the acute phase than in the chronic phase and in the control group. No significant differences in these parameters were found between the chronic phase data and the control group (Kawahara et al. 2003).

Generalized Brain Damage, Impaired Consciousness, and HRV

Ultimately, brain damage is a consequence of ischemia. Most frequent causes for brain damage are stroke, trauma, or tumor. Some aspects of brain damage and its relation to HRV are discussed in this chapter (stroke), other important aspects in the previous chapter about intensive care. In this paragraph, we are interested in the relation between consciousness and HRV including prognostic aspects.

As Riganello et al. (2012) noted, there is emerging evidence that the autonomic system can also mediate in patterns of brain activation. Thus, measures of HRV might be interesting for description and decisions in patients with severe disorders of consciousness.

Subjects in a vegetative state, today also referred to as unresponsive wakefulness syndrome after severe brain injury, are, by definition, disconnected from the environment, with no indication of awareness, voluntary or otherwise, purposeful movement, or communication (Riganello et al. 2012). As noted in earlier chapters, higher brain regions are connected with central elements of the autonomic nervous system. The previous chapter detailed how severe brain damage has profound effects on

HRV, sometimes eliminating it almost entirely. But what is the relation between consciousness and HRV itself?

Our current conception of the brain is that of a precise structure of interconnected modules and with parallel processing. We know that these modules can to some extent work autonomously. For instance, circadian synchronization is dependent on the perception of light. Extensive experiments whereby subjects were isolated from this normal perception have shown that the human brain has its own time control with a period slightly longer than 24 h. This system is dominated by a specific center in the brain. The American biologist Curt Richter spent several decades working to identify this center, damaging countless brain regions and connections in animals. Finally, the suprachiasmatic nucleus, a tiny neuron network situated before the hypothalamus, was identified as the master clock. But at the same time it was discovered that every brain module isolated from the others had its own autonomic circadian rhythm. In fact, even every (brain) cell develops its own rhythm if it is isolated.

One central idea of consciousness is based on the connections between brain modules and their synchronization. If this synchronization fails, consciousness disappears. It is important to remember that consciousness is not a Boolean condition, where we either are "on" or "off." Between complete consciousness and complete unconsciousness, many intermediate states can be observed.

In subjects with severe brain damage in a vegetative state, interaction with near relatives, but not with other persons, can provoke changes in LFnu (Dolce et al. 2008). Gutiérrez assessed responses to auditory stimulation with emotional content by HRV in a case series of patients and found a pattern of changes induced by auditory stimulation in some patients (decreased heart rate, increased HRV, decrease power in the low, and increased power in high frequencies) consistent with increased cardiovagal stimulation. Both time- and frequency-domain changes were more pronounced during affective than during non-affective auditory stimulation (Gutiérrez et al. 2010). Most of the studies in this area have been done by the group around Riganello and included only a few patients (Riganello et al. 2012).

HRV might be used to investigate whether and how patients in the vegetative state perceive external stimuli. Based on the possibility of HRV to monitor sympathetic activation as a surrogate of general arousal, HRV might be a useful part of a test battery for this patient group, for example, similarly to the test battery recommended for autonomous neuropathy. Further investigations are required before more general conclusions can be drawn.

Stroke

Introduction

Stroke is a major cause of mortality and a leading cause of adult disability in many countries. Main causes for stroke are ischemic disease or acute bleeding in the brain, the first responsible for more than 80 % of strokes. The incidence of stroke

increases with age. Many of the arterial and cardiac disorders underlying these diseases are preventable; the morbidity and mortality have in fact been diminished the recent years, possibly due to increased primary and secondary prevention.

Cerebral ischemia occurs if a reduction of cerebral blood flow lasts longer than a few seconds. First – reversible – symptoms happen already after 10 s; if they are more pronounced, we talk about transient ischemic attack (TIA), which today is considered as an alerting symptom indicating increased risk for stroke and a need for a clinical workup. Stroke is usually associated not with general but rather with focal ischemia or infarction caused by thrombosis of cerebral vessels themselves or by emboli from proximal arterial sources or the heart. Cerebral hemorrhage produces similar neurologic symptoms to ischemic changes by producing a mass effect on neural structures and by the toxic effects of blood itself.

Increased probability for stroke is found in patients with a family history of stroke, advanced age, diabetes mellitus, hypertension, tobacco smoking, elevated blood cholesterol levels, and other risk factors for atherosclerosis. Several cardiac conditions predispose for stroke, particularly atrial fibrillation and recent myocardial infarction. Since the probability of stroke is increased in several conditions known to be related to abnormal HRV findings, it is not surprising that HRV has been used to evaluate patients at risk for stroke or after stroke. Many of the studies focused on general cardiovascular morbidity and mortality, including stroke, are summarized in the cardiology chapter. Some of the pathophysiological phenomena are similar to the symptoms discussed in the neurogenic cardiomyopathy chapter. Most studies have been conducted under and after stroke, in both cases with an interest in the pathophysiological changes and in the possibility of stratifying patients in risk groups or of evaluating rehabilitation potential.

Acute Stroke

ECG changes frequently in association to stroke. In a series of 100 consecutive stroke patients already published in 1977, 90 % of the subjects studied showed abnormalities on the ECG compared with 50 % of a control population of 100 patients admitted for carcinoma of the colon (Dimant and Grob 1977), which was also shown by Orlandi et al. (2000). Conflicting results, however, have been presented in patients in the acute poststroke phase.

Frequency-domain values in sleeping patients after acute stroke showed an increase in VLF and a decrease in HF (Giubilei et al. 1998). In another study, spectral power and SDNN were reduced both in the initial phase and in a 6-month follow-up period whereas complexity measures (among them, ApEn and detrended fluctuation analysis for fractal correlation properties) remained similar compared to a control group (Korpelainen et al. 1999).

Forty-four patients were investigated within 10 h of the onset of stroke symptoms; Holter monitoring was performed after admission in the hospital and

thereafter on the third and seventh day. 70.5 % of patients had arrhythmia at admission. HRV on admission and after 3 days was significantly different in patients with stroke plus arrhythmia, compared to patients with stroke alone and to controls. pNN50 and SDNN were reduced and LF/HF increased (around 6!) in the first group. No further differences were discovered on the seventh day. LF and HF were not reported separately (Orlandi et al. 2000).

HRV and plasma NE levels were studied in six patients with medullary and eight patients with non-medullary brain stem stroke. HF and LF were smaller in the acute phase of patients with medullary strokes; LF and HF of patients without medullary stroke did not differ from controls. On the contrary, plasma levels of NE of patients with non-medullary stroke were higher than in controls (Meglic et al. 2001).

Poststroke

The already mentioned study of Korpelainen showed stable HRV reductions in spectral power and SDNN initially and after 6 months without abnormalities in nonlinear indices (Korpelainen et al. 1999). Ischemic lesions in the insula had significantly lower power spectrum analysis of HRV (myocardial necrosis ruled out by echocardiography and CK-MB measurements), suggesting that cardiac autonomic tone may be regulated by insula and that the patients are more prone to cardiac complications such as arrhythmias and sudden death due to autonomic imbalance (Tokgözoglu et al. 1999).

In contrast to Korpelainen's results, 25 patients with cerebral infarction in an age below 50 had a similar poststroke HRV taken 9 months after the event compared to age-matched healthy controls (Kouakam et al. 2000). Another study compared 86 patients after stroke with 86 matched healthy controls. Stroke patients were included 4–12 weeks after the initial symptoms, and HRV was obtained by Holter monitoring. Patients had a lower HRV than healthy controls (SDNN 96 ± 27 vs. 136 ± 31, TP 1,962 ± 1,338 vs. 3,968 ± 2,857) (Lakusic et al. 2003).

Decrease in all time- and frequency-domain variables and higher LF/HF ratios were confirmed in a study focusing on insula damages on the right hemisphere using 24-h Holter monitoring. It was possible to show that patients with a corresponding lesion in the right insula had even more decreased HRV variables which correlated with the amount of arrhythmias like ventricular couplets, non-sustained ventricular tachycardia, and supraventricular tachyarrhythmia (Colivicchi et al. 2004). This is in accordance to the results of an atrial fibrillation study that showed changed vegetative balances before the onset of paroxysmal fibrillation (Lombardi et al. 2004).

McLaren assessed 76 stroke patients and compared them with 70 age-matched controls on average 9 months after stroke. They used several methods, among others active stand, isometric exercise, Valsalva maneuver, cold pressor, and forced respiration tests. HRV was obtained with Holter monitoring. TP and LF, but not HF, were

reduced in stroke patients. Additionally, a trend for impaired HF ($P=0.111$) in stroke patients was observed (McLaren et al. 2005).

Dütsch monitored HRV (with controlled breathing) in 15 patients after right-sided stroke, in 13 patients after left-sided stroke (both groups 18–43 months after lacunar stroke), and in 21 healthy controls at rest. Patients after right-sided stroke showed a trend toward elevated LF compared with patients after left-sided stroke and controls. HF was reduced in both patient groups (Dütsch et al. 2007).

A retrospective study analyzed 89 patients with an acute ischemic stroke or transient ischemic attack (TIA) who were evaluated with Holter monitoring. All patients underwent continuous ambulatory Holter monitoring within 15–30 days after the clinical events. The SDNN of the patients (103.52 ± 36.26) was significantly lower than that of the controls (121.44 ± 40.11), also SDANN (88.92 ± 34.49 vs. 109.96 ± 37.88). VLF, LF, HF, LF/HF, rMSSD, and pNN50 did not differ between patients and controls (Kwon et al. 2008).

HRV and Stroke Prognosis

A contradictory report included 84 patients with an acute first-ever ischemic stroke who were studied using 24-h Holter ECG and followed up for 7 years. Thirty-three patients died during this period. A power-law slope $\beta < -1.5$ reflecting an altered distribution of spectral characteristics over ultra and very low-frequency bands was the best univariate predictor of death with a hazard ratio of 4.5. Also short-term HR variability α was a predictor, but in multivariate analysis after adjustments for age, power-law slope β stayed the only independent predictor with a hazard ration of 3.8, whereas conventional HRV measures had no prognostic power (Mäkikallio et al. 2004).

Eighty-five consecutive first-ever stroke survivors underwent 24-h Holter monitoring before the beginning of a 60-day rehabilitation program. Outcome after the program and time-domain values were included in the analysis. After the program, an unfavorable functional outcome with dependency (Barthel Index score of <75) was found in 44.7 % of patients. Among others, lower SDNN was an independent predictor of an unfavorable functional outcome (104.4 ± 39.0 vs. 127.7 ± 39.1). SDNN < 100 was a possible cutoff value. 57.9 % of patients did not recover over a Barthel Index of 75. SDANN also showed significant differences but not RMSSD or pNN50 (Bassi et al. 2007). The same research group enrolled 126 stroke patients using Holter monitoring before a rehabilitation program. An unfavorable functional outcome with dependency (Barthel Index score of <75) was found to be associated with SDNN < 100 in men but not in women (Bassi et al. 2010).

Two smaller studies used short-term recordings in stroke patients. Thirty-nine patients were included within the first 48 h after arrival at the hospital. There was a significant linear correlation between severity of neurological deficits and SDNN. Heart rate variability was also positively associated with aerobic ability 2 weeks

after stroke, and lower HRV parameters correlated also with motor performance 3 months later. Interpreting this study is not easy because statistical associations, but not HRV values, are reported (Katz-Leurer and Shochina 2005). The same group included 64 patients, again within the first 48 h after a stroke, using 10–12 min short-term recordings. HF was reduced, but LF was equal to parameters of healthy persons from other studies. HRV parameters did not predict outcome in this study (Katz-Leurer and Shochina 2007).

Summary

Stroke, especially when it involves the insula, leads to changes in HRV, but the published studies showed differing patterns. HRV as predictive value for overall outcome as well as rehabilitation outcome is interesting, but surprising few studies have been conducted in a sufficiently large patient group.

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Chapter 12
Pain

Introduction

The somatosensory system processes four broadly distinct sensory modalities: tactile, proprioceptive, thermal sensations, and pain. Interspersed between the delivery of a noxious stimulus and the subjective dimension of pain is a series of complex chemical and electrical events including local positive feed forward and negative feedback circuits, neuronal networks, and the involvement of several brain modules, including those of the vegetative nervous system. Pain stimulates different physiological responses like increased breathing, heart rate, blood pressure, sweating, and general arousal. Pain is a multidimensional phenomenon being influenced and stimulating different further body systems.

Pain is also a major medical problem. Most patients going to general practitioners do this because of (acute or chronic) pain. The history of pain treatment efforts is as old as humanity, but only in the last 200 years major achievements beyond opium treatment have been made. Today, we are not able to imagine human life without local anesthesia at the dentist, general anesthesia for operations, epidurals in painful births, or pain treatment in cancer. Paradoxically, the burden of pain in the industrialized world seems rather to increase despite better treatment options. While cancer pain in more than 95 % of cases can be treated, if only existing recommendations are used properly, back pain, headaches, or fibromyalgia have a major impact on the quality of life of a sizable part of the population.

HRV has been used to evaluate pain physiology and also to gain insight in pain syndromes that still puzzle us today. The direction is similar to that in other clinical conditions. Can we understand? Can we identify patient subgroups? Do HRV parameters correlate with outcome and can they be used for prognosis?

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Experimental Pain Models and Acute Pain

Experimental pain models have been used for decades and are well established by now. Standards have been described and substantial studies have been published. Models include tools as simple as cold water and the time period until the participant feels pain (pain threshold) and until the pain is unbearable (pain tolerance). Other methods include electrically induced pain, capsaicin (the substance in chilli) injections, heat, ischemia, and others. Pain models are a convenient approach to look at HRV changes.

Subjects undergoing cold pressure tests showed a small increase of normalized total power, decrease in HF, and increase in LF and VLF, all of them statistically not significant Madan et al. (2005). Using the cold pressure test (here: 6 min cold water) in another study showed HRV decreases of LF and HF in healthy subjects (Wirch et al. 2006).

In a study focused on the gender effect of experimenters on subjective pain reports of healthy persons, a heat pain paradigm was used. A 30 × 30 mm aluminum contact electrode was applied on the right volar forearm. Subjects were instructed to let the thermode reach a painful temperature and let it maintain the temperature. It was possible to stop the test by the subject pushing a button. The pain test consisted of 15 heat stimuli of 48° Celsius and a maximum duration of 12 s (the subjects were not informed about the time limit). The interval between the pain stimuli was 2 min; the total duration of the experimental procedure was about 35 min per participant. During the stimuli, the participants rated their pain on pen-and-paper visual analogue scales. The group used spectral analysis with the LF/HF ratio. The LF/HF ratio in pain free intervals was about 1.25, during pain conditions about 1.75 with a rather low distribution. In the article it is not specified how they measured during the pain periods, e.g., if they calculated the frequency-domain values out of 12 s pain or of the 15 accumulated pain periods (Aslaksen et al. 2007).

In another pain model, 13 subjects received subcutaneous or intramuscular injections of saline solutions. Regardless of whether the muscle pain was superficial or deep, LF/HF ratio increased (the mean ratio from 1.18 ± 0.26 at rest to 2.96 ± 0.49 during pain) as did MSNA (Burton et al. 2009).

Appelhans used frequency-domain measures of HRV derived through spectral analysis. Fifty-nine participants provided ratings of pain intensity and unpleasantness following exposure to 4 °C thermal pain stimulation and indicated their thresholds for barely noticeable and moderate pain during three exposures to decreasing temperature. Greater low-frequency HRV was associated with lower ratings of 4 °C pain unpleasantness and higher thresholds for barely noticeable and moderate pain. High-frequency HRV was unrelated to measures of pain sensitivity (Appelhans and Luecken 2008).

Increased baroreceptor reflex decreased pain sensitivity in two studies (Bruehl and Chung 2004; Duschek and Reyes del Paso 2007).

Cluster headache is in many respects a naturally existing pain model. It occurs frequently, is interrupted by pain free periods, and the pain has a high intensity. In

this regard it is relevant that no changes in HRV were observed in a group of cluster headache patients in pain states (van Vliet et al. 2006).

Several neuropathic pain forms are sympathetically maintained, for instance, nerve blocks blocking sympathetic inputs (but not sensory inputs) can diminish neuropathic pain. The periaqueductal gray is both involved in HRV processing and pain processing. In this context an interesting study showed that deep brain stimulation in the PEG did alter HRV with increase of HF and consecutive decrease of LF/HF, which again correlated with pain relief through stimulation (Pereira et al. 2010).

Induction of anesthesia with propofol in ten women undergoing laparoscopy led to reduction of TP, LF, and HF; maintenance with propofol in further reductions of TP and LF, but not HF. Placement of the laparoscopic trocar as acute pain incident lead to an increase in HF (Deutschman et al. 1994). Maximal surgical stimulation induced an increase in LF and LF/RF (respiratory frequency 0.06 Hz) (Schubert et al. 1997).

