
Heart Rate Variability (HRV) Signal Analysis

CLINICAL APPLICATIONS

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Edited by
Markad V. Kamath
Mari A. Watanabe
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Preface

The field of medicine has greatly benefitted from the quantitative precision demanded by the fields of physics, chemistry, mathematics and engineering. This book demonstrates how a record of beat-to-beat heart rate, which requires precision of the order of milliseconds, can contain enormous amounts of embedded and useful information. It is also relevant that such information can only be unraveled by signal processing methods that utilize modern computational platforms. Assessment of the autonomic nervous system used to involve qualitative clinical tests, but heart rate variability signal analysis provided a quick quantitative evaluation of the balance between sympathetic function and parasympathetic function. An important goal of a physician is to apply his or her knowledge to each patient on a case-by-case basis. In this context, heart rate variability signal analysis provides a personalized yardstick to measure the performance of a relatively inaccessible autonomic nervous system.

Study of the heart rate variability signal was the exclusive domain of a handful of laboratories, until only a few years ago. But as science and technology associated with heart rate variability have become ubiquitous, we find it inspiring to observe that the new discipline of heart rate variability signal processing has been used to investigate dozens, if not hundreds, of clinical pathologies across the globe.

Because the heart rate signal can be easily obtained in a number of settings, varying from a physician's clinic, human experimental laboratories to animal models, the only factor limiting the development of novel applications has been the imagination of the researcher. Ideas from both linear signal processing and non-linear dynamics led the initial foray of identifying fruitful investigations in this field.

While engineers and mathematical physicists have long been cheerleaders for clinical application of heart rate variability analysis to multiple disciplines, adoption of heart rate variability as a tool by physicians in non-cardiology fields has been slow and is still largely limited to prediction of morbidity and mortality following myocardial infarction and stroke. Scientific skepticism is very much alive in identifying limitations of the technique and interpreting its results. Rigorous studies are still needed to validate several concepts underlying heart rate variability signal analysis and mathematical modeling. Many such questions are examined in this book.

Thus, it is our view that heart rate signal analysis will provide a rich array of challenging issues to be explored for many years to come.

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Acknowledgments

This book contains contributions by engineers, physicians, physiologists, nurses, biostatisticians and other allied health professionals. Each author is an established professional in the field of heart rate variability. We thank all authors who generously provided us with their well-written chapters and made this book possible. As editors we are privileged to have worked with them.

Dr. Markad V. Kamath recalls, with gratitude, countless meetings and exclusive mentorship provided by Dr. Ernest L. Fallen, MD, who initiated the work on heart rate variability at McMaster in 1984. He also acknowledges many insightful discussions and the integrative approach provided by Dr. Adrian R.M. Upton, MD, in addition to over 30 years of research collaboration. It has been a privilege to work with both of them. Markad's wife Padma has been patiently supporting throughout his research career and deserves a special mention of thanks for her cheerful attitude and team work. His sons Anand and Gautam also helped him at crucial moments of this book writing project. He acknowledges the funding support from Canadian Heart Foundation and Natural Sciences and Engineering Research Council of Canada. Finally, he wishes to place on record his gratitude to his guru Swami Shivom Tirth, who inspired him in his pursuits in the spiritual domain.

Dr. Mari A. Watanabe wishes to acknowledge several of her role models. She would like to thank first, cardiac electrophysiology pioneer and her father Dr. Yoshio Watanabe, who showed her electrograms from beating Langendorff heart preparations as a child and taught her how to read ECG traces as an adult; second, Robert F. Gilmour, Jr., for showing her how to wed her dual interests in mathematics and cardiology; and, last but not least, Georg Schmidt, who introduced her to heart rate turbulence and who never ceases to amaze her with his brilliant ideas. She would also like to thank her family Mark and Francis for putting up with her working late many a night on this book.

Dr. Adrian R.M. Upton has been impressed by the way this book has facilitated cooperation between professionals from widely different fields. There has been a trend for greater specialization in many disciplines, but this book provides evidence that knowledge can be advanced by an integrative approach. By contributing to this effort, many of us have learned very useful information about areas we would not have encountered without this book.

Much of the work reported herein is the result of painstaking investigations on thousands of human subjects throughout the world. We are grateful to them for taking part in various studies. It is their participation that has expanded the frontiers of knowledge and is the basis for better therapy for patients, in the future.

Editors

Dr. Markad V. Kamath qualified with a B.Eng. degree from Karnataka Regional Engineering College (recently renamed as National Institute of Technology), Surathkal, Karnataka, India. He has earned a PhD in biomedical engineering from the Indian Institute of Technology (Madras) and a PhD in medical sciences from McMaster University. His research interests focus on applications of digital signal processing, image processing and pattern recognition in clinical medicine. He is the editor of the journals *Critical Reviews in Biomedical Engineering* and *Critical Reviews in Physical and Rehabilitation Medicine* (Begell House) and is the founding editor of a new journal, *Visualization, Image Processing and Computation in Biomedicine* (Begell house). Dr. Kamath is a professor in the department of Medicine, with associate membership in Computing and Software Engineering and Electrical and Computer Engineering departments, at McMaster University Hamilton, Ontario, Canada. He is a registered professional engineer in the province of Ontario, Canada.

Dr. Mari A. Watanabe received her MD from Nippon Medical School in Tokyo and PhD in physiology and applied mathematics from Cornell University. She has conducted research in cardiology, mathematics and physics at various institutions, including the University of Pennsylvania, Beth Israel Deaconess Medical Center in Boston, University of Utah and Glasgow University in Scotland. She has received research grants from the American Heart Association, National Institute of Health and British Heart Foundation. She is currently an assistant professor in the cardiology department at St. Louis University. One of her research interests is in the application of mathematics to cardiac problems, such as non-linear dynamical analyses of electrophysiological properties of the ventricles, effects of the autonomic nervous system on such properties and circadian rhythms in the cardiovascular system. A second area of interest is in Holter indicators of cardiac mortality, especially heart rate turbulence, which has led to collaborations with Dr. Georg Schmidt and Dr. Phyllis Stein. She publishes papers in both clinical and basic science journals.

Dr. Adrian R.M. Upton, MD, FRCP(C), FRCP(E), FRCP(G), is a professor of medicine at McMaster University. Dr. Upton qualified as a physician in the United Kingdom and has held a number of senior positions, including the director of the neurology department and director of the Diagnostic Neurophysiology Laboratory at Chedoke-McMaster hospitals, Hamilton, Ontario, Canada. His research has focused on developing novel therapeutic options, including brain stimulation for neurological diseases such as epilepsy, migraine and Parkinson's disease. He has published over 400 papers in areas such as autonomic stimulation, evoked potentials, electroencephalography and electromyography, among others. He has also trained many student physicians, residents, graduate students and post-doctoral fellows. He holds 12 patents.

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1

Heart Rate Variability: A Historical Perspective

Markad V. Kamath, Mari A. Watanabe and Adrian R.M. Upton

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1.1 Introduction

Heart rate variability (HRV) and blood pressure (BP) variability have emerged as multi-disciplinary areas of research mainly due to continuous interactions between engineers, physicians and physiologists. Physicists and mathematicians have also contributed concepts from their respective fields. This chapter provides a brief historical perspective of HRV and speculates about its future.

Some of the earliest studies on the significance of the beat-to-beat variability of heart rate (HR) were reported by Hon and Lee. They studied fetal HRV during labor and delivery and its relation to fetal health (Hon, 1963, 1965; Hon and Lee, 1963). A seminal article by Hyndman et al. (1971) documented spontaneous 10 s variations in BP and provided a control system model to describe their discovery. Subsequently, Wolf et al. observed that higher RR interval variance was associated with lower in-hospital mortality in patients with acute myocardial infarction (Wolf et al., 1978). Using pharmacological interventions, Akselrod et al. (1981) demonstrated that sympathetic and parasympathetic nervous activities of the autonomic nervous system make frequency-specific contributions to the HR power spectrum. They also reported that the renin-angiotensin system activity strongly modulated the amplitude of the spectral peak located at 0.04 Hz.