Irritable Bowel Syndrome

Irritable bowel syndrome (IBS, not to be confused with inflammatory bowel syndrome) is defined as a functional bowel disorder in which abdominal pain is associated with defecation or a change in bowel habit with features of disordered defecation and distension. Three mainly interrelated factors are distinguished in the pathophysiology of IBS:

- Altered gut reactivity (motility and secretion) resulting in symptoms of diarrhea and/or constipation
- Gut hypersensitivity
- Dysregulation of the brain–gut axis (Mulak and Bonaz 2004)

Irritable bowel syndrome is a common problem with an estimated prevalence between 10 and 20 % in the US and the Japanese population (Tori and Toda 2004). It affects females more often than males. Its natural history shows fluctuations over time. In patients with IBS, prevalence of depression, anxiety, and other major psychiatric disorders is high. There are considerable discussions about the resemblance between irritable bowel syndrome and pelvic pain (Matheis et al. 2007) and, in general, with fibromyalgia-like symptoms.

IBS is of special interest for HRV issues due to the involvement of the vegetative nervous system. The function of the gastrointestinal system is modulated by exogenous (neural, hormonal) and endogenic (neural, hormonal, mediators) factors. Control is synchronized by coupling between the central nervous system and the enteric nervous system (ENS). The innervation of the gut is through two pathways, the vagal (and sacral) and the spinal (sympathetic). A control model involves four control levels (Fig. 12.1). Note that the ENS has been described to have a similar structure as the brain, consisting of sensory neurons, interneurons, and effector neurons. It has autonomous activity depending on local factors but can be overridden by the vegetative nervous system and higher brain centers, respectively.

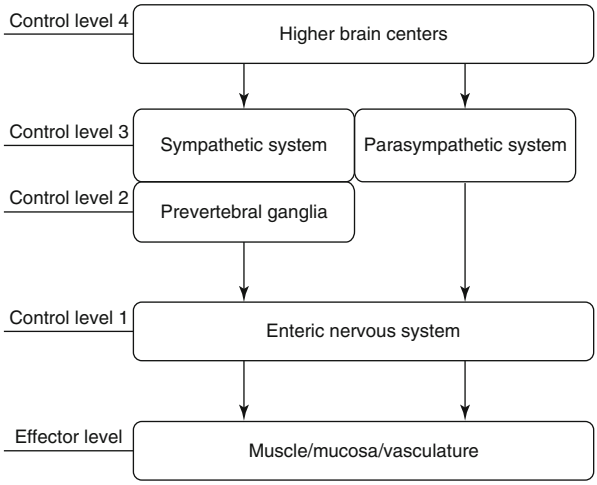

Fig. 12.1 Neural control of the gastrointestinal tract (Mulak and Bonaz (2004), with permission)

Irritable bowel syndrome might possibly begin due to changes in the CNS in the vegetative nervous system or due to local changes. It has been shown to be associated with autonomic dysfunction (cholinergic and adrenergic). Aggarwal showed that vagal dysfunction is particularly associated with a constipation subtype and patients with sympathetic dysfunction with a diarrheic subtype. The study included 21 patients and assessed autonomic function (HRV, postural adjustment ratio), colon transit time, and psychological profiles (Aggarwal et al. 1994). Women with irritable bowel syndrome ($n=103$) and without ($n=49$) were explored with expiratory/inspiratory ratio, Valsalva, posture changes, cold pressure test, and spectral and time-domain HRV (24 h). Generally, there was little difference between the groups. A subgroup analysis of women with severe irritable bowel syndrome revealed differences between the constipation-predominant group and the diarrhea-predominant group. The first had lower HF than the latter (Heitkemper et al. 2001). Postprandial saliva cortisol concentration is increased in IBS patients with predominant diarrhea, but not in constipation-type IBS (Elsenbruch et al. 2001; Elsenbruch and Orr 2001) (Fig. 12.2).

In an initial study, 18 patients with IBS were compared with 36 controls. Patients with IBS had higher sympathetic values than controls, but no differences in parasympathetic activity (Karling et al. 1998).

In another pilot study, women with and without IBS were tested with HRV Holter monitoring in the mid-luteal phase. IBS patients had a lower vagal tone (lower HF) and a flattened 24-h pattern of HRV, with lower levels of vagal tone during sleep (Heitkemper et al. 1998).

Thirty-five patients and 18 healthy controls were tested in supine, standing, and deep breathing modes. In the supine position, VLF was higher than normal. Standing up, the controls had higher VLF and LF than patients, HF remained unchanged. Changing to the deep breathing mode, controls had more increase in HF and decrease in VLF, LF did not change, in contrast to IBS patients, where HF remained

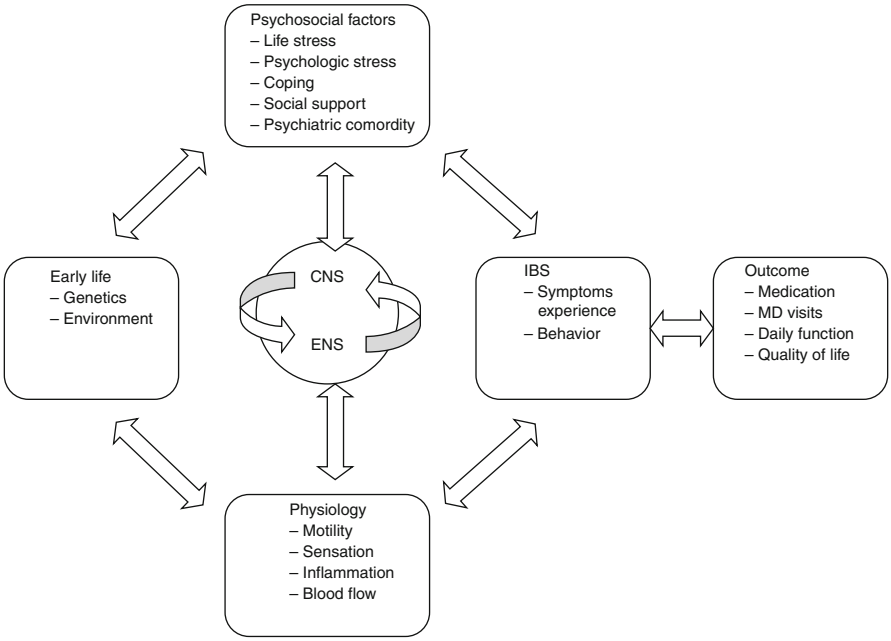

Fig. 12.2 Biopsychosocial model of IBS (Mulak and Bonaz 2004)

constant and LF increased and VLF was reduced. This was discussed as a reduced sympathetic reaction on orthostatic stress and diminished vagal response on deep breathing (Adeyemi et al. 1999).

LF was greater in IBS patients while awake; during REM sleep, there were no differences in HF in a sleep study with 15 patients and 15 controls (Orr et al. 2000).

Predominant diarrhea IBS patients showed an increase in LF/HF postprandial and a decrease in a postmeal period, which was different to controls and patients with constipation-type IBS. The latter also had a postprandial increase in saliva cortisol. There was a correlation between postprandial symptoms and the vagal response (Elsenbruch et al. 2001; Elsenbruch and Orr 2001).

Severe pain in 106 female IBS patients (and 41 controls without pain) was associated with lower parasympathetic tone, but was higher in women with postprandial pain (Burr et al. 2000).

A study with 103 female patients with IBS and 49 female controls showed no or little differences in HRV between the groups. In a subgroup analysis with women with severe IBS symptoms, however, there were differences. Parasympathetic tone was lower and ANS balance higher in the constipation than in the diarrhea group (Heitkemper et al. 2001).

Postprandial mental stress in women with and without IBS was tested by a stressful mental test. HRV and cortisol were not different between the groups and cortisol was not elevated due to the test either (Elsenbruch et al. 2001; Elsenbruch and Orr 2001).

In a sleep study, patients were stratified in patients with only lower abdominal symptoms and patients with both lower and upper abdominal symptoms (dyspepsia). HF was lower in IBS only patients compared to the other group and controls. LF/HF was higher during REM sleep in IBS only patients. IBS only patients had higher sympathetic dominance due to lower vagal activity during sleep (Thompson et al. 2002).

In a study targeting autonomic changes during sleep in women with IBS, participants were stratified in patients with and without depressive symptoms. In addition to HRV, subjective sleep quality and symptom severity were obtained with standardized instruments. Depressive patients had more sleep complains than non-depressive patients and controls, and had more symptoms. There were no HRV differences between the groups (Robert et al. 2004).

HRV differences during rest and under a rectal balloon distension model were tested in IBS patients and controls with the goal to test sex differences. One-hundred and thirty IBS patients and 55 controls were used. Peak power ratio (PPR) and peak power high frequency (PPHF) were calculated as measures for sympathetic balance and parasympathetic response, respectively. Skin conductance tests were also performed. IBS showed a larger skin conductance response than controls under the distension paradigm. They had a higher PPR and a lower PPHF than controls. Male IBS patients had higher conductance, PPR, and lower PPHF than controls (Tillisch et al. 2005).

HRV and MSNA were obtained before, under, and after a meal in male IBS patients and controls. Pre- and postprandial Valsalva tests, cold pressure test, and a deep breathing test were conducted and VAS for pain and nausea asked. During food intake there was no difference in blood pressure, heart rate, and MSNA, but LF/HF was higher in IBS. MSNA increase due to the pain test was higher in IBS than in controls. This was interpreted as reduced parasympathetic activity (van Orshoven et al. 2006).

Experimental pain in IBS patients and controls was caused by a standardized cold water immersion test (cold pressure pain, as mentioned above) on the forefoot. In healthy controls, heart rate increased more than in the IBS group when pain perception was statistically controlled. IBS and healthy controls had opposite reactions on pain; IBS had increased parasympathetic and decreased sympathetic response (Tousignant-Laflamme et al. 2006).

In a sleep study with IBS patients, those with diarrhea had lower parasympathetic (REM and non-REM) and higher sympathetic dominance (only non-REM) than those with alternating patterns. Interestingly, lower pain correlated with sympathetic dominance during sleep. The diarrhea patients were different to the patients with alternating but not with constipation pattern (Robert et al. 2006).

Ten patients with a mixed IBS pattern and ten healthy controls were compared by short-time HRV, deep breathing test, and data from Holter monitoring. In short-time HRV, all parameters were decreased in comparison to the control group (VLF468 vs. 906 ms^2, LF 437 vs. 811 ms^2, HF 271 vs. 854 ms^2). The same pattern occurred under the deep breathing test. In circadian HRV recordings, nuHF was

increased, nu LF decreased in all periods; generally the parasympathetic component was increased (Dobrek et al. 2006).

In a larger study, 45 constipation-predominant IBS patients were compared with 64 diarrhea-predominant IBS patients, 56 with alternating pattern, and 50 healthy controls. Holter monitoring was accomplished. Severity of pain was asked retrospectively for this period. Among women with severe pain, those with constipation had lower HF and higher LF/HF than women with severe pain and diarrhea. In contrast, in women without severe pain the difference was smaller and in opposite direction (Cain et al. 2007).

If the colon is distended in IBS patients ($n = 8$ vs. 8), changes occur. HF decreases already after feeding in IBS, but not in healthy controls. LF/HF was higher in IBF, but decreased under colon distension. IBS patients demonstrated altered response of the ANS after feeding and distension compared to controls (Ng et al. 2007).

Women with IBS (distinguished after subgroups) compared to healthy controls ($n = 35$ vs. 38) were tested on HRV differences during sleep in dependence of their sleep stadium. Generally, there was no difference between the groups. However, women with diarrhea-predominant IBS had increased parasympathetic modulation compared to constipation-predominant patients and patients with a mixed pattern (Jarret et al. 2008).

In a recent study, 23 patients with IBS according to the Manning criteria and 30 healthy controls were compared with the help of HRV and gastric myoelectric activity. IBS patients showed gastric dysrhythmia with lower LF and HF, increased LF/HF ratio, and increased serum catecholamine concentrations. The authors discussed an increased sympathetic drive as reason for the gastric dysrhythmias (Mazur et al. 2007).

In conclusion IBS does not produce a uniform picture. Most studies showed differences between IBS patients and controls (but it is possible that there exist a publication bias for studies without differences). Early studies distinguished only between patients and controls, but there is some evidence for differences between the three classic subgroups in IBS, diarrhea predominant, constipation predominant, and alternating. Different paradigms and tests were used. Some studies showed increased sympathetic tone (e.g., Karling et al. 1998; Orr et al. 2000; Tillisch et al. 2005), one decreased (Adeyemi et al. 1999) but most no changes (e.g., Heitkemper et al. 1998; Burr et al. 2000; Heitkemper et al. 2001; Elsenbruch and Orr 2001; Elsenbruch et al. 2001; Robert et al. 2004; Van Orshoven et al. 2006; Tousignant-Laflamme et al. 2006 and Cain et al. 2007). One study showed increase in vagal tone (Tousignant-Laflamme et al. 2006), some studies no influence (Karling et al. 1998; Orr et al. 2000; Heitkemper et al. 2001; Elsenbruch and Orr 2001; Elsenbruch et al. 2001 and Robert et al. 2004), or decrease (Heitkemper et al. 1998; Adeyemi et al. 1999; Burr et al. 2000; Thompson et al. 2002; Tillisch et al. 2005; Van Orshoven et al. 2006; Cain et al. 2007). Physical stress (cold pressure) and pain was associated with bigger changes. Sex differences were rarely tested, most studies used female participants only, but the menstruation cycle was usually not controlled. Diarrhea subtype patients seem to have more differences than the other groups.

Back Pain

As Gordon Waddell noted, back pain is a syndrome that is a twentieth century medical disaster (Waddell 1999). It can be related to simple muscle stiffness, which does not need any specific treatment, but it can also be based on spinal metastasis due to breast cancer, for instance. Prevalence of (uncomplicated) back pain is as high has 40 % in the adult population of an industrialized country. Many possible causes for nonspecific back pain have been presented and discussed, but the real origin is still not known. And although many today call it prolapse instead of back pain, also in this latter, radiology-based diagnosis, no conclusive evidence for causes exist. Using HRV on back pain is therefore difficult, because it affects a heterogeneous patient population with sometimes only pain itself in common. However, quality of life is probably more influenced by disability than pain intensity, and disability again correlates most with treatment approaches. Patients with similar pain intensity but higher disability are likely to be treated with operations and other invasive procedures, while patients with lower disability are not.

Heart rate variability measures were used on a group of 16 patients with back pain and sciatica for 3–12 months undergoing epidural treatment with a local anesthetic and a steroid. HRV and pain were measured before and after treatment. Patients with no significant pain relief were used as controls. HRV was analyzed for a series of 500 normal RR intervals. Point correlate dimension (PD2) and ApEn were used as HRV algorithm. PD2 was significantly increased after pain relief (Storella et al. 1999).

Gockel et al. (2008) enrolled 46 back pain patients. HRV was analyzed from short (5 min) ECG recordings during controlled and spontaneous quiet breathing. Deep breathing and active orthostatic tests were performed to exclude cardiac autonomic neuropathy. Gockel and colleagues used the Oswestry score, an established instrument, to describe disability. HRV was significantly lower among those with an Oswestry score $\geq$20 % than among those with a score <20 %, the highest difference in RMSSD (36.3 ± 8.4 vs. 56.5 ± 32.5). HRV did not differ to a high degree among the patients with a low ($\leq$5) or high (>5) NRS pain score (Gockel et al. 2008). This is supported by results from a Taiwanese study. This is interesting because the authors there evaluated disability in a culturally different population but found similar results. They included 121 patients with chronic neck pain and performed cluster analysis to define different patient groups. The second group included middle-to-older-aged women, and presented a higher level of pain, psychological distress, sleep disorder, and disability. Reduced heart rate variability was associated with subjective disability in these patients (Kang et al. 2012).

In a study, 51 participants were randomly allocated to a control group, treatment, and to sham treatment groups. A pulse watch was used to obtain data. A short-term HRV (5 min) was obtained before treatment and after treatment. LF/HF increased significantly after treatment in the pain free group (Roy et al. 2009).

Headaches

Migraine

Migraine is a primary episodic headache disorder characterized by various combinations of neurological, gastrointestinal, and autonomic changes. Prevalence is about 15 % in women and 5 % in men. Formal diagnostic criteria were published in 1988 by the International Headache Society. They recognize seven subtypes of migraine with two major varieties: migraine with aura (formerly classic migraine) and migraine without aura (formerly common migraine). Against all rumors, migraine is not personality dependent, not prevalent in special subgroups of the population (e.g., female teachers), not a female syndrome, and psychosomatic influences are not dominant. Today it is rather considered as a classical somatic disease with a high genetic influence. Pathophysiological mechanisms have been proposed. Treatment recommendations exist and work acceptably in the majority of patients.

An early study identified only minor differences in HRV between migraineurs and healthy controls and no differences between patients with migraine with and without aura (Pogacnik et al. 1993b).

Tabata studied 27 patients with migraine in a headache-free period and 24 healthy controls with help of Holter monitoring and discovered significant differences in circadian rhythm in SDNN, RMSSD, pNN50, and HF between the group with migraine and controls (Tabata et al. 2000).

Shechter investigated migraine patients, subdivided in groups with and without disabling headache, and used SDNN obtained by paced breathing. Disabled migraine cases had significantly lower SDNN compared with nondisabled migraine cases and controls (Shechter et al. 2002).

Ebinger tested 70 children and adolescents with migraine during the headache-free period (and 81 healthy age-matched controls) with the help of heart rate variability during spontaneous breathing at rest and during metronomic breathing. He found a diminished mean heart frequency and at a breathing frequency of 6 breaths/min, a lower LF/HF ratio (Ebinger et al. 2006).

Only moderate differences were found between 16 female migraine patients without aura aged 18–30 years and 14 age-matched healthy female controls (Nilsen et al. 2009).

These few studies do not reveal whether or not there are significant HRV differences in migraine patients, especially because disability usually was not taken into the statistical models.

Tension-Type Headache

Pogacnik compared 51 patients with tension-type headache with the same number of controls and did not observe differences in HRV, neither between the episodic (19

patients) and chronic (32 patients) tension-type headache subgroups (Pogacnik et al. 1993a). This is in contrast to their findings in migraineurs mentioned above (Pogacnik et al. 1993b).

Cluster Headache

Cluster headache is a distinct clinical and epidemiological entity known since 1958. Its importance as a primary headache derives from its extraordinary morbidity. It is characterized by a devastating pain. Headache attacks occur in series lasting for weeks or months (cluster periods), with an attack frequency between one every other day up to ten times a day or more. The cluster periods are separated by remission usually lasting months or even years. The International Headache Society's criteria for cluster headache require at least five attacks of severe, unilateral, orbital, suborbital, and/or temporal pain lasting 15–180 min if untreated and associated with at least one of the following points: conjunctival injection, lacrimation, nasal congestion, rhinorrhea, forehead and facial sweating, miosis, ptosis, or eyelid edema. Cluster headache has clear signs of ANS involvement, showing both signs of sympathetic dysfunction (Horner's syndrome) and parasympathetic overactivity (e.g., lacrimation, nasal congestion, and injection of the eye).

Thirty-nine patients and 30 healthy controls were investigated with 24-h Holter ECG recording, 9 of them also in headache periods. The data obtained indicate a possible existence of a disordered chrono-organization in cluster headache (phase shift of approximately 1 h of heart rate rhythm during the cluster period) together with a moderate lower heart rate variability and a higher occurrence of arrhythmias in cluster headache patients with right-sided pain (Micieli et al. 1993).

Tubani followed eight patients with cluster headache during attacks and compared HRV data during their headache-free periods with those of normal controls. During spontaneous attacks the parasympathetic indices are at once increased at the onset with a mild reduction of the sympathetic indices, and all these modifications slowly disappear at the end of each attack. Comparison of the average low-frequency and high-frequency values during headache-free periods showed a significant reduction in LF even when LF/HF was normal (Tubani et al. 2003). In contradiction to these results, no differences in HRV were observed in patients with cluster headache during headache or in a headache-free period in another study (van Vliet et al. 2006).

Fibromyalgia

In fibromyalgia (also called fibromyalgia syndrome), chronic widespread pain that persists in all four quadrants of the body is often accompanied by a range of symptoms including fatigue, sleep disturbance, functional impairment, cognitive dysfunction, variable bowel habits (also IBS), depression, stiffness, and more. Fibromyalgia patients have frequently reduced pain thresholds (hyperalgesia) and

feel pain with normally innocuous stimuli (allodynia). Diagnostic criteria published in 1990 by a group of the American College of Rheumatology are currently used to diagnose the clinical disease. It is unclear whether these criteria characterize a homogeneous or rather a heterogeneous group of patients. Treatment is frustrating both for patients and practitioners and fibromyalgia causes suffering in a big group of population, mostly women.

Autonomic dysfunction characterized by persistent ANS hyperactivity at rest and hyporeactivity during stress has been consistently demonstrated in FM patients (Staud 2008). ANS hyporeactivity appears to be correlated with persistent fatigue and other clinical symptoms associated with FM, including low blood pressure, dizziness, and faintness (Vaeroy et al. 1989; Staud 2008).

Cohen studied 22 women with FM and 22 healthy controls with 20 min HRV. Heart rate was significantly higher in FM patients compared with controls. FM patients had significantly lower HRV compared with controls, higher LF, and lower HF. Quality of life, physical function, anxiety, depression, and perceived stress were moderately to highly correlated with LFnu, HFnu, and LF/HF (Cohen et al. 2000c).

Thirty patients with fibromyalgia and 30 healthy controls were assessed with a 24-h ambulatory recording of heart rate variability. Fibromyalgia patients had a decreased SDNN (126 ± 35 ms vs. 150 ± 33 ms in controls) and a decreased pNN50. Patients lost the circadian variations of sympathovagal balance, with nocturnal values significantly higher than those of controls at time 0 and at 3 (Martinez-Lavin et al. 1998).

A study examined resting HRV in a sample of 84 patients with chronic benign pain, a subgroup of whom had fibromyalgia. Fibromyalgia patients experienced higher levels of depression and greater difficulties with physical functioning, but there were no significant differences in any of the HRV indices between the two groups. Across all pain conditions, age, gender, physical health functioning, pain anxiety, and pain sensations were all significant predictors of HRV suggesting that each is involved in the relationship between chronic benign pain and autonomic function (Mostoufi et al. 2012).

The Case of Disability

In the last decade, disability has been identified as a major problem in chronic pain. Disability has been described as an umbrella term, covering impairments, activity limitations, and participation restrictions. Impairment is a problem in body function or structure; an activity limitation is a difficulty encountered by an individual in executing a task or action, while a participation restriction is a problem experienced by an individual in involvement in life situations. Thus, disability is a complex phenomenon reflecting an interaction between features of a person's body and features of the society in which he or she lives.[1] Pain intensity and disability do not correlate

[1] From WHOs fact sheet. World Health Organization. http://www.who.int/topics/disabilities/en/. Retrieved 30 March 2013

necessarily. Back pain, for instance, has worldwide a similar variance in pain intensity, but the disability varies extensively between different geographic regions, often discussed under "cultural differences."

Until today several studies have shown that decreased HRV correlates with disability, so in back pain, where lower HRV correlates with disability, but not pain (Gockel et al. 2008) or with a moderately higher level of pain, psychological distress, and sleep disorder (Kang et al. 2012). Extended sick leave (>121 days) compared with short sick leave (<29 days) was associated with higher heart rate and lower heart rate variability (only frequency domain used particularly in LF and TP) in a study enrolling 65 persons on pain-related sick leave (Kristiansen et al. 2011). It is an interesting question whether the observed HRV increase after pain relief is due to diminished pain intensity or to decreased disability (Storella et al. 1999).

Conclusion

Pain causes distress and this alone would be sufficient to cause changes in HRV. This was observed in several but not all studies. However, it fits into the picture when disability, principally subjective, is associated with attenuated HRV parameters. With few exceptions, pain syndromes are generally heterogeneous, which is reflected in varying results found in IBS, back pain, tension-type headache, or neuropathic pain. Probably more homogeneous are cluster headache and migraine, but only few studies have looked at these. In pain, studies with HRV have focused mostly on pain syndromes with disappointing therapeutic results like IBS or fibromyalgia. Whether or not HRV can provide information on the feasibility of sympatholytic treatments for neuropathic pain is a major research question with clinical relevance. Another exciting question is whether or not specific constellations of HRV are associated or even predict pain treatment results.

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Chapter 13
HRV in Oncology and Palliative Medicine

Cancer Pathophysiology

Autonomic nervous system dysfunction is a problem that can be detected in about 50–100 % of patients with advanced cancer (Bruera et al. 1986; Walsh and Nelson 2002; Strasser et al. 2006). It has been described in various primary malignancies (Table 13.1).

It is, however, not easy and often not possible to distinguish between autonomous neuropathy as consequence of the tumor itself, as consequence of (often chemotherapeutic) treatment, or as consequence of both.

Fadul and colleagues used short-term HRV as well as the Ewing test battery consisting of three tests for the parasympathetic function (heart rate changes after different perturbations) and two tests for the sympathetic system (blood pressure changes after perturbations). Most patients had an Ewing score greater than 2, which is reported as cutoff point to diagnose moderate to severe autonomic dysfunction. Only six (12 %) patients had diabetes before onset of cancer (Fadul et al. 2010).

A decreased HRV parameter can also be based on increased CRP. Many patients with advanced cancer have increased CRP, which has been related to an activated immune system. Already moderate increased CRP again has correlations to lower HRV values, as observed in several studies (Kon et al. 2006; Araujo et al. 2006; Carney et al. 2007; Ziegler et al. 2008).

Explanations for a possible pathophysiological relation between lower heart rate variability and cancer death are interesting issue for debate. In contrast to cardiologic diseases, advanced cancer patients show a plethora of symptoms that can be associated with HRV changes (like depression, cachexia, sleep disturbances, autonomic dysfunction, pain, heart failure). An important point in the discussion is the ultimate reason for a cancer patient's death. This is not as simple. Cancer patients die from a variety of causes. Inagaki et al. (1974) reported on 816 cancer patients and summarized as most important causes of death: infection (47 %), organ failure (25 %), infarction (11 %), carcinomatosis (10 %), and hemorrhage (7 %).

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Table 13.1 Autonomic disturbance in various cancer types

Cancer	Method	ANS abnormalities	Reference
Various	Ewing test	81 %	Strasser et al. (2006)
Various	Test battery	100 %	Walsh and Nelson (2002)
Various	Test battery including HRV	52 %	Bruera et al. (1986)
All survivors	HRV	LF/HF increased, depressed diurnal rhythm	Kamath et al. (1998)

It is important to recall that cancer-related effects like paraneoplastic conditions leading to increased blood glucose may also cause diminished HRV (Haegele-Link et al. 2008).

Prognosis for Cancer Patients in a Palliative Phase

Prognosis is still a challenge in palliative patients. Prognostication in incurable diseases assists clinicians in their decision making and helps them provide patients and their family with information about the (likely) future (Glare and Christakis 2005). Nevertheless, clinical estimation is uncertain (Oxenham and Cornbleet 1998). Score systems have been proposed (Pirovano et al. 1999) and validated (Maltoni et al. 1999); and the European Association for Palliative Care recommends their use. But prognostication is rough, giving information about 30-day survival probability (>70, 30–70, or <30 %). Any further simple approach would be highly beneficial (Glare and Christakis 2005). In a small study of our own, we explored heart rate variability changes in a group of patients with advanced cancer in relation to survival.

In a study with a 10-year follow-up, 347 subjects under 65 were examined with a baseline that included HRV (Holter monitoring, frequency domain, SDNN, and Power slope). Different indices for mortality were found (among them: smoking, prior heart disease, increased glucose, decreased cholesterol (sic)). SDNN, VLF, and LF had an association with mortality, but not HF. The slope was the best univariate predictor with a cutoff value of 1.5. In a multivariate regression model, a steep slope of the power law regression line and congestive heart failure were the only independent predictors, with a relative risk of 2.01 and 1.85, respectively. None of the measures of HRV had a univariate association with cancer death or other nonvascular reasons for death (Huikuri et al. 1998).

A case cohort study was conducted within a longitudinal study of 15,792 middle-aged men and women. A sample of 900 subjects without prevalent coronary heart disease in baseline was drawn and compared with all subjects with CHD and all subjects who died before follow-up. HRV was determined by a 2-min rhythm strip where RR distances were later measured half-automatized. In addition plasma levels for cholesterol, HDL, LDL, triglycerides, serum

Table 13.2 HRV in cancer patients short before death (Ernst and Rostrup 2013a, b)

	Study	Fadul	Sztajzel (2004)	Schumacher (2004)
SDNN	25.32 ± 20.75	51.4 ± 24.33	141 ± 39	
RMSSD	24.9 ± 28.41		27 ± 12	
TP	409.32 ± 898		21,222 ± 11,663	
LF	86.33 ± 159	356.4 ± 228.39	791 ± 563	1,170 ± 416
HF	32.92 ± 52.1	477 ± 321.99	229 ± 282	975 ± 203
LF/HF	2.33 ± 1.85		4.61 ± 2.33	1.5 – 2.0
Sampen	2.0526 ± 0.416		–	

In comparison results from advanced cancer patients (Fadul et al. 2010) and from healthy persons (Sztajzel 2004; Schumacher 2004)

insulin, and glucose were determined and diabetes was diagnosed according to the fasting blood glucose levels. Blood pressure, waist and hip circumferences, and carotid intima-media thickness were assessed. Four measures of HRV were determined: SDNN, rMSSD, SDSD, and pNN50, but no frequency-domain measures. Generally, low HRV was associated with an adverse cardiovascular risk profile and elevated risk of death from all causes, including cancer, and of incident CHD. The elevated risk could not be attributed to other risk factors. Relative risk of low SDNN was lower than from the other parameters. The authors conclude that low HRV possibly precedes different manifest diseases (Dekker et al. 2000).

Thirty-five patients with metastatic carcinoid tumors were studied with the help of 24 h Holter ECG calculating SDNN, rMSSD, and pNN50. During the follow-up of 18 ± 7 months, 15 of 35 (43 %) patients died. Patients with the combination of SDNN <100 ms and presence of carcinoid heart disease had a worse prognosis compared to the other patients (Hoffmann et al. 2001).

Fadul examined 47 patients with advanced metastatic solid cancers with a median survival of 139 days after inclusion (but a wide range between 4 and 2,266 days) using short-term HRV (20 min). Frequency-domain measures were not associated with survival. They report a trend toward a significant association between survival and SDNN ($p = 0.056$) (Fadul et al. 2010).

We conducted a study that included 24 patients with advanced cancer due to solid tumors. Short-term HRV (10 min) was taken at course of the disease, if available, several times. The last available HRV taken in mean 33 days before death was significantly lower than healthy controls from other studies (Table 13.2).

Most HRV parameters, with exception of SampEn did not change the last 3 months before death (Table 13.3).

It is not clear whether or not HRV can have a role in survival estimation for cancer patients. Only a few studies with a low number of patients included have been published. Only our small study examined cancer patients more than one time in the course of the disease. On the other hand we have some bigger longitudinal studies that show a statistical relation between lower HRV parameters and cancer mortality. More studies have to be conducted before conclusions can be drawn.

Table 13.3 HRV changes in cancer patients during disease progression (Ernst and Rostrup 2013a, b)

Survival	>60 days	30–59 days	7–29 days	<7 days
SDNN	24.71	25.87	21.56	21.38
RMSSD	17.6	17.12	33.55	14.2
TP	243	525	88.9	438
VLF	115	29.8	39	118
LF	68.7	46.8	19.8	90.1
HF	30.9	28.5	42.7	20.96
LF/HF	2.3	1.46	1.64	2.4
Entropy	**2.2013**	**2.0350**	**1.9391**	**1.8555**

Cancer Treatment and HRV: The Case of Anthracyclines

Particular challenges in cancer treatment are chemotherapeutic agents that induce cardiac dysfunction. In some treatment programs, evaluation of heart function at baseline and during the process is an integral part of the treatment, for instance, with anthracyclines. Since their introduction in the late 1960s, doxorubicin and epirubicin have been used successfully in the treatment of a wide variety of hematopoietic and solid tumors. However, their use is limited by the occurrence of cardiotoxicity, which may result in congestive heart failure (Meinardi et al. 1999). This has resulted in maximum dosage recommendations to avoid major heart disease. To detect cardiac dysfunction in patients who are treated with anthracyclines, regular monitoring of the heart function during treatment is important. After completion of chemotherapy, detection of cardiac dysfunction is also of relevance, since this might lead to timely medical intervention aiming at improving the cardiac prognosis. Multigated radionuclide angiography (MUGA) is a noninvasive technique that makes use of intravenously injected radionuclides (^{99}Technetium) that bind to erythrocytes and enable the cardiac pool to be visualized with a γ-camera. MUGA is widely considered a gold standard.

The value of HRV analysis for the detection of anthracycline-induced cardiotoxicity has been evaluated in some studies.

Postma studied 31 young patients for late cardiotoxicity (9 years follow-up) with several techniques (MUGA, echocardiography) and also HRV. No correlation between the anthracycline dose and echocardiographic and MUGA parameters was found, but HRV analysis revealed a significantly impaired HRV in the patients who received more than 400 mg/m^2 doxorubicin compared to those who received less than 400 mg/m^2. This suggests that HRV could be a sensitive indicator for cardiotoxicity (Postma et al. 1996). Tjeerdsma et al. (1999) found significantly impaired HRV in breast cancer patients who had been treated with anthracyclines and high-dose chemotherapy compared to healthy age-matched females. They included 20 patients with LVEF >50 %. They used Holter monitoring technique and time and frequency domain. SDNN and SDANN were not different to healthy controls. In contrast, PNN50 and rMSSD were significantly lower in patients than in healthy controls. All frequency-domain indices were reduced.