The continuous development of computer technology and signal processing algorithms (Kay and Marple, 1981; Jenkins and Watts, 1968) accelerated the science of understanding rhythms embedded in the electrocardiogram (ECG) and BP with great vigor and frequency (Kitney and Rompelman, 1980, 1987; Baselli et al., 1986). The discovery that the autonomic nervous system was compromised in clinical conditions such as diabetes (Ewing and Clarke, 1982) and could be studied using power spectral analysis of the HRV signal provided the impetus for further progress in the field. Cardiac diseases such as myocardial infarction (Lombardi et al., 1987) and sudden cardiac death (Myers et al., 1986) were found to be related to reduced HRV. Through an extensive analysis of several hundred Holter tapes from patients who had suffered a myocardial infarction, it became evident that a frequently used time domain statistic, namely the standard deviation of the mean heart

rate computed from 24 h Holter ECG, could be used as a predictor of mortality (Kleiger et al., 1987).

Much of HRV analysis is based on linear signal analysis theory, which states that under conditions of statistical stationarity, a signal can be broken up into its constituent components, and physiologists can relate these components to sympathetic and vagal influences impinging on the sino-atrial node. Decomposition of HRV by power spectral analysis dominated research on HRV during much of the 1980s (Bigger et al., 1988; Pagani et al., 1986). The usefulness of HRV slowly expanded from cardiac applications to diverse pathological conditions as delineated in well-documented reviews and books (Malik, 2010; Malik and Camm, 1995, 2004; Eckberg, 1997; Kamath et al., 1987; Kamath and Fallen, 1993; Malliani, 2000; Stein et al., 1994; Table 1.1). Areas of applications include functional reinnervation in patients with cardiac transplants (Fallen et al., 1988; Sands et al., 1989), esophageal stimulation (Tougas et al., 1997; Kamath et al., 1998), chronic renal failure (Forsström et al., 1986), critical care medicine (Prietsch et al., 1994), exercise (Arai et al., 1989; Kamath et al., 1991), fibromyalgia (Raj et al., 2000), hypertension (Baselli et al., 1987), asthma (Kazuma et al., 1997), congestive heart failure (Saul et al., 1988), myocardial infarction (Lombardi et al., 1987; Kleiger et al., 1987; Bigger et al., 1988; Bekheit et al., 1990), non-cardiac chest pain (Tougas et al., 2001; Hollerbach et al., 2000) and vagal stimulation (Kamath et al., 1992), many of which are discussed in this book. By contrast, there is less research on BP variability, perhaps because it is easier to identify peaks in the ECG waveform (Pan and Tompkins, 1985; Friesen et al., 1990) than in the BP waveform. However, BP and HR are closely intertwined, and more research needs to be conducted on BP variability if we are to make progress in understanding the mechanisms underlying HRV (Eckberg, 1997).

In this respect, two of the newer HRV analysis methods included in this book are HR turbulence, which was initially published in 1999 (Schmidt et al., 1999), and phase-rectified signal averaging, which appeared for the first time in 2006 (Bauer et al., 2006). These methods have been proven to be of significant clinical use and have also increased our knowledge about the interaction between BP and HR. The chapter on HR turbulence gives an introduction to the procedure and mechanism of the phenomenon, and the interested reader is directed to the many review articles on this newly evolving field (Watanabe, 2003; Watanabe and Schmidt, 2004; Watanabe and Watanabe, 2004; Francis et al., 2005; Lombardi et al., 2008).

Techniques derived from deterministic chaos have also provided an alternative method for studying HRV and mechanisms responsible for deleterious arrhythmias (Sugihara and May, 1990; Goldberger, 1990; Glass and Kaplan, 1993). Measures such as approximate entropy (Pincus, 1991), sample entropy (Lake et al., 2002; Richman and Moorman, 2000), detrending fluctuation analysis (DFA) (Peng et al., 1994, 1995), multi-scale entropy (Costa et al., 2002, 2005) and Lempel-Ziv complexity (Ferrario et al., 2004) have helped to quantitatively unravel the mechanisms of chaos embedded in the HRV signal. As an example, DFA-derived parameters perform better than spectral measures

TABLE 1.1

Number of Publications on Heart Rate Variability and Blood Pressure Variability Over the Last Three Decades

	1981–1990	1991–2000	2001–2010
Heart rate variability	269	2574	5115
Blood pressure variability	86	287	405

Source: OVID Technologies, Wolters Kluwer Inc.

to distinguish sleep stage and apnea severity (Penzel et al., 2003). Numerous applications of all these methods have been described in this volume.

1.2 Structure of the Volume

This book consists of two parts. The first part comprises Section I (Chapters 2–6), which highlight how both HRV and BP variability signals can be analyzed using signal processing methods. The chapters on HR turbulence and phase-rectified signal averaging are included in this part, describing methods and their clinical applications. The second part comprises Sections II–IV (Chapters 7–25), which provide a detailed evaluation of autonomic dysfunction in a variety of pathological conditions using techniques described in Section I of the book. The subjects of these chapters are diverse and are contributed by researchers with many years of experience in their fields and who have made their mark in the literature.

1.3 Thoughts about the Future

Much progress has been reported in the scientific literature toward understanding mechanisms due to research on the HRV, BP variability and baroreceptor sensitivity. Non-linear analyses and newer methods have supplied a fresh set of tools for studying diseases and states already analyzed with the time domain and frequency domain methods of signal processing. Some outstanding issues of this field as a whole include a lack of standardization of methods and data length and poor knowledge of the interpretation of powers in various frequency bands. For example, we in the field acknowledge that it is overly simplistic to interpret the power in the lower-frequency bands as a reflection of a combination of sympathetic and parasympathetic components, while power in the high-frequency band reflects the parasympathetic component only. HRV is also still far from being accepted by physicians as a routine part of their clinical practice, even in cardiology. It would be of mutual benefit for us in the field to reach out to physicians, demonstrate the utility of this wonderful tool for the benefit of their patients and gain cooperation in organizing larger studies that validate long-standing hypotheses. We challenge the readers of this book to get excited about the different ways in which HRV can be applied to illuminate the workings of our body, in sickness and in health, and also push the boundaries of this field, where it is needed.

Abbreviations

BP	Blood pressure
DFA	Detrending fluctuation analysis
ECG	Electrocardiogram
HR	Heart rate
HRV	Heart rate variability

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Section I

Heart Rate Variability Techniques

2

Methodological Aspects of Heart Rate Variability Analysis

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2.1 Introduction

There are numerous methods and approaches available for time-series analysis. This chapter presents selected methods, which are or at least could be useful when analyzing biosignals, especially heart rate variability (HRV). The methods described here differ greatly, and some of them are commonly used characterization methods. One must always select the method to use, case by case.

The analysis methods are often divided into *linear* and *non-linear* methods. The term “non-linear methods” is in fact not quite appropriate and is actually even misleading, because those methods themselves are no more non-linear than common spectrum analysis using fast Fourier transform (FFT) algorithm. The idea behind the naming convention is merely related to the fact that the system producing the time series is non-linear, which in the case of biological systems might well be true. Sometimes these methods are described using the term *chaos-theoretical approach*. This is true only of some of the methods in which the assumption that the system’s trajectory in a phase space is actually a chaotic small-dimensional attractor. There is very little proof for the existence of this in biological systems. In particular, if we are studying the cardiovascular blood pressure regulatory system and typical time series such as the sequence of RR intervals, we can find in the literature a growing number of results that indicate this system to be stochastic rather than chaotic.

Biosignal time series, in general, are very difficult to analyze, in many ways. Many methods demand that the time series has thousands of data points, which may be impossible or difficult to achieve, depending on the measurement method used. When the time series is long, notable changes in the biological system will occur almost inevitably and the time series will start to drift in the parameter space of the system due to either internal or external influences. Such instability has a negative effect on all analysis methods in which a specific characteristic of the whole time series is to be compressed into a single statistic. Of course, calculations will produce some result, but what is the meaning of the statistic? Other disturbing factors in these signals are notable noise levels, strong discreteness of the signals due to a limited amplitude resolution of the digitization and regular strong periodic signals, for example, breathing modulation on top of the otherwise possibly chaotic or stochastic signal. It should be remembered that most of the methods described in this chapter were originally developed in physics for analyzing very different, and often practically ideal systems.

Despite warnings stated earlier, an analysis of biosignals using such methods may still yield useful information. Even though the calculated statistic might not exactly

describe the characteristic it was originally designed to represent, it could still play an important role when searching for a correlation with other clinically interesting parameters. However, basic assumptions and limitations accompanying each method should be clearly understood when interpreting results and searching different explanatory models.

2.2 ECG Recording and Generation of RR Interval

2.2.1 RR Interval Time Series

HRV analysis is based on the RR interval time series, the sequence of intervals between successive fiducial points of R peaks of QRS complexes in the electrocardiogram (ECG). It should be noted that the RR interval time series are actually an event series and not an equally sampled continuous signal. This fact is important, especially when performing frequency domain analysis. It should also be noted that HRV analysis does not measure the rhythms of the sinoatrial node, which is the pacemaker of the heart, since it is not based on P-P intervals. Therefore, HRV reflects fluctuations in the atrioventricular conduction superimposed on the P-P interval. Nevertheless, it has been shown that beat-to-beat changes in RR intervals reflect the variability of the sinoatrial node quite accurately. In theory, it would be better to use P-P intervals for HRV analysis, but in practice, the amplitude of the P wave is small, which makes the accurate determination of P wave peak difficult, especially in the presence of noise. In turn, this would affect the accuracy of P-P interval measurement.

2.2.2 Time and Amplitude Resolution of ECG Recording

The sampling frequency and amplitude resolution of ECG recording are important parameters in HRV analysis. The sampling frequency determines the temporal resolution of R peak recognition of QRS complexes, and, therefore, it determines directly the accuracy of the measurement of RR intervals. Too low a sampling rate produces digitization noise and introduces errors in all HRV measures, whether in time and frequency domains or in non-linear analyses. In most cases, a sampling rate of 200 Hz corresponding to a temporal resolution of 5 ms is high enough, and higher sampling rates do not give any better results. If the overall variability of RR interval is very low, as it can be, for example, with some heart failure patients, HRV analysis requires a higher sampling rate, since changes in the length of RR intervals cannot be captured below that resolution.

The amplitude resolution of the analog–digital conversion of ECG signal is rarely a limiting factor. The commonly used resolution of 12 bits is normally sufficient. However, the effective amplitude resolution is always less than the resolution of the conversion because the full dynamic range of input signal in the converter is rarely utilized in order to avoid signal clipping or saturation in the case of a large ECG signal or a wandering baseline.

2.2.3 Duration of the Recording

The duration of the recording is determined by the method used for HRV analysis, the aim of the study, and stationarity issues. Typically, frequency domain methods are preferred

for short-term measurements and time domain methods for long-term measurements of HRV. Some non-linear methods are likewise suitable for short-term analyses and others for long-term analyses. It is important to note that although the same mathematical method is used for the analysis of both short-term and long-term ECG recordings, the physiological interpretation can be different, that is, they cannot necessarily be considered as the surrogates for each other just with a different duration. There are also non-linear methods where results depend directly on the number of data points, and thus, it is inappropriate to compare the HRV measures obtained from recordings of different durations, with each other. This is also true of most linear methods.

2.2.4 Stationarity of the Recording

The stationarity of the signal is of great importance. There are many methods available for evaluating the stationarity of a signal, depending on how we define stationarity. Stationarity can mean, for instance, that there is no shifting in the base level of the signal or that the amplitude distribution, spectrum and autocorrelation function of the signal do not change, as a function of time. More generally, we can say that a signal is truly stationary if parameters that define the working point of the system remain constant in time. This evaluation is extremely difficult to undertake in the case of physiological systems, since we have a limited knowledge of the background dynamics and most physiological parameters are unknown.

Stationarity is strongly linked to the duration of the recording. The longer a recording is, the less stationary it is, because inevitably there are changes in the physiological state of the subject. Whatever method is used for the analysis of long recordings, the result is always a complicated and often a non-intuitive average over physiological states. Unless the method is designed for such a situation (e.g., see DFA), this kind of analysis should be avoided. Hence, the best approach is to divide the recording into shorter segments and perform separate analyses on them. This confers several advantages: shorter segments are often more stationary and results more reliable; the temporal change of results is a measure of stationarity (or lack thereof), which can be used to investigate the time evolution of the system; and finally, changes over segments can be utilized when estimating the statistical relevance of the results. The last advantage is most useful because normally we get a single statistical estimate as a result, but have no possibilities to quantify the statistical significance of this number.

2.2.5 Removing Trends

Most non-stationarities of the signal are not evident until they are revealed by a more advanced analysis. The trend in RR interval time series is easily seen, and it is often interpreted as a sign of non-stationarity, which can be removed by subtracting the trend from the data. However, *a priori* there is no way to separate the “real” signal and its trend; the signal is *never* a sum of them. In theory, even large trends can be an essential part of the dynamical behavior of a stationary system. But in practice, many HRV analysis methods are useful only if there is no significant trend in the data irrespective of its origin and in these circumstances, the trend should be removed from the data. Normally, only the linear trend is removed, since the removal of non-linear trends may create a significant bias. From the point of view of spectral analysis, the trend removal decreases the contribution of the

lowest frequencies; thus, further analysis is focused on faster oscillations. And finally, it must be remembered that the removal of a trend does not restore the stationarity of data. The only way to overcome the problem of non-stationarity is to minimize all internal and external disturbances during the study.

2.2.6 Ectopic Beats, Arrhythmias and Noise

The ECG signal can contain technical artifacts or QRS complexes originating outside the sinoatrial node, which introduce errors, since HRV analysis is based on assessment of the variability of sinus rhythm. Artifacts can seriously affect HRV analysis and thus cannot be ignored.

Technical artifacts, such as missed beats (due to problems in the R peak detection) or electrical noise (bad contact in the electrode, movement artifacts), can be easily edited by cleaning the data by a proper interpolation based on the preceding and successive QRS intervals. When interpolating the RR interval time series, it is important that the cumulative time is not altered; RR interval is an event series where the time stamp of each beat is the sum of all preceding beats. For example, the respiratory modulation on RR interval encounters a small phase shift if the time line changes after an interpolated segment. Similarly, time synchronization with other signals should be preserved.

The editing of ectopic beats is more problematic. Ectopic beats are usually premature beats and they produce a very short RR interval followed by a compensatory delay and a prolonged RR interval. Such a short-long pair can be edited without affecting the cumulative time of the beats by lengthening the first interval and shortening the second interval, so that they have equal intervals. However, ectopic beats and most arrhythmias result in reduced stroke volume and cardiac output, leading to transient drops in the blood pressure. This activates autonomic reflexes and induces changes in the efferent autonomic activity. Since these true physiological responses can last 10–30 beats, editing of just the two intervals on either side of ectopic beats does not remove all of the changes in HRV produced by them.

The raw recorded ECG signal should always be inspected. QRS complex identification should be carefully verified. If there are any artifacts or ectopic beats present, the best option is to select a signal segment free of them. If an artifact-free recording is not available, editing can be considered. If an excessive editing of ectopic beats is needed, it should be recognized that HRV analysis can then lead to erroneous results. Very few analysis methods are so insensitive to ectopic beats that the ECG needs no editing at all.

2.3 Time Domain Analysis

The most common time domain estimate of HRV is the standard deviation of RR intervals (SDNN; normal-to-normal deviation of intervals measured between consecutive sinus beats). SDNN can be calculated, for instance, over 5 min segments (called SDANN) or over 24 h. These two estimates should not be compared because HRV is not a stationary process, that is, a process in which the mean and the variance are independent of the record

length. In long-term recordings, the low-frequency (LF) variations contribute a major proportion of the overall HRV power and also to the SDNN. Since HRV normally decreases at higher levels of the heart rate, SDNN can be normalized against this effect by dividing it by the mean RR interval.

Some commonly used HRV measures are based on the differences between RR intervals, such as the root mean square of successive differences of RR intervals (RMSSD), the number of pairs of adjacent RR intervals differing by more than 50 ms (NN50 count) and the ratio of NN50 count to the count of all RR intervals expressed as a percentage (pNN50). Since all of these measures use RR interval differences, they reflect mainly high-frequency (HF) variations of heart rate and are almost independent of long-term trends. Furthermore, these measures are highly correlated with each other and can thus be considered as surrogates of each other.

All time domain HRV estimates are easily calculated; they do not need time-consuming computation. Also, they do not require stationarity in the same manner as most frequency domain and non-linear analyses do. The main limitation of time domain methods is their lack of discrimination between effects of sympathetic and parasympathetic autonomic branches.