Ekholm looked at nine women treated for metastatic breast cancer with docetaxel. They were studied prior to the docetaxel treatment and after the third or fourth course and exhibited no differences in HRV (Ekholm et al. 2000).

Nousiainen was not interested in cancer, but in left ventricular dysfunction. Knowing that doxorubicin causes decreased LVEF, he investigated patients receiving this agent as a clinical model and focused on neuroendocrinological changes. After cumulative doxorubicin doses of 400 and 500 mg/m^2, there was a decrease of HFnu and increase in LFnu leading also to an increase of LF/HF. However, after the cumulative doxorubicin dose of 500 mg/m^2, the changes in HRV components returned toward baseline. This might suggest that doxorubicin-induced left ventricular dysfunction is associated with an early change in sympathovagal balance toward sympathetic predominance. Further progression of left ventricular dysfunction is then associated with an attenuation of sympathetic tone (Nousiainen et al. 2001).

Meinardi followed breast cancer patients treated with five cycles of fluorouracil, epirubicin, and cyclophosphamide (FEC). Mean LVEF declined from 0.61 at T0 to 0.54 during the treatment course, but no HRV changes were observed (Meinardi et al. 2001).

Twenty-four breast cancer patients were treated with docetaxel alone and 34 with a combination of docetaxel and epirubicin. Already after a therapeutic course of 3 weeks, HRV alterations could be observed (Syvanen et al. 2003).

Salminen followed breast cancer patients treated with eight cycles of an epirubicin–docetaxel combination. The patients had no clinical symptoms of cardiotoxicity. Neither echocardiography nor HRV (Holter monitoring) changed compared to baseline (Salminen et al. 2003).

Brouwer followed doxorubicin-treated survivors of a malignant bone tumor (osteogenic sarcoma and malignant fibrous histiocytoma) with echocardiography and HRV (Holter monitoring) 22 years after treatment. Compared with age-matched controls, patients showed lower values of HRV parameters except for LF/HF and LFNU. Almost all HRV parameters decreased compared with the measurements in 1997 while LF/HF and LFnu increased (Brouwer et al. 2006).

So *in conclusion* I have found conflicting results. Brouwer's long-time follow-up study convincingly showed deterioration of former doxorubicin-treated patients while earlier studies had shown promising results. Later studies, however, were not able to show HRV decline during or after the treatment course, even in patients where mild echocardiographic was described. As usual in the HRV field, the studies are (too) small. In addition, no nonlinear indices were used.

Cancer Symptoms and HRV

Only few studies have been conducted on the association between different cancer symptoms and changes in HRV. *Cardiac cachexia* is associated with a lower LF, BRS, and higher catecholamine concentrations than matched controls of

noncachectic cardiac patients or healthy controls (Ponikowski et al. 1999a, b). In an experimental study, 17 female (healthy) subjects were exposed to *nauseogenic* visual stimuli and HRV changes were analyzed. LF/HF increased associated with the extense of nausea, 1.54 ± 2.11 in relation to moderate, 2.57 ± 3.49 to strong nausea, suggesting increased sympathetic involvement. They also observed short increases of HF preceding increased nausea (LaCount et al. 2011).

Fatigue is the most common problem among long-term cancer survivors, particularly observed in breast cancer survivors. Fagundes included women who had completed treatment for stage 0–IIIA breast cancer within the past 2 years (except for tamoxifen/aromatase inhibitors) and were at least 2 months post-surgery, radiation, or chemotherapy. HRV was continuously measured with the Polar s810 wristwatch and wearlink 31 belt band. HRV (only RMSSD documented in the publication) was lower among more fatigued women compared to those who were less fatigued (22.145 ± 13.327 vs. 28.875 ± 16.905) (Fagundes et al. 2011).

Cheyne–Stokes respiration patterns reduce LF and HF power, but increase VLF (Mortara et al. 1997).

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Chapter 14
Psychiatry

Introduction

Emotional regulation has been related to HRV patterns (Thayer 2000; Appelhans and Luecken 2008). Emotion regulation ability has been operationalized and associated with lower or higher HRV (Appelhans and Luecken 2008; Thayer and Fischer 2009; Thayer et al. 2009). Thus, a meta-analysis proposed that "HRV is important not so much for what it tells us about the state of the heart as much as it is important for what it tells us about the state of the brain" (Thayer et al. 2012).

Depression

Depression has a prevalence of between 8 and 12 % around the world (Andrade et al. 2003). It is expected that depression will have the biggest health impact after cardiovascular disorders by 2020 (Murray and Lopez 1997; Kemp et al. 2010). Interesting enough, depression and cardiovascular disease do not develop independently. Rather, there is a clear association between depression and cardiovascular disease. Twenty to forty percent of patients with CVD have at the same time depression (Woltz et al. 2012). The relation is bidirectional – it seems that patients with depression can develop CVD more readily and patients with CVD can develop depression more readily (Pratt et al. 1996; Woltz et al. 2012). HRV changes are well documented both in CVD and in depression. Here some recent theories regarding the genesis of depression will be introduced. In a second part the relation between depression and heart disease will be examined and the findings of HRV changes in relation to depression will be discussed in greater detail.

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Pathophysiology of Depressive Disorders

Major depressive disorder is the official denomination of the malady commonly called depression. The idea of depression includes a wide variety of disorders. A cursory look at concomitant ICD codes reveal depressive symptoms in bipolar affective disorders, depressive episodes, recurrent depressive disorders, and anxiety disorders, not to mention several kind of somatization disorders where depressive symptoms might be more or less existent. One problem is gradation to differentiate between mild, moderate, and severe depression. Another problem regards diagnosis. It is, for instance, a well-known problem that several symptoms related to advanced cancer disease (e.g., anorexia, fatigue, sleep problems) might be due to the original disease, a coexistent depression, or a combination of both. Similar problems exist in the combination of severe cardiac diseases and depression. While at least diagnostic instruments can make it easier to collect a unitary group of study patients, it is far more difficult to agree on the pathophysiology of depressive disorders, in case there is just one.

Major depressive disorder (MDD) is regarded as a familial disorder and some scientists argue that its familiarity is due to genetic factors, suggesting that parental social behavior and other familial environmental risk factors are not as important in the pathogenesis of MDD as previously assumed. However, there is no solid evidence for specific genes and specific gene-by-environment interactions in the pathogenesis of MDD (Hasler 2010). The influence of genetic factors might be up to 40 %. Non-genetic factors, explaining the remaining 60 % of the variance in susceptibility to MDD, are individual-specific environmental effects mostly adverse events in childhood and ongoing or recent stress due to interpersonal adversities, including childhood sexual abuse, other lifetime trauma, low social support, marital problems, and divorce (Sullivan et al. 2000; Kendler et al. 2002, 2006; Hasler 2010), that is, if it is at all possible to find clear causal links. The point here is that, due to its genetic origin, depression probably cannot be circumvented, but once it manifests, several psychosocial concomitant circumstances can be used to control the symptoms.

Today's ideas around the pathophysiology of depressive disorders focus on stress and maladaptive responses of the HPA axis, pathological changes in endogenous monoamines, the neurotrophic hypothesis, ideas around altered glutamatergic and GABAergic subsystems, and combinations of those theories. I summarize them here only briefly with a main focus on theories that include similar brain structures as those involved in generating of HRV.

Stress Reactions and Immune System

There is a long history of discussion of the role of the endogenous stress system and its relation to depression. Stress response differs between genders; men have a higher stress response regarding achievement challenges, whereas women develop

more stress responses related to social situations. Generally, women show higher stress responses, which would match the higher prevalence of depression in women. Not matching are numerous studies that do not show impaired HPA patterns in MDD (Pariante and Lightman 2008). It is unclear whether HPA dysfunctions have an impact on the effect of antidepressive drugs (Schule 2007). One possible role of the endogenous stress system exists in depressed subjects with a history of childhood trauma. Several lines of evidence, in other animal, experimental and clinical studies suggest an influence of the HPA system on the disorders. Most recently, this is based on newer epigenetical ideas indicating that the effects of genes switched off (or on) as a consequence of trauma in childhood can be transferred to the following generations without changed genes.

Some sickness behavior, for instance that related to influenza, is well known to mimic several traits of depression. It shares many symptoms with depression, including fatigue, anhedonia, psychomotor retardation, and cognitive impairment. Recent theories (Maier and Watkins 1998; Dantzer et al. 2008; Raedler 2011) focus on brain systems that might be activated in association to this sickness behavior. The behavioral changes are mediated by pro-inflammatory cytokines such as interleukin-1α, tumor necrosis factor-α, and interleukin-6, which activate the HPA axis and impair the central serotonin system. Depressive symptoms all the way up to suicide are a well-known serious adverse effect of treatment with immunological active substances like interferon. Some studies report drugs like aspirin and celecoxib with known effects on the synthesis of prostaglandins caused by inflammation might have inherent or increase effects of antidepressive drugs (Rahola 2012). Depression, so the idea, might be induced by an inflammatory process, which is extended in the brain causing depressive effects.

Monoamines

Most of the noradrenergic and dopaminergic neurons are located in midbrain and brain stem nuclei and project to large areas of the entire brain. Their role is similar to that other nuclei with specific receptors projecting to most of the brain – to have influence reactive patterns and to trigger general responses such as cholinergic or opioidergic neurons. All these systems are involved in the regulation of a broad range of brain functions, including mood, attention, reward processing, sleep, appetite, and cognition. This led early on to the idea that deficiencies in the monoaminergic neurons could cause depression. The well-known properties of antidepressive drugs, to modify and mainly increase the release or the stay of monoamines in the synaptic gap, supported apparently this idea. Almost every compound that inhibits monoamine reuptake, leading to an increased concentration of monoamines in the synaptic cleft, has been proven to be a clinically effective antidepressant (Belmaker and Agam 2008; Hasler 2010). Serotonin is the most important candidate receptor. Decreased availability of this receptor has been found in multiple brain areas of patients with MDD. Despite several experimental approaches supporting this idea,

there are also conflicting results and the overall evidence is still contradictory (Hasler 2010; Rahola 2012). Also dysfunction of the central noradrenergic system has been discussed, but in part because of difficulties in depleting isolated central noradrenaline, its role is unclear.

Almost all established antidepressants target noradrenaline or serotonin receptors. However, full and partial resistance to these drugs and their delayed onset of action suggest that dysfunctions of monoaminergic neurotransmitter systems found in MDD represent the downstream effects of other, more primary abnormalities. Antidepressive drugs have far more effects than only on the monoaminergic receptor, among others also effects on the brain immune system and intracellular translation mechanisms. Despite these limitations, the monoamine deficiency hypothesis has proved to be the most clinically relevant neurobiological theory of depression until today. The monoamine hypothesis is particularly interesting for the interpretation of HRV because it is also related to the function of the ANS. In addition (as discussed above and below), several antidepressant drugs have profound effects on HRV.

Glutamate and GABA Receptors

Gamma-aminobutyric acid (GABA) and glutamate are two further ubiquitous-appearing transmitter–receptor systems in the brain. While gamma-aminobutyric acid has a generally inhibitory effect, glutamate is exhibitory and has effects on long-term changes in neurons as well. Changed GABA concentrations and diminished GABA receptor function has been reported in depressive patients. Contradictory evidence of the GABA hypothesis of depression includes the lack of effects of GABAergic drugs on core depressive symptoms (Birkenhager et al. 1995).

The role of the glutamate system received more attention recently when several studies showed decreased depressive symptoms short after application of ketamine, a glutamate receptor antagonist in depressed patients. Glutamate release inhibitors have also shown antidepressive effects. Additionally, abnormal NMDA (a glutamate receptor subtype) function has been shown in depressive patients. All this suggests that this theory is promising and might offer a new therapeutic approach.

Neurotrophic Theory

The continuing function of (brain) neurons is dependent on the regular release of neurotrophic factors. Dysfunctions of neurotrophic systems have been shown in chronic pain and psychiatric diseases (Martinowich et al. 2007). Brain-derived neurotrophic factor (BDNF) has been studied most. Preclinical studies have shown correlations between stress-induced depressive-like behaviors and decreases in

hippocampal BDNF levels, as well as enhanced expression of BDNF following antidepressant treatment (Martinowich et al. 2007; Hasler 2010). The administration of ATDs normalizes the levels of BDNF as has been observed both in studies with animals and in postmortem studies on human brains of people suffering from mood disorders (Rahola 2012). A different argumentation is based on the recently discovered phenomena that even in the adult brain cell division occur in at least two places, among them the hippocampal subgranular zone (SGZ). This is interesting in depression where the hippocampus is one of the involved brain regions. Blockade of hippocampal neurogenesis slightly inhibits the effect of antidepressant treatments in rodents (Kempermann 2008) and antidepressant treatments increase the concentrations of different hippocampal growth factors that influence neurogenesis (Rahola 2012). This is significant because neural progenitors of the hippocampal subgranular zone (SGZ), which differentiate and integrate into the dentate gyrus, need about 2–3 weeks to reach the hippocampus, fitting with the number of weeks antidepressive drugs normally need to have an effect.

Depression and Heart Disease

Observed as early as 1937 (Maltzberg 1937), clear associations between depression and coronary heart disease have been reported many times (recent review (Nemeroff and Goldschmidt-Clermont 2012)). There is also a clear relationship between the magnitude of depressive symptoms and increased cardiac morbidity. Already low scores in the Beck Depression Inventory of 5–9 are associated with an increased frequency of cardiac events (Sheps and Rozanski 2005; Kunzansky 2005). But there are some interesting details in this relationship that are worth a closer look. First, the association of depression and cardiac problems is robust and has been shown repeatedly with the help of statistical models where further common associated risk factors like smoking, overweight, diabetes, and lack of exercise were taken into consideration. Most studies included patients with major depression. For instance, in one study about 400 patients with clinical depression and 400 matched controls, depressive persons had a two-third increased likelihood to develop serious physical illnesses including cardiac disease (Holahan et al. 2010). Another example is a study of 2,832 adults without history of CAD followed up in mean 12 years. Depressed mood and lack of hope was associated with an increased risk of fatal and nonfatal ischemic heart events (RR 1.5 and 1.6, respectively) in a statistical model taking in other risk factors (Anda et al. 1993). Also bipolar disorders are associated with an increased risk for hospital admission due to ischemic events (Callaghan and Khizar 2010).

Several lines of evidence show the bidirectional effects of depression. Depression in patients with different cardiac diseases has a negative effect on the short- or long-term outcome, so in congestive heart failure (Lesman-Leegte et al. 2009), AF (Frasure-Smith et al. 2009), and after MI (Glassman et al. 2009). Also anhedonia, the incapability to feel pleasure, is strongly associated with fatal outcome after myocardial infarction (Davidson et al. 2010).

However, not all reports are clear without ambiguity. Working in clinical practice, it is not possible to overlook a clear association between risk factors for CVD and depression. Depressive patients smoke, eat too much, exercise too little, and in addition take drugs predisposing them even more to excess weight. In the Heart and Soul study of 1,017 patients with coronary heart disease focused on depression and its consequences, the researchers argue that they were able to identify physical inactivity, non-adherence to medications and other negative behaviors as main reason for cardiac disease (Cohen et al. 2010). The study is excellently conducted but has earned some critical remarks regarding the study population (Nemeroff and Goldschmidt-Clermont 2012).

On the pathophysiological level, several explanations have been proposed that can only be mentioned briefly here. One line of argumentation is based on the common inflammatory properties of both diseases. Depression is characterized by a sustained inflammation (Raedler 2011). As mentioned, some authors argue that depression might mimic a motivational pattern normally associated with peripheral infections ("flu"), where chronic immune signaling to the brain causes enduring depressive symptoms (Dantzer et al. 2008).

As mentioned earlier, depressive symptoms are associated with a wide range of immune system parameters, including increased numbers of peripheral leukocytes (particularly neutrophils and monocytes), decreased lymphocytes, and elevated cytokine production (e.g., IL-6) and acute phase proteins (e.g., CRP). Depressive symptoms are also associated with reduced functional tests such as natural killer cell activity and mitogen-induced lymphocyte stimulation. There is overlap in the characteristic immune system correlates of depression and the immune system-related risk factors for coronary artery disease (e.g., elevated CRP levels, pro-inflammatory cytokines such as IL-6 and TNF-alpha, leukocytes, and increased antibody levels to viruses) (Kop and Gottdiener 2005). Several studies have shown increased CRP, not surprisingly also increased IL-1 and IL-6 (Howren et al. 2009). Evidence is conflicting, however. In one study inflammatory changes could be explained mainly by existing risk factors like diabetes, hypertension, obesity, and smoking (Morris et al. 2011). The relationship between depression and immune system parameters is supposed to be bidirectional: central nervous system correlates of depressive symptoms result in immune system changes and vice versa (Kop and Gottdiener 2005). Administration of pro-inflammatory cytokines results in elevated extracellular cerebral serotonin (Capuron 2004) as well as depressed mood, increased sleep, and general malaise (Maier and Watkins 1998).