2.4 Frequency Domain Analysis

The main idea behind the frequency domain analysis of HRV is the observation that HRV is composed of certain well-defined rhythms, which are related to different regulatory mechanisms of cardiovascular control. Time domain HRV measures are mainly markers of overall HRV, although some of them can contain information about heart rate oscillations in certain frequency bands (e.g., RMSSD mainly quantifies fast changes in RR intervals). In order to get more detailed information on the dynamics and frequency components of HRV, more advanced analysis methods, such as power spectral density (PSD) analysis, have to be applied. PSD analysis decomposes the signal into its frequency components and quantifies their relative (and also absolute) intensity, named *power*. In other words, it provides estimates of the PSD function of the heart rate, namely, the distribution of frequency components. There are two commonly used methods to compute the PSD function: Fourier transform and autoregressive (AR) modeling.

2.4.1 Fourier Transform

The Fourier transform can be used to convert the time domain data into the frequency domain data and back. The Fourier transform is a one-to-one transform, that is, no information is lost or added; the data just has two different *representations* (Marple, 1987). The normal Fourier transform is defined for continuous functions over the whole real axis. In the case of RR interval time series, the original Fourier transform must be replaced with the discrete version of the transform. The discrete Fourier transform has some unique features which one should be mindful of when using it.

For the equally sampled time series $x(t_k)$, where $t_k = k\Delta$ is the time moment of the data sample, Δ is the sampling interval (the inverse of the sampling rate; see comments below

on the resampling of time series) and $k = 0, 1, 2, \dots, N-1$, the discrete Fourier transform $X(f_n)$ is

$$X(f_n) = \Delta \sum_{k=0}^{N-1} x(t_k) e^{-2\pi i f_n t_k} = \Delta \sum_{k=0}^{N-1} x(t_k) e^{-2\pi i k n / N}, \text{ where } f_n = \frac{n}{N\Delta}. \quad (2.1)$$

When the time series $x(t_k)$ consists of real values, as it is in our case, $n = 0, \dots, N/2$. The discrete Fourier transform (Equation 2.1) gives us $N/2$ complex numbers (real and imaginary parts*), thus there is an equal number of data points in $x(t_k)$, and $X(f_n)$ since the first and last $X(f_n)$ has only the real part. The power spectral density is $\text{PSD}(f_n) = |X(f_n)|^2$ corresponding to the squared amplitude of the frequency component f_n .

The discrete Fourier transform (Equation 2.1) has several important features. First, the frequency scale is discrete, since only f_n components are possible. The resolution of frequency scale depends inversely on the number of data samples N and the sampling interval Δ . The highest-frequency component ($n = N/2$), called the Nyquist critical frequency, is $f_c = 1/(2\Delta)$. If the time series $x(t_k)$ is a pure sine wave of a frequency exactly equal to one of the frequencies f_n , only $X(f_n)$ is non-zero, as we can expect. However, if the frequency f of the oscillation is between two adjacent f_n s, there are many non-zero spectral components $X(f_n)$ around f . This is called leakage from one frequency to another in the power spectral estimate, and it is characteristic only of the discrete Fourier transform. This problem can be partially overcome by using *data windowing*.

2.4.1.1 Data Windowing

The discrete Fourier transform (Equation 2.1) can be interpreted as a Fourier transform of the product of the infinitely long time series with a square window function, which turns on at $t = 0$ and off at $t = (N-1)\Delta$. Because of this rapid switching, its Fourier transform has substantial components at higher frequencies, causing the leakage from one frequency to another. To remedy this situation, we can multiply the time series by a window function that changes more gradually from zero to maximum (in the middle of the time series) and then back to zero. There are numerous window functions (named *Welch*, *Parzen*, *Hanning* and so on), but for the purpose of HRV analysis, there is effectively little or no difference between any of them.[†]

Smoothing

The statistical reliability of the PSD is very low. In fact, the standard deviation (SD) of the PSD estimate is always 100% of the value, and it is independent of N , that is, we cannot get more precise estimates by increasing the number of data points; we just get more discrete frequencies f_n . This means that the amplitude of each spectral component is always unreliable from a statistical point of view. Luckily, in HRV analysis, we are not interested in the amplitude of some specific frequency component but in the spectral power over a certain frequency range. If we want to look at the details of the PSD, the

* Complex number $X(f_n)$ can be interpreted as a two-dimensional vector. Each $X(f_n)$ carries information on the amplitude of the spectral component (the length of the vector) and the phase of the corresponding oscillation (the angle of the vector).

[†] The difference of the window functions lies in subtle trade-offs among the various figures of merit that can be used to describe the narrowness of the spectral leakage functions.

statistical reliability can be increased by smoothing the data using certain methods, for example, the triangular weighting function, but unfortunately, one pays the price of a lower effective frequency resolution. For a 5 min recording, the smoothing range should not be more than 0.01 Hz.

2.4.1.2 FFT Algorithm

The discrete Fourier transform can be computed directly using Equation 2.1, but such an operation would be very time consuming. The FFT is a very effective *algorithm* to evaluate the discrete Fourier transform (Marple, 1987; Kay and Marple, 1981). It has one limitation: the number of data point N must be an integer power of 2. Since normally the length of the time series is not a power of 2, the data can be padded with zeros up to the next power of 2. This operation corresponds to the interpolation of the original data. Since the actual N used in the FFT calculation is different from the original one, the f_n s are also slightly different.

2.4.2 Autoregressive Modeling

The AR model is based on the idea that the future values of a time series depend linearly on the previous values (Akaike, 1969). This kind of approach is totally generic, and it can be used to model large sets of different systems. The AR model is determined from the following equation:

$$x_k = \sum_{j=1}^p a_j x_{k-j} + u_k, \quad (2.2)$$

where x_k is the sample of the time series, a_j is the model parameter, p is the model order and u_k represents the noise, the part of the signal that cannot be explained by the previous values of the signal. The computational task is to find optimal model order p such that parameters a_j of the model describes the system as well as possible. When we have such a model, it is possible to compute the corresponding PSD in the form

$$\text{PSD}(f) = \frac{a_0}{\left| 1 + \sum_{j=1}^p a_j z^j \right|^2}, \quad z = e^{-2\pi i f \Delta}, \quad (2.3)$$

where f is the frequency and Δ is the sampling interval, as usual. The PSD (Equation 2.3) is capable of modeling sharp peaks since all free parameters are in the *denominator*, which can be made arbitrarily small.* The PSD approximation (Equation 2.3) is also called an *all-poles model* and *maximum entropy method*. There are many algorithms to find the best choices for the parameters a_j , but Burg's method is commonly used. Because the AR spectrum is based on a modeling approach, there are no restrictions for the maximal number of frequency components, that is, PSD can be evaluated using as high a frequency

* In fact, the denominator can be, at least in theory, even zero at certain frequencies. These zeros (also called the *poles* of Equation 2.3) correspond to the spectral peaks.

resolution as one desires (f in Equation 2.3 is actually a continuous variable), in contrast to the Fourier spectrum where the frequency resolution is determined by the number of data samples. Furthermore, the AR model makes it possible to resolve the central frequencies (the frequency location of each peak) analytically. In clinical setups, this feature is rarely useful, but in research work, it could be interesting.

2.4.2.1 Model Order

The model parameters can be estimated if the model order p is fixed. It could be imagined that the model would be best when using as high a model order as possible. However, in practice, time-series data always include some noise (the term u_k in Equation 2.2), so an excessively high model order leads to the model capturing the noise, producing a spectrum with spurious peaks. Too high a model order can also split peaks. Again, too low a model order will strongly smooth spectral peaks, their positions can be shifted and some peaks can even be missing. Some methods have been developed based on information theory for estimating the optimal model order, such as Akaike information criteria (AIC), final prediction error (FPE) or minimum description length (MDL) (Akaike, 1969; Rissanen, 1983; Partzen, 1974). The analytical assumptions underlying these methods are hardly ever fulfilled when analyzing the RR interval time series. Thus, they provide only limited assistance in determining the model order. Therefore, it is recommended that the AR method be used in conjunction with the Fourier transform method (or some other direct method) to help choose the correct model order and to avoid getting spurious spectral features.

2.4.3 Resampling

The RR interval time series is an event series, as stated previously, and each interval has a time stamp, which is the cumulative sum of all preceding intervals. The data can be interpreted as a hypothetical continuous function that has been sampled *unevenly* in time at the moments of R peaks. In spectral analysis, either in Fourier transform or in AR modeling, the input data ($x(t_k)$ in Equation 2.1 or x_k in Equation 2.2) are assumed to be the data sampled evenly in time. Hence, the original RR interval data must be converted to such a form by interpolating each interval and resampling this apparently continuous function.* Interpolation can be linear (each interval is interpolated by a straight line) or based on splines.[†] The method of interpolation makes no essential difference in HRV analysis.

The resampling frequency must clearly be higher than the *effective sampling rate* of the RR interval data, but it is not critical. The effective sampling rate is equal to the mean heart rate, typically around 1 Hz (= 60 bpm). In practice, a resampling rate of 2–5 Hz is adequate, and there is no need to use a higher rate. In Fourier transform analysis, the highest-frequency component is $f_c = 1/2\Delta$, and it increases by a resampling of the data. However, resampling cannot increase the information content of the data, and thus, the highest relevant frequency component is still half of the (effective) sampling rate according to the general sampling theorem (Nyquist criteria); with 60 bpm mean

* The spectrum of event series can be computed correctly without any interpolation and resampling by using the Lomb–Scargle (also called Lomb periodogram) method. This method makes it possible to calculate the spectrum up to frequencies *above* the Nyquist frequency (= half of the sampling rate or mean heart rate).

[†] Splines are second-order or higher-order polynomials. If the order is 2, then the spline curve is a parabola with three free parameters, two of them are fixed by demanding that it goes through the data points of the interval and the last one is fixed by demanding that the derivative of the curve is continuous at the data points.

heart rate, $f_c = 0.5$ Hz. This is also true in the case of AR modeling, although the PSD estimate can be evaluated up to any frequency. One should notice that when increasing the resampling rate, the order of the AR spectrum must be increased correspondingly.

Sometimes the resampled data are low-pass filtered using a cutoff frequency of 1 Hz (or half of the resampling frequency). Although this operation can, in theory, improve the statistical reliability of the data, it has no real significance in HRV analysis.

2.4.4 Spectral Powers

The total power (TP) of the RR interval data is represented by the area under the PSD curve from zero to the highest relevant frequency f_c , and it is equivalent to the variance of the signal. In a typical short-time (≥ 5 min) spectral analysis, the spectral power is divided into three frequency bands: *high frequency* (HF; 0.15–0.40 Hz), *low frequency* (LF; 0.04–0.15 Hz) and *very low frequency* (VLF; 0–0.04 Hz). In long-term recordings, an *ultralow frequency* (ULF; 0–0.003 Hz) component can be calculated. The HF component corresponds to heart rate variations related to the respiratory sinus arrhythmia and HF fluctuations are mediated almost exclusively by fluctuations of efferent parasympathetic activity. The central role of sympathetic nervous system on the LF component is well known, but fluctuations in the LF band are also markedly influenced by parasympathetic nervous system. The LF band is important when characterizing baroreflex sensitivity using spectral methods (see Chapter 3). Oscillations at frequencies in the VLF band are often related to the vasomotor tone of thermoregulation or to the dynamics of hormonal systems, but a precise origin of oscillations in this band is still unknown.

The magnitude of HRV in each frequency band is expressed as power. Since the unit of PSD function is either ms^2/Hz or s^2/Hz depending on the unit of RR interval time series, the unit of HRV power is ms^2 or s^2 . Because the TP and power in each frequency band vary considerably even among healthy subjects of equal age, direct comparisons of power between two subjects can be misleading. For this reason, powers are usually expressed in normalized units, by dividing each power by TP less VLF power. Therefore, normalized powers are not absolute measures either, since they partially reflect the relative powers of LF and HF components.*

The confidence we can have in the accuracy of the power in VLF, LF and HF bands varies, since it is related to the number of full periods of oscillations in each band. If we have a 5 min recording, there are roughly 0–12 periods of the oscillation in the VLF band, 12–45 periods in the LF band and 45–120 periods in the HF band. Although the recommended minimum length of recording for a short-term spectral analysis is 5 min, sometimes it is necessary to use shorter segments due to artifacts, ectopic beats and so on. As a rule of thumb, one can use the criterion that the minimum number of periods be six.[†] In order to have a reliable power estimate, for instance, in the whole LF band, we need at least 2.5 min worth of usable recording. Similarly for ULF power, the minimum recording length is about 1 h.

A typical example of spectral HRV analysis performed with FFT and AR modeling is presented in Figure 2.1. The length of the RR interval time series was 5 min, and it consisted of 349 intervals. The mean RR interval was 856 ms, corresponding to a heart rate of 70.2 bpm. The spectral analysis was done over the whole time series. Before any analysis,

* If we have two cases with equal absolute LF powers but different HF powers, the normalized LF powers are not equal.

[†] This is actually an arbitrary number of periods, but in practice, it has proven to be a useful minimum number.

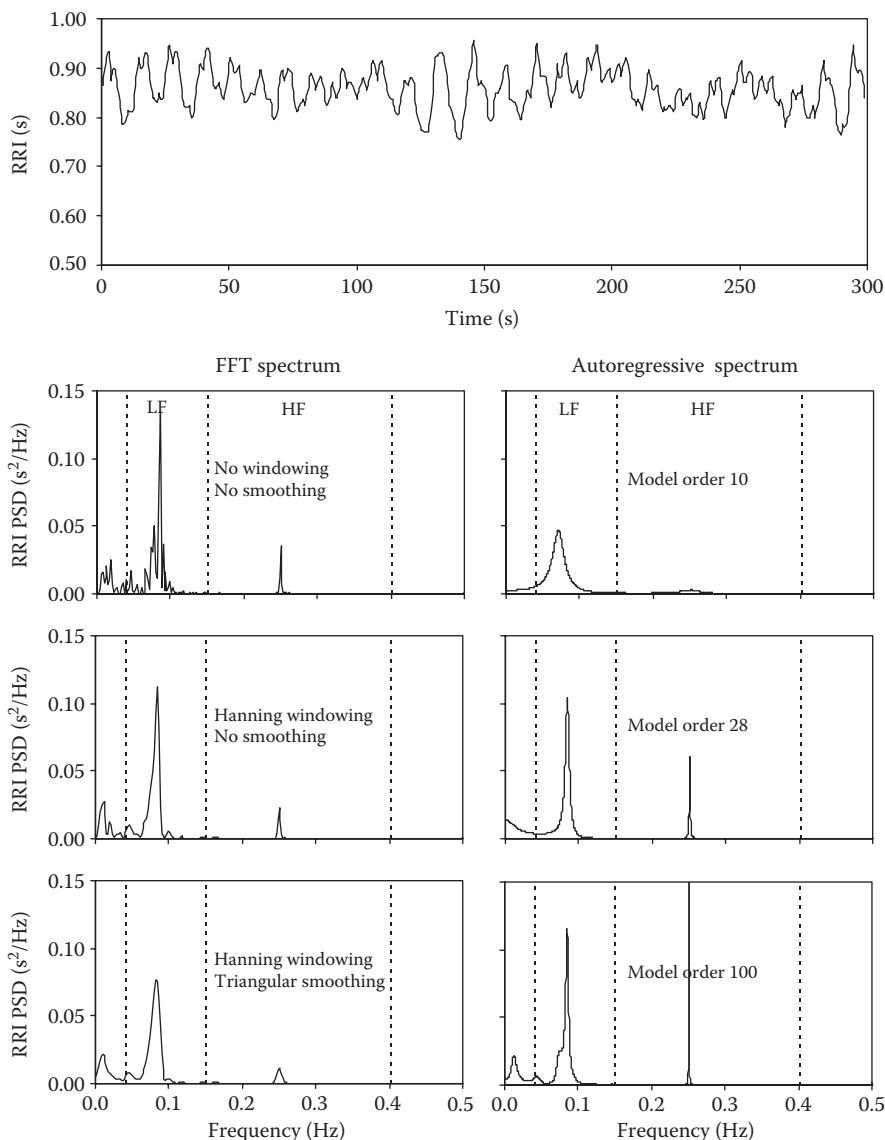
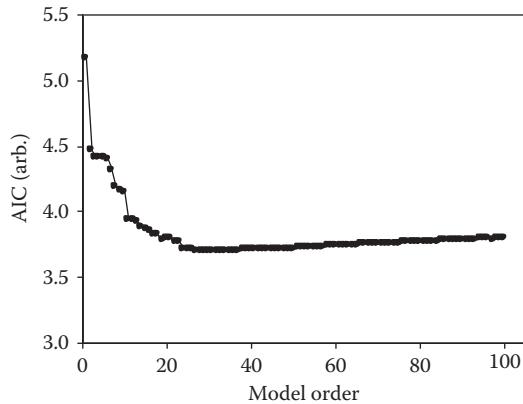


FIGURE 2.1
RR interval time series and corresponding FFT and autoregressive spectrum.

the linear trend was removed. The time series was linearly interpolated and resampled using a sampling frequency of 2 Hz. According to the mean heart rate, the highest relevant frequency f_c was $70.2 \text{ (beats/min)} / 60 \text{ (s/min)} / 2 = 0.585 \text{ Hz}$, well above the upper end of the HF band. The frequency resolution of the FFT spectrum is 0.00195 Hz^* . There are clear peaks in both the LF and the HF bands in all versions of the FFT spectrum (left panels). The HF component is very sharp since metronome-controlled breathing was used.