Another argumentation line is related to the platelet clotting cascade, whose role in coronary heart disease is well known (Nemeroff and Goldschmidt-Clermont 2012). Platelet activation is increased in patients with depression even without cardiac disease or medicaments (Musselman et al. 1996). The platelet function in depressive patients without coronary disease, with risk factors for it or with coronary disease, is either comparable or even declined compared to patients with coronary heart disease without depression (Bruce and Musselman 2005). There are some evidence that antidepressants of SSRI type have an anticoagulant effect including an increased risk for gastrointestinal bleeding, something that has not

been observed with traditional tricyclics (Bruce and Musselman 2005). Also, endothelial dysfunction (Tomfohr et al. 2008), oxidative stress, and impaired arterial repair (Dome et al. 2009) have been linked with depressive disorders.

As discussed in Chap. 6, some interesting models track the different interacting variables in depression and cardiac disease (Thombs et al. 2008; Stapelberg et al. 2011).

Depression and Changes in HRV

In 17 patients with major depressive disorder, 5-min short-term HRV measurements were conducted before and after treatment with antidepressants using SDNN and RMSSD. Depression was assessed with the Hamilton Rating Scale (HRS). Changes in HRV did correlate with posttreatment HRS and differences of HRS pre- and posttreatment. These relationships were strongest in patients who responded positively to nontricyclic antidepressant medications. HRV before treatment was not predictive of treatment response nor did HRV reliably reflect the severity of depressive symptoms (Balogh et al. 1993). Thirty-two previously not medicated patients with major depression and 32 matched control persons were tested for heart rate variability (SDNN) while resting and during paced breathing. There were no differences between the groups before therapy. The patients were randomly allocated for daily treatment with 150 mg amitriptyline, 150 mg doxepin, 150 mg fluvoxamine, or 20 mg of paroxetine. During treatment with either amitriptyline or doxepin, SDNN had significantly decreased after 14 days, whereas patients treated with fluvoxamine or paroxetine showed no significant changes (Rechlin 1994; Rechlin 1994). In this context it is relevant to point out that SSRI can increase HRV variability (Khaikin et al. 1998), whereas amitriptyline decreases variability (Rechlin 1994; Rechlin 1994).

Medically healthy patients have elevated levels of noradrenaline as result of an increased total body sympathetic activity (Veith et al. 1994). Carney compared 19 depressed and 19 nondepressed CAD patients (with positive angiography) with Holter monitoring. He found a significantly lower SDNN in depressed patients (90 ± 35 vs. 117 ± 26 ms) (Carney et al. 1995).

Patients with depression were tested before and after treatment with imipramine or mirtazapine in a small double-blind randomized study (ten patients in each group). HRV was studied before and after 4 weeks. They calculated LF, MF, and HF. Before treatment, all 20 patients were compared to age-matched controls. Depressed patients showed more suppression of HR variability (both mid- and high-frequency band fluctuations) indicating stronger vagal inhibition and a reduced increase of BP variability (mid-frequency band fluctuations). All patients had a decrease of HRV after 4 weeks of treatment (Tulen et al. 1996).

Regarding the bidirectional relation between immune changes and depression (Kop and Gottdiener 2005), it is interesting to observe that administration of proinflammatory cytokines result in elevated extracellular cerebral serotonin

(Capuron 2004) as well as depressed mood, increased sleep, and general malaise (Maier and Watkins 1998).

Twenty-seven patients after MI and with depressions were randomized to either sertraline 50 mg/day or placebo. Eleven post-MI patients without depression were used as a control group. HRV was taken 1–2 weeks after MI and at 6, 10, 14, 18, and 22 weeks after being randomized. The rate of recovery of HRV was determined by use of a growth curve model based on repeated measures analysis of variance. SDNN increased linearly in the sertraline-treated group in comparison to the control group, in difference to a modest decline in SDNN in the placebo group from 2 to 22 weeks (McFarlane et al. 2001).

Subjects with depressed mood showed greater reductions in HF during a cognitive stress test (speech) and lower reductions in a cold pressure test (an ice bag 3 min on the forehead). This suggests that the parasympathetic tone is diminished in subjects in depressed mood (Hughes and Stoney 2000). Subjects with depression showed lower normalized ULF, VLF, and LF, but not HF after other adjusted risk factors (Carney 2001). Patients with depression treated with fluoxetine or doxepin had an increased SDANN in case of response but a decreased SDANN and SDNN in case of nonresponse in a small study ($n = 13$) (Khaikyn 1998). An interventional therapy with cognitive behavioral therapy reduced heart rate and increased rMSSD, but produced no changes in other time-domain measures (Carney et al. 2000). In a study comparing 21 depressed persons with healthy subjects using Holter ECG and both spectral and time-domain measures, there was no difference between the groups (Sayar et al. 2002).

Depression is a risk factor for medical morbidity and mortality in patients with coronary heart disease. Congestive heart disease patients show low VLF depending on their depressive state – VLF was low in 47 % of those who were moderately to severely depressed, in 29 % of those who were mildly depressed, and in 13 % of those without depression (Stein et al. 2000). Bär conducted a small study including 18 patients with depression (without prior treatment with antidepressants) and 18 matched controls. Before treatment, there were no differences in HRV. Differences developed after the start of treatment with antidepressants (Bär et al. 2004). In 873 patients with stable cardiovascular disease, depression was assessed and found in 195 of them. Holter monitoring using usual time and frequency-domain algorithms did not show any difference between CVD patients with or without depression (Gehi et al. 2005).

Cross-sectional analysis of a major depression cohort study included 524 controls, 774 patients with a diagnosis of major depression earlier in life (remitted depression), and 1,075 patients with current depression. HRV was recorded over 1.5 h, SDNN and RSA was used. Both depression groups had a lower SDNN and RSA. Anxiety and lifestyle factors in the analysis did not change this effect. Depressed patients who used SRIs, TCAs, or other antidepressants had a significantly lower SDNN and RSA. So most of the HRV reduction was due to medicaments and not due to the illness (Licht et al. 2008).

Holter monitoring in 63 adult depressive but otherwise healthy patients was used to observe HRV changes. In addition, portable devices recorded physical activity,

social interaction, and negative mood. Depression was associated with higher heart rate and negative mood during the day. Persons with higher depression scores tended to have lower HRV. Participants had lower HRV indices while alone and higher HRV indices while in social interaction. The authors discuss whether or not social interaction can buffer adverse health effects of depression (Schwerdtfeger and Friedrich-Mai 2009).

In an intervention study with randomized administration of sertraline or placebo, patients with major depression had initially decreased HRV (Holter monitoring, using frequency-domain values). It had been hypothesized that after 16 weeks of sertraline treatment, HRV would partially recover, which did not occur (Glassman et al. 2007).

The already mentioned seminal "Heart and Soul" study investigated 863 outpatients with stable CHD on depressive syndromes and HRV changes (Holter monitoring, time and frequency domain). It found an association between somatic depressive symptoms and lower HRV, but not with cognitive depressive symptoms. The inverse association of somatic symptoms with HRV was largely explained by differences in comorbidities and lifestyle factors (de Jonge et al. 2007).

Another multicenter study examined depression patients using 15–30 s strips or manual 30 s pulse measurement to calculate SDNN and following patients for over 10 years. The resting heart rate was significantly higher in patients with more severe depressive symptoms. There was no significant association of low HRV and QTc-prolongation with depressive symptoms or mortality. An increase in resting heart rate/SD, adjusted for age, was associated with a 26 % increased risk of cardiovascular mortality (Kamphuis 2007).

In 26 elder patients, short-term HRV (5 min) was conducted: time domain, frequency domain, DFA, sample entropy. The study used Charlson comorbidity index (CCI) and the Yesavage Geriatric Depression Scale (GDS). DFA was correlated with CCI, but not sample entropy. Interestingly, GDS was correlated with higher entropy, thus contradicting the notion that normally lower entropy is related to more severe illness (Blasco-Lafarga et al. 2010). Summarizing these studies, Servant concluded recently that at the moment there is no evidence of a link between decreased HRV and depression independent of CVD (Servant et al. 2009).

In the Cardiovascular Health Study, Kop evaluated 907 persons of an average age of 71 and without clinical symptoms of CVD. The study used a wide range of measures including time domain, frequency domain, DFA, and heart rate turbulence (Holter monitoring) and analyzed these indices together with inflammation parameters like C reactive protein, IL-6, fibrinogen, and white blood cell count. Participants were followed for up to 15 years. One-hundred and thirty-one patients had depressive symptoms at the time of assessment. As expected, depression was associated with increased CVD mortality. Depression was associated with changes in daytime HRV (there with reduced DFA, but no other HRV indices). None of the 24-h parameters were associated with depression. The authors consider the associations as relatively weak. Importantly, ANS reductions correlated with depression and CVD mortality were largely explained with CVD alone (Kop et al. 2010).

In 2010 Kemp published a review and meta-analysis about the impact of both depression and antidepressant treatment on HRV that included 18 published studies.

The review concluded that depressed patients had reduced time domain and HF, increased LF/HF ratio, and decreased nonlinear indices (relative high frequency of largest Lyapunov (sic) exponent, minimum embedding dimension of the QT interval) in drug free individuals in severe depression. Surprisingly, the authors found no differences in pre- and posttreatment measurements with TCA (amitriptyline, doxepin, and imipramine), SSRIs (paroxetine, escitalopram, venlafaxine), mirtazapine, nefazodone, and rTMS. First after secondary analysis, it was shown that, unlike other antidepressive drugs, TCA reduced HRV (Kemp et al. 2010).

Conclusion

I agree with Kemp et al. (2010) that there is clear evidence of an inverse association between depression and HRV parameters and that the effect size is rather small. Several confounders can make interpretation difficult, such as medications and anxiety (Stapelberg et al. 2012).

Use of HRV as diagnostic parameter for depression alone might not be appropriate at the moment as long as new studies with more predictive parameters fail to appear. However, reflecting the high comorbidity of CVD and depression, HRV can play nevertheless an important role in a comprehensive evaluation of depressive patients regarding their cardiovascular risk. Prospective intervention studies are lacking. We need studies that address potential preventive treatments in depressive patients with reduced HRV parameters and the effects thereof. Use of HRV in further research can be useful provided that it is part of a research hypothesis and not only one of several parameters. It is important not to confuse HRV as outcome parameter. Increase in HRV does not necessarily signify a better outcome even if associations are reported. I agree with Stapelberg et al. (2012) that HRV is a good starting point to investigate the causal network linking depression and CVD, but the causal relationships have to be discussed cautiously.

Psychosis

Besides suicide and accidents, schizophrenic patients have an up to three times all-cause mortality and SCD has been discussed as important cause (Koponen et al. 2008). HRV has only been used in some few studies. In 23 patients with schizophrenia or schizoaffective disorder, 24-h Holter monitoring demonstrated a bimodal distribution: 11 of 23 patients had a PNN50 of > and = 8.0, and 12 had a PNN50 of < and = 4.0; no subject had a PNN50 value between 4.0 and 8.0. All 12 patients with low cardiovagal tone (vs. only 6/11 of the other patients) had schizophrenia. PNN50 was not associated with present age, gender, smoking, IQ scores, or symptomatology (Malaspina et al. 1997). Same patients in psychotic states show decreased HF without changes in LF, suggesting psychotic states suppressed the parasympathetic

function without affecting the sympathetic function (Toichi et al. 1999). In 53 patients with chronic schizophrenia, no difference was noted between them and a control group regarding HRV. HRV was measured in 17 first-episode patients with psychosis previously not treated with neuroleptics and 21 healthy controls during two tests. RMSSD and HF were significantly reduced in patients and remained unaltered during the tasks; whereas, in controls the HRV diminished with increasing mental stress. The authors conclude that acute psychosis might be characterized by a limited capacity to respond to external demands at the level of the autonomic nervous system (Valkonen-Korhonen et al. 2003). Patients with schizophrenia had decreased frequency-domain patterns compared to controls, especially in LF. This was exacerbated in patients receiving atypical antipsychotics (Mujica-Parodi et al. 2005). Fifteen patients with schizophrenia had lower complexity measures (approximate entropy, compression entropy, fractal dimension) and increased QT-variability compared to matched healthy controls (Bär et al. 2008). Jindal was unable to replicate these results in a group of neuroleptic naive patients with psychosis, except for some minor changes (Jindal et al. 2009).

Phobias

The Normative Aging Study enrolled 581 men between 47 and 86 years old and free of coronary artery disease and diabetes. Symptoms of anxiety were assessed using the Crown-Crisp index, an instrument that in previous prospective studies was a strong predictor of the risk of sudden cardiac death. HRV was assessed with the paced-breathing technique, SDNN. The maximal minus minimal HR over 1 min was calculated. Men with higher levels of phobic anxiety had lower SDNN (Kawachi et al. 1995). Fifty-four flight phobics were assessed with HF and sample entropy (paced breathing and under a fearful sequence of audiovisual stimuli at the end of treatment and at 6 months follow-up) and the results related to treatment outcome. A regression model could only be established when HR entropy was added to the HR variability measure in a second step of the analysis. HR variability alone was not found to be a good outcome predictor (Bornas et al. 2007).

Stress-Related Disorders

Introduction

After Selye introduced the notion of stress, definitions have been debated for many decades. Some distinguish between positive and negative stress; whereas, others focus exclusively on “negative” forms like threats or anticipated perturbations of safety (Thayer et al. 2012). Stress is also discussed as a psychological and somatic

reaction when the adaptive capacity of the individual is exhausted. There is increased interest in this adaptive capacity, also described as resilience, and there is no doubt that it relies on the social, psychological, but also genetic and epigenetic background.

For the mental processing of stress, the amygdale is understood to be a central structure. This brain structure has been characterized as a first responder to potential threats and as an important part of adaptive fear responses (LeDoux 1996). Some argue for a function both for aversive and appetitive stimuli (e.g., Whalen and Phelps 2009), while others conclude on a predominant role in negative stimuli (e.g., Cunninham 2008). The role of prefrontal areas are usually underestimated due to many animal models based on rodents, only more recently newer imaging technology has shifted the focus to humans.

Psychological stress is more and more identified as an important risk factor, not the least for cardiovascular disease (Steptoe and Kivimäki 2012). Associated to the idea of variability as a sign of the stability of the whole system, higher indices of HRV should indicate robustness against stressors. In fact, this has been shown (Weber et al. 2010) in studies discussed below.

Physiology and Pathophysiology of Stress

Classical stress reactions include hormonal changes, activation of SNS, and decreased activity of PNS. The hormonal pathway is the well-known hypothalamic–pituitary–adrenocortical axis. Stress activates hypothalamic neurons secreting corticotropin-releasing hormone (CRH) and vasopressin. CRH promotes release of the adrenocorticotropic hormone (ACTH), which acts on the adrenal cortex, causing release of glucocorticoids. The released corticoids themselves trigger a negative feedback circle stopping further release of CRH and ACTH (Fig. 14.1).

The SNS activation is associated with increased levels of adrenaline and noradrenaline with the already discussed consequences. In addition, it has effects on the immune system, probably mediated in lymphatic nodes (which are innervated by SNS fibers). Stress has remarkable effects on the immune system. Short stress

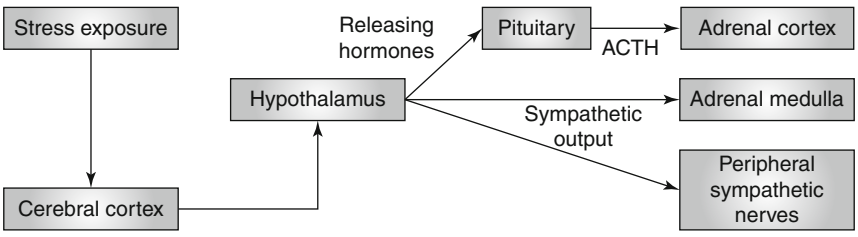

Fig. 14.1 Physiological stress response (Reproduced with friendly permission of Nature publishing group of (Steptoe and Kivimäki 2012))

situations usually trigger augmented immune activity, whereas chronic stress situations lead to immune depression.

A classical cardiologic disease associated with stress is coronary heart disease. The INTERHEART study included patients and controls from 52 countries and used a chronic stress classification that included stress at work, at home, financial problems, lack of control, and depression. The study took into account stress variables in a statistical model and added classical causal factors like apolipoprotein ratio, obesity, smoking, diabetes, hypertension, and others. Independent of other risk factors, the odds ratio for MI was doubled in case of stress. This was independent of gender, nationality, and age (Yusuf et al. 2004). Not surprising, a temporal dose–response pattern between (work related) stress and metabolic factors has been observed (Chandola et al. 2008), as have been clear associations between long working time and CHD (Virtanen et al. 2012).