* After resampling at the sampling rate of 2 Hz (the sampling interval $\Delta = 0.5 \text{ s}$), the 5 min time series has 600 data points. This has been zero padded to the next power of 2; here, it is 1024. The frequency resolution is $1/N\Delta = 1/(1024 \times 0.5 \text{ s}) = 0.00195 \text{ Hz}$.

**FIGURE 2.2**

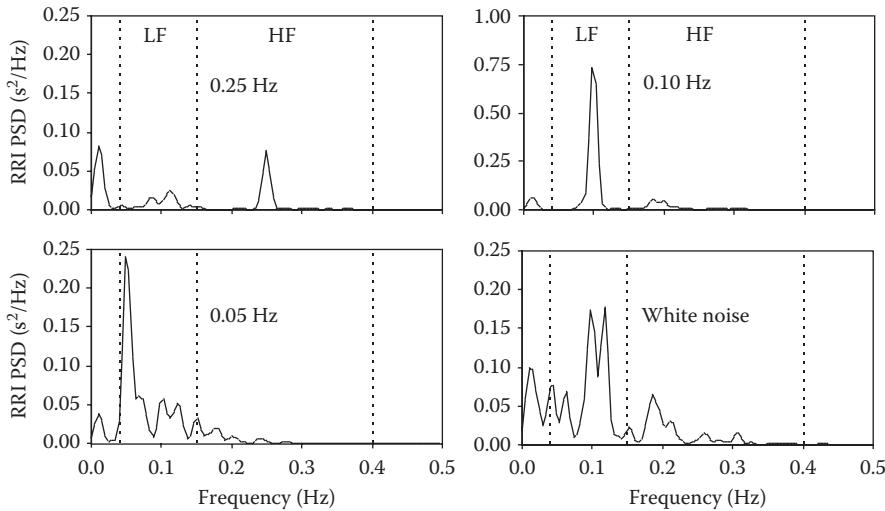
The Akaike information criteria (AIC) of the time series of Figure 2.1 as a function of the model order. The minimum of AIC is reached at the model order of 28.

Without windowing or smoothing, the FFT spectrum clearly includes HF components, which disappear after using the Hanning window function. By also applying triangular smoothing (range 0.01 Hz), the spectrum has even less detail, but the statistical reliability of the spectral features has increased. The AR spectrum (right panels) with the model order of 10 cannot capture all essential features. If the model order is increased to 28 (the optimal model order according to AIC, that is, the order at which AIC is at its minimum value, see Figure 2.2), the spectrum resembles the FFT spectrum. If the model order is further increased up to 100, more spectral details can be seen, especially in the lowest frequencies. It is remarkable how similar the spectral details below 0.05 Hz are in both FFT (windowed and smoothed) and AR spectra (model order 100). Although AIC has a minimum value at 28, it increases very slowly with increasing model order. Thus, it is not always obvious which model order should be selected.

2.4.6 Effects of Respiration

The respiratory component of HRV depends strongly on the breathing volume and its frequency. The HF component decreases markedly as breathing volume decreases. In addition, the power of respiratory peak increases as its frequency decreases. If the breathing frequency is below 0.15 Hz, it becomes measured not as the HF component but as a part of the LF component. The effect of the breathing frequency on HRV is presented in Figure 2.3. The breathing volume was fixed in all cases. When the breathing frequency was fixed at 0.10 Hz (the upper right panel in Figure 2.3), the amplitude of the respiratory peak was approximately 0.25, ten times higher than at the breathing frequency of 0.25 Hz (the upper left panel; note the different scale in the *y*-axis). At a breathing frequency of 0.05 Hz, the peak was still three times higher (the lower left panel).

In practice, the HF component can be used as a measure of parasympathetic tone and vagal activity only in situations in which the breathing frequency and volume are carefully controlled. Controlled respiration at a constant rate, however, can induce some stress, which might affect the function of the autonomic nervous system and therefore interfere with HRV. Using a respiratory frequency that is as close as possible to the natural breathing rate of the subject, one can minimize the stress. This can be accomplished by first measuring the

**FIGURE 2.3**

RR interval FFT spectra at three different breathing frequencies of 0.25, 0.10 and 0.05 Hz and using white noise breathing. Note that the y -scale is different in the case of 0.10 Hz.

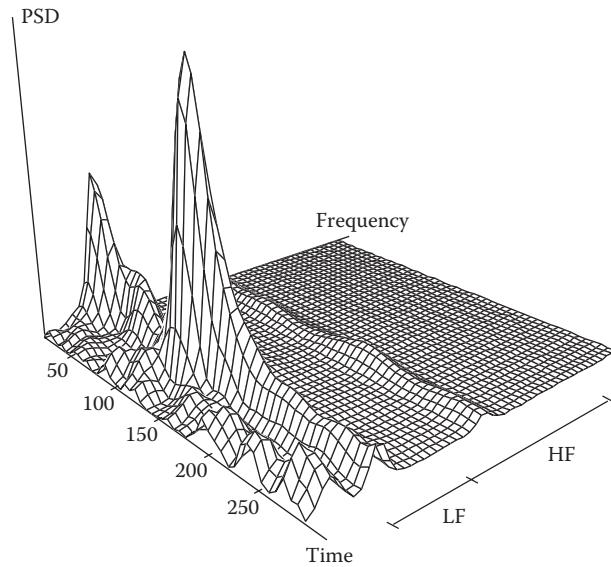
breathing rate and then adjusting the frequency of metronome accordingly. Another possibility is to use white noise breathing, that is, a metronome guides the subject to breathe at variable rates with constant distribution (see the right bottom panel in Figure 2.3).

2.4.7 Time–Frequency Analysis

When considering perturbation of the autonomic nervous system, usual steady-state spectral analysis methods are no longer useful, since they cannot determine exactly when critical frequency components change in amplitude or frequency. Conversely, if information about temporal variations of frequency components were available, spectral features of slowly changing system could be analyzed in more detail, for instance, to estimate the stationarity of a time series. There are many different approaches to perform a time–frequency analysis, and most of them are based on various integral transforms of the original data. The main limitation on all of them is the trade-off between temporal resolution and statistical reliability of spectral components. It is not possible to determine the amplitude of a certain frequency locally because we always need a time window to measure it. A shorter time window can capture more rapid changes within the power spectra in time, but a longer time window can give a more reliable estimate of the amplitude or spectral power.

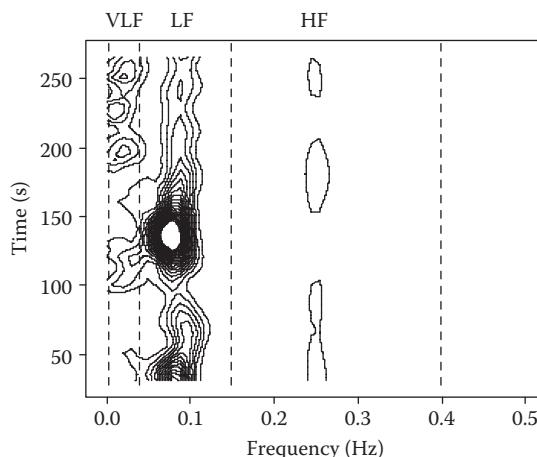
2.4.7.1 Windowed Fourier Transform

The most simple and straightforward time–frequency analysis is called the *windowed Fourier transform* (WFT, also called short-time Fourier transform or STFT). In this approach, the time series is covered by a reasonably short time window that slides over the data in small steps. In each window, the PSD is calculated as described above (e.g., using data windowing, zero padding, trend removing and resampling). As a result, one gets a set of PSDs. In Figure 2.4, we present the results of a WFT performed on the same RR interval data shown in Figure 2.1 as a three-dimensional plot. The width of the window was 60 s

**FIGURE 2.4**

Time-frequency analysis of the RR interval time series using windowed Fourier transform method.

and the step 5 s. The RR interval has prominent low-frequency oscillations around 140 s (see the upper panel in Figure 2.1), and this can be also seen as a large peak in Figure 2.4. Furthermore, the respiratory modulation (the shallow peak in the HF band) seems to be almost constant in time. Although the window step is 5 s, the real-time resolution of the analysis is still approximately 60 s. If there had been an abrupt change in the spectral features of the signal, it would be seen in all the windows covering that moment in time. The same analysis is presented as a contour map in Figure 2.5. This representation reveals that there are a lot of variations in the VLF and LF bands.