The pathological factors leading to CHD under chronic stress conditions are still under discussion. Greater morning increase of cortisol and reduced heart rate variability (see below) as a sign for attenuation of ANS and neuroendocrine function have been reported (Chandola et al. 2008). Additionally, an increase of hypertension in relation of stress has been shown (Markovitz 2004), though not always in association with an increased incidence of CHD (Chandola et al. 2008). The association between depression and CHD is well known (Nemeroff and Goldschmidt-Clermont 2012). And there is evidence of an association between chronic stress and depression (Netterstrøm et al. 2008). Other observed factors include the already mentioned suppressed immune function (Cohen et al. 1997), reduced telomere length (Brouilette et al. 2007), and metabolic syndrome (Chandola et al. 2006). Stress triggers health risky behavior like smoking (Kouvonen et al. 2005; Rod et al. 2009), decreased physical activity (Rod et al. 2009), shortened sleep, or sleep disturbances (Virtanen et al. 2009).

Acute stress can indeed cause MI events, as was first shown systematically after a major earthquake in Athens (Trichopoulos 1983), terrorist attacks in the US (Feng et al. 2006), and missile attacks on the population in Israel (Kark et al. 1995). Even after dramatic soccer games, increases of cardiovascular events have been reported (in the Dutch study quoted, only in men) (Witte et al. 2000; Wilbert-Lampen et al. 2011). The biological bases to acute stress-related MI are not completely clear, but procoagulant factors, disturbed rhythm, and transient ischemia have been discussed (Steptoe and Kivimäki 2012).

HRV Changes in Stress-Related Disorders

Different mental states and their consequences on HRV in laboratory were assessed in healthy normotensive men and women. Spontaneous breathing subjects and subjects under paced breathing showed no changes. Mental distraction (word puzzle) and mental stress (computer quiz) led to decreased HRV (Madden and Savard 1995). HRV was tested to measure stress responses during sleep following a standardized task and showed changes in frequency-domain values (Hall et al. 2004)

Of particular interests are studies investigating the recovery after stress stimuli and their relationship to pretest HRV. Weber and colleagues tested 44 healthy men between 20 and 50 years old. As stress tests they used the manometer test (a test to recognize features on a screen under time pressure) and mental arithmetic tests. They analyzed both frequency domain and time domain (RMSSD), reporting a correlation between RMSSD and HF (of r 0.9). They divided the group by variability of HRV with help of RMSSD (split point 35.5 ms) resulting in one "low group" (with 25.8 ± 6.5 ms) and one "high group" (with 51.7 ± 13.9 ms). These groups did not differ in certain aspects with exception of age (age was consequently used as covariate in further analysis). Most importantly, they observed significant differences between the groups. Subjects with low baseline HRV had a more pronounced increase of diastolic blood pressure under the tests and did not recover in the following 5 min resting phase. The high-HRV group showed decrease of HRV under stress, returning immediately after tests to the pretest level. By contrast, the low-HRV group retained a lower HRV also under resting conditions. Additionally, cortisol decreased more slowly in this group and the recovery of the THF-alpha level was delayed. The authors concluded that the high group showed physiologically better coping of stress (Weber et al. 2010). This can be of importance. Delayed recovery of BP after stress can predict increases in BP several years later (Steptoe and Marmot 2006).

One study focused on the effects of *work stress* on blood pressure, heart rate, and heart rate variability. One-hundred and nine male white collar workers were included and their work stress level was assessed with a paradigm that included job overcommitment (inability to withdraw from job obligations) and imbalance between effort and reward (Siegrist model for work stress). The study used 24 h-ECG and RMSSD as measure for the vagal tone. Men with a high imbalance had higher blood pressure. Overcommitment showed no association with blood pressure. There was a trend, but no significant effect, for the RMSSD to be lower for subjects with imbalance, but not overcommitment. Large standard deviations for RMSSD were observed (Vrijkotte et al. 2000).

Caregivers (of patients with Alzheimer disease) compared to noncaregivers with a similar age and gender showed increased pre-ejection period values, whereas RSA values were not different. The authors regard this as evidence of increased sympathetic activity (Cacioppo et al. 2000).

5-minute heart rate variability in frequency domain was measured in healthy subjects and correlated with self ratings of *trait anxiety and perceived emotional stress*. There was an inverse relationship between emotional stress and HFnu, which was independent of age, gender, trait anxiety, and cardiorespiratory fitness (Dishman et al. 2000).

Mental stress reaction in subjects with several apolipoprotein E phenotypes caused different changes in HRV. Subjects with apoE4/2, 4/3, and 4/4 showed a stress-related decrease in HRV, while E3/2 and E3/3 showed a slight increase (Ravaja et al. 1997)

Short mental stress leads to physiological reactions in individuals. The amount of the stress reaction, however, is different and a study identified different groups characterized either by high sympathetic markers for heart rate, high immunological activation and higher levels of steroids and norepinephrine, or lower reactions in all areas (Cacioppo et al. 1995).

In *generalized anxiety disorders,* diminished heart rate variability, especially in the HF band, has been reported (Thayer et al. 1996; Friedman and Thayer 1998; Cohen et al. 2000a, b, c).

Nine patients with *post-traumatic stress disorder* with fluoxetine treatment, nine PTSD patients without fluoxetine, and nine healthy controls were tested with 15-min HRV measures. In PTSD patients with fluoxetine, HRV measures were normal compared to the untreated PTSD patients (Cohen et al. 2000a, b, c). Six female rape victims with PTSD were treated with CBT. This resulted in decreased HRV during REM sleep in 5 responders, whereas the nonresponder showed an increase (Nishith et al. 2003).

In 59 adults with post-traumatic stress disorder, HRV was taken in a laboratory setting where the subjects were confronted with neutral or trauma-related stimuli. A significant proportion of the group had no elevated basal heart rate. The subgroup with elevated basal HR had significant correlations with RSA. In their conclusion the authors outline a possible association between basal elevated heart rate and parasympathetic alteration independently of sympathetic influences in a subgroup of subjects with PTSD (Hopper et al. 2006).

In pregnant and non-pregnant women, use of a standardized stress model (Trier Social Stress Test) led to decreased HF, increased LF/HF, and in tendency of increased LF. No differences between pregnant and non-pregnant women were recorded, neither differences between pregnancy in second and third trimester (Klinkenberg et al. 2009).

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Chapter 15
Diabetes

Introduction

Diabetes mellitus (DM) comprises a group of common metabolic disorders sharing the phenotype of hyperglycemia. Several subtypes are described and today much is known about the causes. In complex interaction, genetics, environmental, social, and lifestyle factors contribute to a phenomenon that more and more often is being called a diabetic epidemic. Depending on the etiology of DM, factors involved may include reduced insulin secretion, decreased glucose usage of the body, and increased glucose production. DM causes a plethora of pathophysiological changes in multiple organ systems that impose a tremendous burden on individuals and health systems. In the US, DM is the leading cause of end-stage renal disease, lower extremity amputations, and adult blindness.

Up to 50 % of patients with diabetes develop diabetic neuropathy. NIDDM patients have an increased likelihood to develop mononeuropathy and other forms (Boulton et al. 2004). Diabetic autonomic neuropathy causes substantial morbidity and increased mortality, particularly if cardiovascular autonomic neuropathy (CAN) is present (Boulton et al. 2005). The effects of DM on cardiac health are so profound that some cardiologists have termed DM as a cardiac disease with at the same time elevated blood glucose levels.

Diabetic autonomic neuropathy (DAN) is a common consequence of diabetes. It is related to an increased risk of cardiovascular mortality and associated with multiple symptoms and impairments. Various prevalences have been reported, in part because of the methods of assessment. In cohorts of asymptomatic individuals with diabetes, approximately 20 % had abnormal cardiovascular autonomic function already in early illness. DAN frequently coexists with other peripheral neuropathies and other diabetic complications, but DAN is frequently isolated, preceding the detection of other complications.

Major clinical manifestations of DAN include resting tachycardia, exercise intolerance, orthostatic hypotension, changed sudomotor dysfunction, constipation, gastroparesis, impaired neurovascular function, hypoglycemic autonomic failure,

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and erectile dysfunction. GI disturbances are common, and any section of the GI tract may be affected. Gastroparesis should always be suspected in individuals with erratic glucose control. A radiographic gastric emptying study can definitively establish the diagnosis of gastroparesis; a reasonable approach can also be use to conduct ultrasound exams (Kashyap and Farrugia 2010). Constipation is the most common lower GI symptom but can alternate with episodes of diarrhea and DAN can mimic irritable bowel syndrome. Diagnostic approaches should assess autonomic function and rule out neoplasia. Disruption of microvascular skin blood flow and sudomotor function may be among the earliest manifestations of DAN and lead to dry skin, loss of sweating, and the development of fissures and cracks that allow microorganisms to enter. These changes ultimately contribute to the development of ulcers, gangrene, and limb loss. Cardiovascular autonomic neuropathy (CAN) is the most studied and clinically important form of DAN usually characterized by heart rate variability. DAN is associated with an increased risk of silent myocardial ischemia and mortality. Proceedings from a consensus conference in 1992 recommended that three tests (RR variation, Valsalva maneuver, and postural blood pressure testing) or longitudinal testing of the cardiovascular autonomic system be conducted in diabetic patients (Vinik et al. 2003).

Early detection of DAN in a diabetic patient is of paramount importance since it can cause prompt therapeutic interventions with a significant survival benefit (Karayannis et al. 2012). Measurement of HRV at the time of diagnosis of type 2 diabetes and within 5 years after diagnosis of type 1 diabetes (unless an individual has symptoms suggestive of autonomic dysfunction earlier) serves to establish a baseline, with which 1-year interval tests can be compared. Regular HRV testing provides early detection and makes early diagnostic and therapeutic interventions possible. Interventions include improving metabolic control and using therapies such as ACE inhibitors and beta-blockers are proven to be effective for patients with CAN (Vinik et al. 2003).

In diabetic autonomic neuropathy several test batteries are used. Minimal examination procedures should include (1) heart rate response during deep breathing (six times per minute), (2) Valsalva maneuver, and (3) postural blood pressure testing. (1) Heart rate response during deep breathing can be used without or with HRV algorithms.[1] It is possible to use either 24 h Holter ECG or 7 min HRV measures if frequency-domain measures are used (Vinik et al. 2003). The first point (paced breathing) has been challenged. Most probably, usual HRV procedures with spontaneous breathing are sufficient (Denver et al. 2007; Wittling and Wittling 2012). Normative values have been proposed (Ziegler et al. 1992; Risk et al. 2001) and HRV is mentioned as one of three standard techniques besides autonomic innervation imaging techniques, microneurography, and baroreflex analysis for detecting DAN (Karayannis et al. 2012).

[1] Note that paced respiration has rather historical reasons related to early studies and to make newer data comparable with them. For a more extended discussion see Chap. 4.

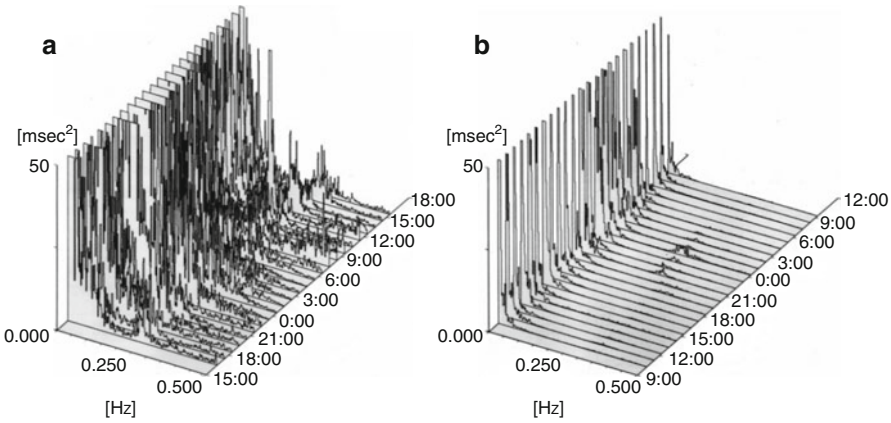

Fig. 15.1 Two typical examples for power spectra during 24 h. (**a**) A 56-year-old man without diabetes. (**b**) A 64-year-old female with diabetes (Nishimura et al. (2004), with permission of Oxford University Press)

HRV and Diabetes

Because of the early recognition of the association of HRV and autonomous dysfunction, diabetes is one of the most established areas in which clinical studies include HRV measurements. The Diabetes Control and Complications Trial Research Group (1988, 1993) conducted a major study looking at the effect of better diabetes treatment on different measures of outcome using HRV among others. They followed changes in autonomic tone by a paced-breathing approach. HRV as a measure of CAN remained significantly higher in the former intensive treated group compared with the former conventional group (Pop-Busui et al. 2009). Marked abnormalities in heart rate variability were significantly associated with and predictive of progressive renal deterioration at 1 year in diabetic patients. Heart rate variability was a significant and independent predictor of abnormalities in creatinine clearance in this small study (Burger et al. 2002).

In a study with 217 nondiabetic and diabetic dialysis patients with and without left ventricle hypertrophy, 24 h HRV was obtained. Mean pNN50 and SDANN, TP, LF, and HF were lower in diabetic than in nondiabetic patients, but LF/HF ratio did not differ. In diabetic patients LVMI correlated negatively with pNN50 ($r=-0.270$) and HF ($r=-0.277$). In nondiabetic patients LVMI did not correlate with any HRV variables (Nishimura et al. 2004) (Fig. 15.1).

In a longitudinal epidemiological study on a population-based cohort of 6,245 individuals, a 2-min HRV measure was taken in the beginning and a 6 min recording after 9 years. Due to the short-term recording, only SDNN and rMSSD were calculated. Diabetic subjects had lower SDNN and rMSSD than healthy participants. Diabetic persons had a greater decrease in SDNN and rMSSD by factors of 1.4 and 1.9 (Schroeder et al. 2005) (Fig. 15.2).

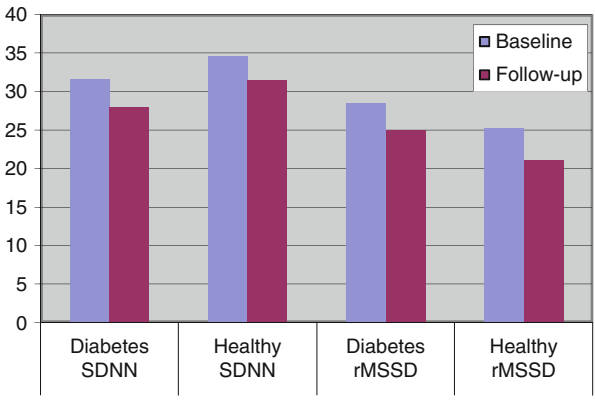

Fig. 15.2 Changes in SDNN and rMSSD in $n = 3{,}567$ healthy persons and $n = 457$ persons with diabetes (Adapted with data from Schroeder et al. (2005))

In a study, 30 patients with painless and painful DN were followed over 2 years and examined with help of HRV, electrophysiological measures, and qualitative sensory testing (QST). Vibration thresholds deteriorated over time and c-fiber function correlated with pain intensity, but there was no correlation between HRV values and painful DN (Krämer et al. 2004). Reduced heart rate variability (HRV) has been also related to diabetic sensorimotor polyneuropathy. Eighty-nine diabetic subjects and 60 healthy volunteers were assessed: SDNN had an inverse relationship with ordinal categories of increasing DSP severity. Despite statistical significance, there was substantial overlap of SDNN between diabetic patients and the healthy volunteers. Higher glycated hemoglobin A(1c) and systolic blood pressure, and measures of large and small fiber neuropathy, were independently associated with lower SDNN. In some control subjects without polyneuropathy, HRV was also low (Orlov et al. 2012).

In a population-based survey, 1,030 males and 957 females were assessed for cardiovascular risk factors like diabetes, hypertension, obesity, dyslipidemia, smoking, and low physical activity. In men, after adjustment for alcohol intake and age, independent determinant for low SDNN were diabetes, obesity, and smoking; in women only diabetes. The authors conclude that diabetes is the primary determinant of reduced HRV in the general population (Ziegler et al. 2006).

In a diabetes prevention program, early treatment options were tested on adults who were at high risk for developing diabetes (i.e., BMI $\geq$24 kg/m^2, fasting glucose 5.3–6.9 mmol/l, and 2-h glucose 7.8–11.0 mmol/l). The 2,980 participants were randomized to three different groups: (1) standard lifestyle recommendations plus placebo twice daily, (2) standard lifestyle recommendations plus 850 mg of metformin twice daily, and (3) an intensive program of lifestyle modification and followed up for 3, 2 years, with annual examinations. HRV measures were based on 10-s digital rhythm strips; SDNN and RMSSD were calculated. The lifestyle group showed lower basal heart rate and higher HRV with metformin and placebo arms. Increasing SDNN and rMSSD during the study were associated with lower diabetes risk in the lifestyle arm (Carnethon 2006).

A study showed a relationship between subjects with different degrees of insulin resistance and HRV alterations. In detail, SDNN showed significant reduction in all tested groups compared with a healthy control group. At night LF nu was higher in all patient groups. Patients with several other potentially confounding factors had been excluded. Interestingly, the insulin-resistant subjects with not yet impaired glucose regulation showed reduced SDNN values already. The subjects with type 2 diabetes mellitus had greater autonomic dysfunction than the insulin-resistant subjects in the other groups (Perciaccante et al. 2006). In a mixed group ($n = 34$) with peripheral neuropathy due to diabetes, alcoholism, paraneoplasia, and lack of B12, HRV in rest (RMSSD), associated with Valsalva maneuver and posture, was reduced compared to 190 non-matched healthy controls (Haegele-Link et al. 2008).

Heart rate variability correlates with lung diffusion capacity for carbon monoxide (DLCO), a general measure for lung diffusion capacity in diabetes patients without clinical pulmonary abnormalities. The autonomic function was assessed by Holter monitoring. Strongest correlations were found with SDNN and LF. The authors debate a possible influence of a disturbed autonomic function on lung diffusion capacity in early diabetes (Pitocco et al. 2008).

Metabolic syndrome in younger adults is associated with lower LF, Hf, and TP in short-term HRV. In men, waist circumference was the strongest individual metabolic syndrome component associated with HRV ($n = 1{,}889$ subjects between 24 and 39) (Koskinen et al. 2009).

Five-minute HRV was inversely correlated with IL-6 in 30 male patients with metabolic syndrome compared with 153 controls (Brunner et al. 2002). Patients with impaired glucose tolerance had increased TNF alpha, TNF alpha receptor II, and IL-6, but there were no correlations between HRV and inflammatory parameters (Diakakis et al. 2005). Looking further at these interactions, nondiabetic controls, newly diagnosed, and established diabetic patients were included in a study of inflammatory parameters and short-term HRV. As expected, heart rate variability was reduced in all diabetics. Interleukin-6 was higher in diabetics, as was the high-molecular-weight adiponectin to leptin ratio. Interleukin-6 correlated negatively with HRV. Ratios of adiponectin to leptin correlated positively with measures of autonomic balance (Lieb et al. 2012). This study confirmed and extended results observed in an earlier study where IL-6 correlated with HRV changes in paced-breathing investigations (González-Clemente et al. 2007).

In a study including 57 diabetic and 54 nondiabetic subjects free of coronary heart disease, significant reduction HF nu and TP was demonstrated in diabetic participants. An inverse association between total power and median HbA (1c) was observed (Fakhrzadeh et al. 2012).

In a study of the relationships between HRV and several measures of arterial stiffness in youth with ($n = 344$) and without ($n = 171$) type 1 diabetes, an association between low SDNN and peripheral arterial stiffness was demonstrated. The association remained statistical significant also after adjustment for CAD risk factors (Jaiswal et al. 2013b).

Role of HRV in Evaluation of Diabetic Patients

HRV changes might not only predict cardiac events and mortality, but also progression of carotid atherosclerosis. Studies were carried out 5–6 years after diagnosis (baseline) and repeated 8 years after diagnosis (follow-up). At baseline, patients had decreased LF. Reduced common carotid artery diameter and atherosclerotic intima-media thickness (IMT) both correlated with HRV at baseline. At follow-up, all HRV variables decreased significantly. Furthermore, patients with lower LF power at baseline had a larger increase in the thickness of the carotid bulb intima-media at follow-up (Gottsäter et al. 2006). This is in accordance with the already mentioned study of the Diabetes Control and Complications Trial Research Group (Pop-Busui et al. 2009).

The importance of Holter monitoring has been challenged in a study with a follow-up of 15 years where only LF was an independent risk factor for all-cause mortality, but Valsalva test, heart rate response to standing (30:15 ratio), and handgrip test had a higher predictive value (May and Arildsen 2012). HRV decreases depending on the number of risk factors (Hsiao et al. 2011).

Early Detection of DAN: Desirable or Not Necessary?

Diabetic autonomic neuropathy (DAN) is associated with increased morbidity and mortality and can have an incidence of 23.4 per 1,000 person years in diabetic patients (Witte et al. 2005). As described, several data confirm early HRV changes in different diabetic patients.

Already young diabetic patients around 18 with a mean duration of illness of 9 years have obvious changes in HRV (Jaiswal et al. 2013a). This has been shown in different studies, e.g., in one looking at participants with increased fasting blood sugar showing significantly changed HRV parameters (Thiyagarajan et al. 2012). However, a closer look at the results reveals rather subtle differences. SDNN for instance is 30.94 ± 11.92 in participants with impaired glucose metabolism compared with 37.82 ± 15.61, LF/HF 1.98 ± 1.92 compared with 1.18 ± 1.07. This makes it difficult to identify relevant changes in individual patients.

Vinik writes “Screening for autonomic dysfunction should be performed at the diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes, particularly in patients at greater risk due to a history of poor glycemic control, cardiovascular risk factors, and macro- or microangiopathic diabetic complications” (2012). But are there data showing that early testing of HRV in diabetes patients is beneficial?

Whether early diabetes testing has effects on the development of DAN is still controversial. A recent Danish study was not able to show differences in DAN development in an intensively treated group of patients compared with standard treatment (Charles et al. 2013).

Concluding Remarks

Today there is overwhelming statistical evidence that already early in the course of diabetes different HRV parameters are reduced. During the disease HRV diminishes further, together with changes in other clinical parameters discussed extensively by Vinik (2012). Several diabetologists regard HRV as a standard examination tool and recommend it highly for baseline examinations and follow-up patients. There is limited evidence that interventions can delay further fall of HRV, in some cases even cause an increase, which is considered (but not proven) as a surrogate of better health in this patient group. Considering this, it is surprising that HRV is not more often used in diabetologic outpatient departments.

In contrast to other clinical areas, nonlinear indices are not used very often in the evaluation of diabetic patients (with exceptions such as Khandoker et al. (2009)). This is most probably because HRV seems to be "established" in this area. However, it is desirable to include some of the more often used nonlinear parameters in further studies.

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Chapter 16
Other Studies

Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) is a complex and heterogeneous clinical syndrome found in 6–8 % of the population (Handa et al. 2012), correlated to smoking habits and social structure. Prevalence of COPD in some countries has started to decline in male population, while prevalence in females is still increasing. Today, COPD is also a disease of lower social classes and the Third World, where smoking habits are different to parts of the industrialized world and particularly to the habits of the middle and upper class.

HRV is relevant in COPD patients because of the frequent co-prevalence of cardiac and other diseases. COPD patients frequently develop arrhythmias, common also in disorders of the cardiac autonomic function (Tükek et al. 2003). In addition, microneurography of the peroneal nerve has shown evidence of increased peripheral sympathetic activation in patients with COPD and hypoxemia (Chen et al. 2006a).

Twenty-five moderate to severe COPD patients were compared with 25 healthy controls using Holter monitoring. COPD patients had decreased sNN50, pNN50, SDANN, SDNN, SDNNI, and rMSSD and reduced values of heart rate turbulence (Gunduz et al. 2009). However, another study found HRV values in COPD patients at rest comparable to healthy controls and only becoming first abnormal with challenges like controlled breathing or tilting (Andreas et al. 2005).

In the course of COPD, increasing respiratory muscle weakness is common and due to a variety of causes like cachexia or long-term use of cortisone. Reis included ten older chronic obstructive pulmonary disease patients. The COPD group had lower LF, but no other differences in HRV values. The low number of participants may partially explain this. The study also used a breath cycle-dependent measure of HRV, called the inspiratory–expiratory difference (ΔIE), which is the difference between the mean of the highest HR value obtained during the inspiratory phase and the mean of the lowest HR value obtained during the expiratory phase. IE difference correlated ($r = 0.6$) with maximal inspiratory pressure as a measure of muscle power (Reis et al. 2010).

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In 41 clinically stable COPD patients and 19 healthy controls, no differences were obtained in the time domain and in the low-frequency or high-frequency domain (Holter monitoring). However, LF/HF was lower in the COPD group (1.9 [1.5–3.4] vs. 3.9 [3.2–5.6]) (Bédard et al. 2010).

Carvalho analyzed data from 15 volunteers with COPD and 15 healthy participants, recording HRV for 30 min. COPD patients presented reduced levels of all linear exponents and decreased short-term fractal exponent. Really surprising were the very low values, e.g., of SDNN (14.13 ± 5.03) in COPD patients but also in controls (25.4 ± 9.5). With such low SDNN values, the healthy volunteers would in another context have been characterized as at high risk for, e.g., heart disease. A moderate difference between COPD patients and controls was discovered (0.9 ± 0.18 vs. 1.02 ± 0.09) (Carvalho et al. 2011).

Van Gestel investigated 60 patients with COPD and looked at pulmonary function, quality of life, and results of short-term HRV in an explorative study. RMSSD, HF, and LF/HF showed a moderate correlation with the quality of life score. RMSSD (but also HF) was independently associated with QoL. The HRV values obtained were comparatively low, SDNN, for instance, is 35.84 ± 25.55 (Van Gestel et al. 2011).

Dias de Carvalho studied 17 COPD patients and 17 healthy volunteers, finding differences in triangular index, TINN, SD1, and SD2 (of the Poincaré plot) (Dias de Carvalho et al. 2011).

Corbo studied heart rate variability (HRV) in 30 COPD patients at rest and during the 6-min walk test (6mWT) and the association with lung function impairment, taking into account systemic inflammation. Subjects with elevated CRP values had a significant reduction of SDNN, VLF, and TP. Furthermore, subjects with Inspiratory Capacity-to-Total Lung Capacity ratio (IC/TLC) <36 % had a significant reduced SDNN, VLF, and LF as well (Corbo et al. 2013).

Exercise in COPD Patients

Forty patients with COPD (FEV(1) 39 ± 13 %) were randomized into high- ($n = 20$) or low-intensity ($n = 20$) exercise training of 3 months duration. There was a significant improvement in HRV after the high-intensity protocol (pre vs. post, SDNN 29 ± 15 ms vs. 36 ± 19 ms, rMSSD 22 ± 14 ms vs. 28 ± 22 ms), but not with the low-intensity protocol. A higher SDNN at baseline increased the probability of a better result after training (Camillo et al. 2011).

Conclusion

One study did not show major differences between COPD patients and healthy controls (Bédard et al. 2010); others showed moderate differences. Diminished HRV may occur due to secondary effects, such as heart disease or chronic inflammatory states.

Kidney Disease

Interest in HRV for patients with kidney failure arose in relation to the increased prevalence of sudden cardiac death in end-stage renal disease patients on dialysis. These patients have several known risk factors for SCD and usually much comorbidity (Ranpuria et al. 2008). The annual death rate for prevalent US dialysis patients for 2004 was 230 deaths per 1,000 patient years. The USRDS Cardiovascular Special Studies Center estimated the SCD rate among 2002 prevalent US dialysis patients to be ~7 % per year (US Renal Data System 2006).

End-Stage Renal Disease and Dialysis

Vita investigated 30 chronic uremic patients who were on periodic bicarbonate hemodialysis by a battery of six cardiovascular autonomic tests, in addition to 10-min short-term HRV in supine and tilt position, all that a day after the last dialysis (dialysis-free day). Twenty healthy persons served as control. LF was significantly lower (152 ± 34), compared with the healthy controls (415 ± 82), while HF was nearly identical, also LF/HF. TP was also markedly different between patients and controls (1,808 ± 270 vs. 563 ± 123). LF was not different between patients with or without autonomic neuropathy (Vita et al. 1999). Ranpuria interprets this as an indication that there is early sympathetic involvement that traditional autonomic tests are unable to detect (Ranpuria et al. 2008).

Patients with end-stage renal disease (184 nondiabetic, 60 type 1 and 34 type 2 diabetes) and 64 healthy controls were characterized by 24-h HRV. Five patients had SCD during the study period. SDNN and pNN50 were significantly changed in the patient with fatal outcome. Exercise led to higher HRV (Hathaway et al. 1998; Cashion et al. 2000). Holter ECG of 14 nondiabetic patients with end-stage renal disease without echocardiographic or clinical evidence of heart disease was performed at interdialystic days and was compared to patients after renal transplantation. RR variability and power frequency determinations were all significantly reduced in the uremic patients undergoing hemodialysis. Four patients were studied before and after transplantation, in two HRV increased "dramatically," in one moderately, and in one not at all. The combination of renal failure and amyloidosis led to more decreased HRV than renal failure alone (Rubinger et al. 1999).

Giordano investigated HRV differences between 10 healthy subjects, 10 type 2 diabetic patients, and 20 end-stage renal disease (ESRD) patients (11 nondiabetic and nine type II diabetic) undergoing hemodialysis. HRV was taken once in nondialysis patients and twice (before and after) in dialysis patients. Diabetic dialysis patients had the lowest SDNN, HFnu, and TP and the highest LFnu and particularly LF/HF (7.4 ± 1.4 compared with 5.6 ± 0.3 in nondiabetic dialysis patients, 2.2 ± 0.6 in diabetes-only patients, and 0.8 ± 0.1 in the healthy controls) (Giordano et al. 2001). These results are different to the findings by Rubinger et al. (1999) and Tong and

Hou (2007), in which a decrease in LF/HF and sympathetic activity during dialysis was observed.

Tong included 35 patients, taking HRV before and after hemodialysis. SDNN and LF/HF ratio were significantly reduced after HD, while the blood pressure levels were relatively stable during the HD process. Ultrafiltration rate and urea clearance appeared to be the main determinants of the LF/HF ratio in HD. LF/HF ratio correlated positively with urea clearance and negatively with ultrafiltration volume (Tong and Hou 2007).

There have only been a few longitudinal studies. A small study on 16 patients on hemodialysis or peritoneal dialysis (PD) followed them over approximately 3 years. HRV was obtained using time-domain analysis. The adequacy of dialysis was assessed by uremic clearance in the HD group; however, PD adequacy was measured subjectively by patients' well-being and nutritional status. HRV parameters (SDNN/RMSM and rMSSD) were obtained from 5-min supine ECGs. Improvement in HRV time-domain parameters occurred only in patients who had a mean uremic clearance >1.2. A uremic clearance <0.87 was associated with progressive deterioration of autonomic neuropathy. The four diabetic patients had a severely abnormal HRV at the beginning of the study, which did not improve in the course of the study (Laaksonen et al. 2000).

Dursun conducted a study with a shorter follow-up of 1 year. Twenty patients with end-stage renal disease undergoing different forms of dialysis and 15 healthy controls were evaluated with 24-h EKG-Holter monitoring. Patients with kidney disease prior to the initiation of dialysis were noted to have a significant decrease in all parameters of time-domain HRV. After 12 months of dialysis, a significant improvement was observed in time-domain analysis in patients undergoing continuous ambulatory peritoneal dialysis (CAPD) (Dursun et al. 2004).

Regarding mortality, some small studies were conducted. Hayano observed 30 HD patients after coronary angiography using Holter monitoring between dialysis sessions to assess prognostic value of HRV and followed them over 50 months. Fourteen patients died in this period, of them 11 with SDC. With a statistical model, the study found that a triangular index (TI) < 20 (4.1 risk) and TINN < 328 ms were independently associated with increased risk for all-cause death and SCD. In addition, an SDNN < 88 was associated with a risk of 3.7 (not significant) and an SDNN < 50 with a risk of 3.8 for SCD (Hayano et al. 1999).

The same group conducted afterwards a larger study with a broader patient group. One-hundred and twenty patients receiving dialysis were analyzed with the help of both time- and frequency-domain HRV analysis over a period of 26 ± 10 months. During that time period, 21 died, 10 due to cardiac problems (only two SCD) and 11 due to noncardiac reasons. Survivors and cardiac and noncardiac deaths compared with the healthy population demonstrated a decrease in all time- and frequency-domain HRV parameters. Among time- and frequency-domain HRV, a decrease in TI (17.9 ± 6.2 vs. 25.4 ± 8.9), LF/HF (0.77 ± 0.44 vs. 1.82 ± 1.34), VLF, and ULF (rather marginal, but statistical significant differences) was predictive of cardiac death, though none was able to predict noncardiac death. SDNN differences (77.5 ± 35.0 vs. 96.8 ± 32.3) were not significant and SDNN of cardiac non-survivors

was rather high compared with other studies. But one would have to consider the relatively low number of non-survivors (Fukuta et al. 2003).

In conclusion, I agree with Ranpuria that at this point there are insufficient data showing that normalization of HRV would improve clinical outcomes and patient survival in the ESRD population (Ranpuria et al. 2008).

Transplantation

In 37 *kidney* and 20 *kidney*–pancreas transplant recipients, pre- and posttransplant HRV and quality of life measures were compared, using both time- and frequency-domain indices of Holter ECGs. Frequency-domain changes correlated best with physical functioning. Changes in HRV and QoL were related (Hathaway et al. 2000).

Fifty-one patients on hemodialysis were compared with 53 patients with moderate to severe chronic kidney disease with Holter monitoring. HRV did not differ between the groups. Patients without hemodialysis showed a correlation between HRV and IL-6 (Psychari et al. 2005).

General Conclusion

I agree at this point that there are insufficient data showing that normalization of HRV would improve clinical outcomes and patient survival in the ESRD population (Ranpuria et al. 2008; Zhang and Wang 2013). Both medical and nonmedical strategies could be used to improve HRV, but do they improve survival? We would like to see randomized intervention studies and their effect on patient groups that might challenge the phenomena called "therapeutic nihilism" or "renalism" (Chertow et al. 2004) in end-stage kidney disease patients.