**FIGURE 2.5**

Same as Figure 2.4 but displayed as a contour map.

Since the number of periods within the window of WFT depends on the frequency, the statistical reliability is different for each frequency component as discussed in Section 2.4.4. If the width of the window is set for the lower frequency components, it becomes unnecessarily wide for higher frequencies. This feature can be avoided if the duration of the window is inversely proportional to the analyzed frequency. This kind of analysis is called *selective discrete Fourier transform algorithm* (SDA) and can be implemented by normal discrete Fourier transform, but it is computationally intensive (Keselbrener and Akselrod, 1996).

2.4.7.2 Wigner–Ville Distribution

The Wigner–Ville bilinear distribution (WVD) of the continuous function $x(t)$ is defined by

$$\text{WVD}(t, f) = \int_{-\infty}^{\infty} x\left(\frac{t+\tau}{2}\right) x^*\left(\frac{t-\tau}{2}\right) e^{-2i\pi f\tau} d\tau. \quad (2.4)$$

The WVD maps a one-dimensional function of time into a two-dimensional function of time and frequency (Claassen and Mecklenbräuker, 1980a,b; Hyung-Ill and Williams, 1989; Novak and Novak, 1993). For a discrete time series $x(n)$, the distribution (Equation 2.4) can be written in the form

$$\text{WVD}(n, k) = \sum_{\tau=-\infty}^{\infty} W_N(\tau) e^{2\pi i k \tau / N} \left[\sum_{\mu=-\infty}^{\infty} W_M(\mu) K(\mu, \tau) x(n + \mu + \tau) x^*(n + \mu - \tau) \right], \quad (2.5)$$

if the kernel function K and W is equal to 1. This distribution is also called a *smoothed windowed* WVD because of the window functions W_M and W_N . The function W_M is a rectangular window that has a value of 1 for the range of $-M/2 < \mu < M/2$, and W_N is a symmetrical window (often also rectangular), which has non-zero values for the range $-N/2 < \tau < N/2$. The parameter N determines the frequency resolution of the WVD, while the parameter M determines the level of temporal smoothing.

The frequency resolution of the spectrum calculated by the WVD is two times the resolution of the FFT spectrum when using the same length of time window, therefore making WVD more suitable than FFT for shorter time series. However, WVD has another problem: if there are two frequency peaks f_1 and f_2 close to each other, the WVD spectrum also contains small but significant erroneous components at the frequencies $f_1 - f_2$ and $f_1 + f_2$. In the case of multiple dominant frequency peaks, the background of WVD spectrum can be contaminated by many spurious frequency peaks of low amplitude. This feature of the WVD method forces us to be careful when interpreting the finer details of the spectrum. The cross-terms can be suppressed by introducing a suitable non-trivial kernel function K in Equation 2.5, but unfortunately at the price of lower frequency resolution. One example of such a kernel function is the so-called *exponential distribution*.

2.4.7.3 Complex Demodulation

The complex demodulation (CDM) method is a common non-linear method used to define the amplitude of a time series at a specified frequency or frequency band as a function of time (Kim and Euler, 1997). In other words, for a given frequency ω , we assume the signal is of the form

$$x(t) = A(t) \cos(\omega t + \phi(t)) + z(t), \quad (2.6)$$

for which we need to determine the amplitude $A(t)$ and the phase $\phi(t)$. The term $z(t)$ contains all other oscillating components (having a frequency different from ω) and possible noise. In the CDM method, the original real value signal $x(t)$ is rewritten into complex format

$$x(t) = 0.5A(t) \left\{ e^{i(\omega t + \phi(t))} + e^{-i(\omega t + \phi(t))} \right\} + z(t), \quad (2.7)$$

where i is the imaginary unit. In the next step, all frequency components are shifted by $-\omega$. This operation is equivalent to multiplying $x(t)$ by the term

$$y(t) = 2e^{-i\omega t}, \quad (2.8)$$

which gives us

$$x'(t) = A(t)e^{i\phi(t)} + A(t)e^{-i(2\omega t + \phi(t))} + 2z(t)e^{-i\omega t}. \quad (2.9)$$

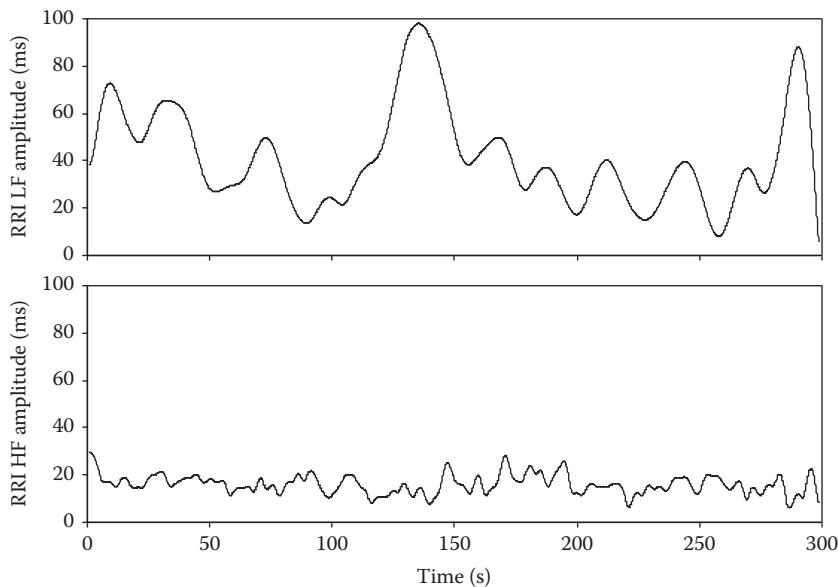
Here, we see that the frequency of the first term is zero and the frequency of the second term is twice that of the component under study. The last term does not contain frequencies around zero, because the component $z(t)$ did not originally contain the frequency ω . If the signal $x'(t)$ is fed into a low-pass filter with a cutoff frequency at zero, we get the signal

$$x''(t) = A(t)e^{i\phi(t)}, \quad (2.10)$$

from which we can easily calculate the slowly and time-dependently changing amplitude $A(t)$ since $A(t) = |x''(t)|$. Likewise, we can get the amplitude of any desired frequency signal as a function of time (by varying ω). If the cutoff frequency is $\Delta\omega$ and not exactly zero, the CDM method picks from the signal only the amplitude of those components with a frequency between $\omega - \Delta\omega$ and $\omega + \Delta\omega$. In this way, it is possible to pick the part of the signal that belongs, for example, to the LF or HF band.

Therefore, theoretically, the CDM method can give the amplitude at every moment of time, but in reality, the temporal resolution depends upon the characteristics of the low-pass filter. If the desired frequency band is to be limited as steeply as possible, one needs to use a higher-order filter, but in that case, one needs more data points to perform filtering, and the time resolution will be lower. In practice, time resolution of the CDM method applied to the RR interval time series is approximately 15 s when analyzing oscillations in the LF band. Any faster changes in the amplitude of oscillations cannot be clearly distinguished. This temporal resolution is, however, clearly better than the resolution obtained with other methods.

The CDM amplitudes of the RR interval data (the same time series as in Figure 2.1) in the LF and HF bands are shown in Figure 2.6. Again we see that there are significant changes in the LF component, but the HF component is almost constant.

**FIGURE 2.6**

The amplitude of the LF and HF components of the RR interval time series (the same data as in Figure 2.1) as a function of time based on CDM method.