Sleep Apnea

Patients with moderate to severe obstructive sleep apnea show increased normalized LF and decreased normalized HF and an increased LF/HF. By contrast, blood pressure variability was increased. These changes seem to occur independent of concurring diseases (Narkiewicz et al. 1998).

LF and HF were not different between 11 snoring patients and 12 controls. HF was increased and LF decreased when they were treated with CPAP or when snoring was abolished, whereas the values did not differ in the control group (Gates et al. 2005).

Sleep apnea was associated with lower HF in a study with 387 included females. There were no other significant differences. Women with a high sleep apnea index

had changes in HRV, but these were similar to those in women with no or nearly no sleep apnea (Kesek et al. 2009).

Complementary Medicine

Acupuncture

Although the usual claim is that acupuncture has been practiced for over 3,000 years in China (e.g., Longhurst 1998), it is in reality based on a heterogeneous theoretical concept that changed over time and is partially contradictory (Unschuld 1980). In practice, treatment consists of inserting needles at exactly defined spots (the so-called acupuncture points) in the body, usually between 10 and 20 needles arranged symmetrically. According to acupuncture theory, the needles influence different functional systems named after organs (which are only partially related to Western ideas of organ systems), but some practitioners also use combinations of acupuncture points out of experience. There are numerous explanations in Western medicine as to why acupuncture works, including activation of endogenous opioids, of the immunological system, or also on neuronal level long-term potentiation or long-term depression mechanisms (Sandkühler 1996). The clinical effect of acupuncture is still challenged in meta-analyses (Ernst 2009). In addition, acupuncture is not without adverse effects (Ernst et al. 2003).

Acupuncture needles stimulate thinly myelinated Aδ and not myelinated C-fibers (Li et al. 1998). Histologic studies using c-Fos as a nuclear activation factor in neuronal regions stimulated in the periphery showed activation of the arcuate nucleus, periaqueductal gray, caudal raphe, nucleus ambiguus, and rostral ventral lateral medulla (among others) (e.g., Li 1998; Guo et al. 2012). Out of such physiological observations, influences on the vegetative nervous system and HRV are possible.

In a study, 15 healthy persons were randomly assigned sham or verum acupuncture in a crossover design. The main goal of the study was to test resting state connectivity, but also HRV changes were tested. After acupuncture there was increased resting state connectivity in a network called “default mode network.” This involves brain regions putatively engaged in self-referential cognition that are deactivated during external tasks. After acupuncture, the DMN network showed increased connectivity with the periaqueductal gray (PAG), substantia nigra, middle temporal gyrus, supplementary motor area (SMA), and anterior cingulate. LFu (normalized LF) correlated with increasing hippocampal formation connectivity to DMN. In addition, increased DMN connectivity was anticorrelated to LFnu and correlated to HFnu (Dhond et al. 2008). In an experimental design, 60 females were randomized to no treatment or three treatments with kidney 6 and lung 7. Short-term HRV was used, and no differences in any HRV parameter were observed after acupuncture (Vickland et al. 2009).

A double-blind randomized study looked at the effect of acupuncture on insomnia after stroke, randomly assigning to either a real intradermal acupuncture group or a sham acupuncture group. The acupuncture group was treated with needles in heart 7 and pericard 6 for 3 days, and the sham acupuncture group received sham treatment on the same points. Sleep was better in the acupuncture group, who also had a greater decrease of the LF/HF ratio. These results were interpreted as a stabilization of sympathetic hyperactivities (Lee et al. 2009).

Meditation: Zen mediation practitioners and control subjects were compared during meditation and rest. Zen meditation practitioners had a decreased LF/HF ratio and LF norm and increased HF norm. The meditation technique involved normal breathing, in contrast to studies that use slow-breathing techniques (Wu and Lo 2008; Wu et al. 2008). Short-term meditation training induced increased HRV, involving the brain region of the anterior cingular cortex (Tang et al. 2009).

HRV Biofeedback

The term "biofeedback" refers to an instrumentation or training process that allows biological information to be recorded, displayed, and communicated back to an individual, allowing the individual to make adjustments in physiological processes that may enhance health or performance. Pure biofeedback training consists of operant conditioning. That is, the subject learns to regulate his or her physiology in the right direction because of the feedback, which can be positive reinforcement like a pleasant image appearing on a computer screen or verbal reinforcement by the therapist (Moravec and McKee 2011). Biofeedback is one of several techniques in "mind–body" treatments that have been used in the last decades to achieve better symptom control (Emani and Binkley 2010). HRV biofeedback is meant to specifically target autonomic function and has been used in some studies with asthma, hypertension, as well as cardiac disorders (Cowan et al. 1990; Del Pozo et al. 2004; Lehrer et al. 2000; Lehrer and Vaschillo 2000).

Cowan did not use HRV actively in training, but to screen effects on six sudden cardiac arrest survivors and observed especially increased HF (Cowan et al. 1990). Del Pozo used it in patients with CAD who were randomly assigned to conventional therapy or to six biofeedback sessions consisting of abdominal breath training, heart and respiratory physiological feedback, and daily breathing practice. HRV was measured by SDNN at pretreatment, after treatment, and at a follow-up after 12 weeks (Del Pozo et al. 2004). Thus, here HRV was used to look at effects within a therapeutic paradigm, but not as a biofeedback parameter on its own.

The group around Lehrer has the most documented experience with HRV in biofeedback. They describe their technique as follows: "The feedback takes several forms. One uses a beat-to-beat cardiotachometer, superimposed on a measure of respiratory activity. The patient is instructed to breathe approximately in phase with heart rate changes, with the goal of maximally increasing amplitude of RSA. In another display, the patient is shown a moving frequency analysis of heart rate,

within the band of 0.005–0.4 Hz. The display is updated approximately every second, and reflects the frequency of heart rate fluctuations within the past minute" (Lehrer et al. 2000; Lehrer and Vaschillo 2000). Their studies are based on earlier experiences, most of them published in Russian journals (Chernigovskaya et al. 1990a; b; Pichugin et al. 1993; Sidorov and Vasilevskii 1994; Vasilevskii et al. 1993).

HRV biofeedback in the HF range was used in children with asthma. In this protocol, the children were taught to engage in relaxed abdominal pursed-lip breathing while they were administered respiratory sinus arrhythmia biofeedback. Participants were also encouraged to exhale for longer periods than they inhaled, where this was comfortable and produced higher RSA. They used an analogue device that outputs a pulse for each R-spike, which in turn is detected by a Schmidt trigger, which triggers a pulse former. The computer calculates cardiac interbeat interval from the time interval between these pulses. Feedback is given for averages of two adjacent pulses. To eliminate noise, the device uses a differential amplifier and contains a filter to eliminate 50-Hz noise. The device uses an amplifier having a differential input and containing active filters to further reduce electrical noise and to ensure reliable selection of cardiac signals. They showed a moderate but significant improvement in FEV1 and FEF50 % after 13–15 daily 20-min RSA biofeedback sessions with 20 children (Lehrer et al. 2000; Lehrer and Vaschillo 2000). In a later uncontrolled study on 45 adults, they did not find age-dependent effects (Lehrer et al. 2006; Lehrer and Vaschillo 2000). A small pilot study with fibromyalgia patients showed promising results (Hassett et al. 2007), as did studies on depression (Karavidas et al. 2007; Beckham et al. 2013), food craving (randomized (Meule et al. 2012) therapeutic effect in spite of that HRV decreased after treatment), constipation (Ding et al. 2012), and more. HRV biofeedback has optimized motoric performance in sports in a small randomized study (Paul et al. 2012) and probably has some effects on hypertension (Lin et al. 2012).

In summary, HRV-based biofeedback might be promising. On the other hand it is rather unclear whether this effect is due to a specific consequence of HRV-based biofeedback or due to a rather unspecific consequence of biofeedback as a relaxation technique. The research field is dominated by small pilot studies and some, though few, small randomized trials. I agree therefore with Wheat and Larkin that "the mechanism by which HRV biofeedback results in salutary effects are unclear" (Wheat and Larkin 2010). Studies with sufficient statistical power are unfortunately still lacking, although the method is used at many institutions.

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Chapter 17
Conclusion

In 1996, a consensus panel issued a set of guidelines regarding the measurement and interpretation of HRV. In the 17 years since that report, there have been major technological advances and hundreds of publications on various patient populations.

There is now wide-ranging evidence of oscillation phenomena in different micro- or macro-systems in humans and other mammals. There is some evidence that disturbances in variations of oscillations may be reflected in changes in the variability of oscillations. In other words: a decrease in complexity shows beginning or advanced deterioration of (organ) systems. But decreased complexity may also cause further deterioration. In this approach, complexity is seen as an entity of its own and not as surrogate for system deterioration (Godin and Buchman 1996). This would imply that any therapeutic strategy that focuses on an increase of complexity would increase survival. Bedside measurement would help to establish trial-and-error interventions, which in turn would improve therapeutic results.

Buchman recently summarized possible advantages of using tools of complexity research in clinical science: (1) the possibility of managing large amounts of parallel data sets, (2) the option to design experiments in cases when a traditional experimental approach is not possible, (3) having a framework to build up mathematical models that are able to show or even explain clinical issues, and (4) an analysis tool can be used both for micro- and macro-systems and even for combinations of both (Buchman et al. 2001). Goldstein concludes, "Despite the multitude of physiologic signals available for monitoring, we suggest that a wealth of potential valuable information that may affect clinical care remains largely an untapped resource" (Goldstein et al. 2003). HRV has been used more often with linear measures like SDNN or power spectra as a predictor for sudden cardiac death, but that has its limitations if HRV rates of patients with already established cardiac disease are examined. The possibility of extracting fractal variables can provide information even if HRV is already significantly reduced (Lombardi 2000).

At the moment it seems that interest in physiological time series is increasing. But there are clear caveats. "As the scientific community continues to explore

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mathematical complexity in biology and medicine and applies basic engineering principles to analyse large physiological data sets, it is important that this is done using thoroughly tested methods" (Goldstein and Ellenby 2000, p. 3940). New methods are usually welcomed and several research groups experiment with them. Very many different measures have been used, and thus, the question arises about to what extent HRV analysis with linear and nonlinear methods is a form of data torturing in order to produce an algorithm with a statistically significant parameter.

Xhyveri (2012) states that HRV has not been incorporated in clinical practice and argues that the time-consuming manual editing is a problem. She calls for further prospective randomized studies "specifically in patients with recent myocardial infarction or chronic heart failure." Brahm Goldstein described HRV to identify neonatal sepsis as a premature tool, mentioning the problem of making possible sufficient discrimination to distinguish between sick and healthy subjects (Goldstein 2005). In several areas HRV might be used clinically already today in a similar manner to the earlier use of erythrocyte sedimentation rate (ESR). ESR is pathologically related to many diseases and presents considerable variation between patients. However, it has been used over decades as a supplement to other clinical information and has contributed to a comprehensive view of a clinical situation. Perhaps at this stage we ought to consider HRV in a similar way.

While I am writing this in 2013, new approaches continue to emerge. QT-variability has been successfully used as prognostic factor in patients with heart failure (Tereshchenko et al. 2012). Modified SDANN techniques have been implemented in standard ICU monitoring, making it far simpler to use in everyday practice (Mowery et al. 2008).

There are still many open questions, such as the following: What is the value of time-domain indices in short-term measures? Is it feasible to take VLF, for instance, in a 10-min short-term measurement? What is the value of all the new algorithms? Probably the most important challenge to clinical researchers is to start intervention studies. I have screened an enormous number of HRV studies. In some areas, such as CVD and CVD and depression, I found clear associations between decreased HRV and mortality in follow-ups. What we are missing are randomized studies in which half of the participants with decreased HRV parameters are treated with a battery of preventive measures. There have been some intervention studies. Hanss successfully used results of an earlier study (Hanss et al. 2005) to prevent hypotension due to spinal anesthesia with clinical interventions for a group of patients with an LF/HF >2.5 (Hanss et al. 2006).

In 2013, 407 studies using heart rate variability are listed, and 163 still open.[1] Not surprisingly, the majority of them focuses on mostly specialized aspects of cardiovascular disease. Many studies address depression. There is still high activity in the field of critical illnesses. Rehabilitation, exercise and prevention, and complementary medicine are also areas with a high use of HRV. Many of the protocols characterized as "other studies" investigate dietary changes, mostly omega-3 fatty acids as dietary supplement (Table 17.1).

[1] www.clinicaltrials.gov, assessed 12 Mar 2013.

Table 17.1 Open studies in www.clinicaltrials.gov. Accessed 12 March 2013

Area	Number of studies
Cardiovascular and hypertension	35
Psychiatry	20
Intensive care, trauma, and anesthesia	15
Rehabilitation, prevention	15
Complementary medicine	14
Brain damage and stroke	9
Diabetes	6
Lung diseases	6
Biofeedback	2
Other studies	41

A closer look at these ongoing studies reveals that HRV is often one of several parameters used. Only about 12 % of the studies focus on HRV directly or at least on the ANS. It seems as if HRV is still often used as a source of additional parameters in observational or interventional studies, simply as a way to have more data. HRV is not often integrated in research hypothesis, but rather analyzed retrospectively and mentioned in case of significant effects either in dichotomous analysis or multivariate models. In such cases it sometimes goes the way of Ronald Coase's[2] famous phrase: "If you torture the data long enough, it will confess." Another set of the studies looking at dietary changes or complementary-medicine approaches appears to use HRV as a surrogate, suggesting that improvements in HRV might reflect general health effects. At times, HRV is used simply to make the studies look more scientific. Only very few studies use HRV in order to select patients for interventions.

HRV as Publication-Generating Machine

Publish or perish is not a new phenomenon in the sciences. Already Albert Einstein used to complain about the pressure on young scientists to produce a vast amount of papers. HRV is very convenient for producing such papers. It is cheap and does not have adverse effects, and the short-term form is conducted rapidly. It delivers several indices that increase the chances of finding differences between groups. It can be interpreted with physiological knowledge and discussed in terms of the ANS in seemingly scientific manner without real causal relationships. In addition, a standard exists since 1996, which makes the methodological part easier. HRV generates basically a row of integer numbers, which again makes it suitable for a vast amount of mathematical algorithms. Many scientists dream of finding a magic formula that could be used as diagnostic tool forever. Not surprisingly, a very high number of

[2] American economist, born 1910, received the Nobel Prize in Economics in 1991, and still scientifically active.

algorithms have been published (Bravi et al. 2011), mostly without any much apparent connection to useful clinical information.

HRV shares some properties with other easy and cheap methods without adverse effects. Not surprisingly, then, it has been used in at least one study in almost all symptom constellations or illnesses. It is used in patient groups where neither the mechanisms nor the effective treatments are known. Examples are fibromyalgia (Petzke and Clauw 2000), tension-type headache (Pogacnik et al. 1993), or the so-called myalgic encephalomyelitis (Togo and Natelson 2013). HRV is also used in areas in which new technologies appeared and about which the general public suspects that such technologies could be detrimental to health (e.g., Lyskov and Sandström 2001, Ahamed et al. 2008). It is easy to find differences between groups in illnesses, which trigger chronic distress, alone that a probable cause for differences to healthy controls. Clearly, there is a risk that HRV can be misinterpreted as "proof" for pathology, harmfulness of some modern technology, environmental pollution, bad working conditions, and so on. HRV with its many indices is in addition an ideal "data torturing" (Mills 1993) instrument that produces "something." Of course, negative studies are rarely published anyway, but probably in the case of HRV, negative studies like in tension-type headache (Pogacnik et al. 1993) are simply rare.

Many studies do not have any clear hypothesis on why they use HRV or what HRV means in the studied patient group and which specific changes can be expected. This is a problematic situation for proper research on HRV. In addition, several studies give the impression that a good number of the ideas presented appeared after the results were on hand. I have expounded the problems of the relationship between ANS and HRV, and this has been discussed extensively. Nevertheless, simplistic conclusions are drawn again and again without even a suggestion that there are major caveats.

I am convinced that HRV can in fact contribute to many scientific and clinical questions. There is – thankfully – strong evidence in some fields that HRV has predictive values and weaker evidence in fewer fields that it can be used to guide interventions. If we really want to appreciate the value of HRV, we need to focus on more scientifically solid argumentation. Otherwise we could end up like the emperor in Hans Christian Andersen's fairy tale: we could be told that the emperor is wearing nothing at all ("The Emperor's New Clothes")!

Conclusion

HRV is a scientific and clinical instrument with some established applications, some experimental applications, and some caveats. Ideally, hard- and software for HRV should be capable of analyzing further clinical time series data (e.g., respiration rate, blood pressure, immunological data), should be able to use different algorithms, or should be able to export digitalized data to be analyzed with MATLAB tools. A bedside tool to digitalize and analyze clinical data would very likely contribute to novel approaches in complex clinical situations.

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