2.4.7.4 Other Methods

In the method of sliding window analysis, the Fourier transform can be replaced with AR modeling. If there are significant changes in the structure of HRV data as a function of time, the optimal model order should be obtained individually in each window. A similar approach called *time-variant autoregressive modeling* is suitable for online monitoring (Bianchi et al., 1997). In this method, a new set of AR parameters is computed whenever a new sample value is available, and the weight of the previous samples is controlled by means of a forgetting factor.

The *Wavelet transform* is a general tool for analyzing the temporal changes in time series (Figliola and Serrano, 1997). The continuous wavelet transform (CWT) of the time series $x(t)$ is defined as

$$\text{CWT}(a, \tau) = \frac{1}{\sqrt{a}} \int x(t) \Psi\left(\frac{t-\tau}{a}\right) dt, \quad (2.11)$$

where $\Psi(t)$ is the basic (or mother) wavelet. The wavelet transform, similar to STFT, maps a time function into a two-dimensional function of a and τ . The parameter a is called the scale^{*}; it scales the wavelet function by compressing or stretching it. τ is the translation of the wavelet function along the time axis. There are an infinite number of valid wavelet functions, but all of them are well localized.[†] By contrast, the STFT uses truncated sine waves, which are not well localized. The shape of the wavelet function must be selected according to the application. Furthermore, by increasing the window width in STFT, the

^{*} Inverse of the scale can be interpreted as a frequency.

[†] The wavelet is well localized since it goes rapidly to zero in infinity.

number of periods increases, but in the wavelet transform, basic shape of the wavelet is same; it is only compressed or stretched. All of these features of wavelets make them ideal for capturing rapid temporal changes. Although wavelet analysis has been applied to the HRV signal, results are not superior to those obtained using more traditional approaches (Wiklund et al., 1997).

2.5 Non-Linear Analysis

2.5.1 Approximate Entropy and Sample Entropy

All frequency domain analyses are based on the recognition of certain predetermined patterns. For instance, in Fourier transforms, the pattern is a sinusoidal wave, and in wavelet analysis, the pattern is a certain wavelet function. Another alternative for characterizing the variability of heart rate is to measure the regularity or complexity of the fluctuations without specifying the form of repeating patterns. Entropy is a general approach for quantifying the regularity or information content of the data (Pincus and Goldberger, 1994; Pincus, 1995; Bettermann and van Leeuwen, 1998; Cysarz et al., 2000). There are many ways to determine the entropy of a time series, but most of them require noise-free data and very long recordings. *Approximate entropy* (ApEn) has been developed for measuring the complexity of relatively short time series and it is most useful for HRV analysis where long noise-free recordings are difficult to obtain (Pincus and Goldberger, 1994). Furthermore, ApEn calculations are not based on specific assumptions regarding the internal structure or dynamics of the system.

ApEn is computed as follows. First we construct the so-called pseudo phase space vectors from the initial time series $x(i)$, in which $i = 1 \dots N$, N being the number of data points

$$u(i) = [x(i), x(i+1), x(i+2), \dots, x(i+m-1)], \quad (2.12)$$

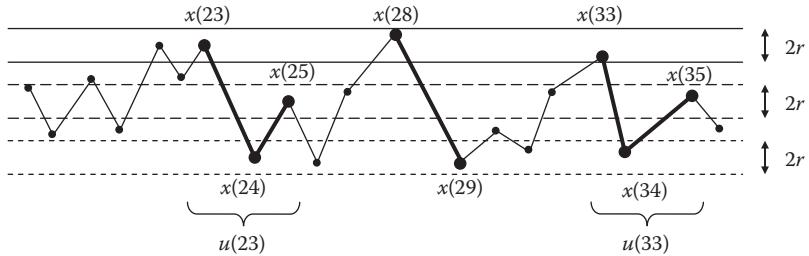
m being the so-called *embedding dimension*.^{*} Vectors $u(i)$ can be interpreted as m -point patterns. First, we select one m -point pattern and search for similar m -point patterns. Two patterns are similar when the maximum distance d between the corresponding components is less than the *tolerance* r (Figure 2.7):

$$d[u(i), u(j)] = \max \left\{ |u(i+k) - u(j+k)| : 0 \leq k \leq m-1 \right\} \leq r. \quad (2.13)$$

The (normalized) number of similar vectors $u(j)$, which are at a distance r from $u(i)$, is

$$C_i^{(m)}(r) = \left\{ \text{the number of index } j \text{ for which, } j \leq N-m+1, d[u(i), u(j)] \leq r \right\} / (N-m+1). \quad (2.14)$$

* The use of pseudo phase vectors is a starting point of many non-linear analysis methods. The idea of these vectors is that they can be used as a *replacement* for the set of true dynamical variables, all of which we cannot measure either for technical reasons or since we actually do not know them. Under certain assumptions, the dynamics of the pseudo phase vectors is similar to the real dynamical variables.

**FIGURE 2.7**

Approximate entropy. An example showing for embedding dimension $m = 2$, a search for similar pseudo phase space vectors. For vector $[x(23), x(24)]$, two nearby vectors, $[x(28), x(29)]$ and $[x(33), x(34)]$, are found to be similar, that is, the distance between $x(28)$ and $x(33)$ and the distance between $x(29)$ and $x(34)$ are both $<$ tolerance value r . Therefore, both $u(28)$ and $u(33)$ increase the quantity $C_{23}^{(2)}(r)$. However, when m is increased to 3, only vector $[x(33), x(34), x(35)]$ is similar to $[x(23), x(24), x(25)]$ and increases $C_{23}^{(3)}(r)$.

Due to normalization, the maximum value of C is 1, and C can be regarded as the probability of finding similar m -point patterns. The same analysis can be performed for all m -patterns. The logarithmic average of probabilities over all m -patterns is

$$\Phi^m(r) = (N - m + 1)^{-1} \sum_{i=1}^{N-m+1} \ln C_i^m(r). \quad (2.15)$$

Approximate entropy is defined as

$$\text{ApEn}(m, r, N) = \Phi^m(r) - \Phi^{m+1}(r). \quad (2.16)$$

One sees that ApEn measures the (logarithmic) conditional probability that similar m -patterns are similar also when looking for $(m + 1)$ -patterns. In other words, ApEn is the averaged probability of finding m -patterns minus the averaged probability of finding $(m + 1)$ -patterns (see Figure 2.7). If the last probability is equal to the first one, $\text{ApEn} = 0$, i.e., the time series is absolutely regular in this sense. However, if the last probability is zero, ApEn gets its maximum value, i.e., the time series is totally irregular.

$\text{ApEn}(m, r, N)$ is dependent on three parameters: the length m of the vectors being compared, the tolerance parameter r , and the number N of data points. This means that direct comparisons always require fixing of parameters. For HRV analysis, $m = 2$ is the value normally used. When the number of data points is increased, ApEn approaches its final value asymptotically. In practice, $N > 800$ and $m = 2$ give a reliable result. ApEn depends strongly on the tolerance parameter r . If r is chosen such that it is a fraction of the SD of the data, ApEn does not depend on absolute variability.* The most frequently used value of r is 15 or 20% of SD.

ApEn is sensitive to smallest trends in the data, because comparison of patterns is based on the absolute values of data. The trend can be removed before ApEn analysis but with

* If r is a fraction of SD, ApEn does not depend on the unit of data, and therefore, it is also possible to compare the ApEn values of different signals, such as RR interval and systolic pressure time series.

cautions as described in Section 2.2.5. One alternative is to use the differentiated data (the difference of successive RR intervals) that eliminate all slow trends, but this operation behaves like a special high-pass filter in the frequency domain. ApEn is not sensitive to changes in single data values if the tolerance parameter is fixed, but if the tolerance parameter is bound to the SD as recommended, the situation could well be different. Ectopic beats especially, if not edited, can alter the SD significantly.

When calculating the number of similar vectors to get ApEn, the similarity of the vector to itself is included in the calculation. This ensures that $C_i^{(m)}(r)$ is non-zero, which is essential for calculating the logarithm. This causes ApEn to give a result most of the time, which implies greater regularity of the signal than may be present.

Sample entropy (SampEn) is calculated in a way that removes the previously described bias (Richman and Moorman, 2000). When calculating the number of nearby vectors, a comparison to the vector itself is prevented:

$$C_i^{(m)}(r) = \left\{ \text{the number of index } j \text{ for which, } j \neq i, j \leq N - m + 1, d[u(i), u(j)] \leq r \right\} / (N - m + 1). \quad (2.17)$$

The average of the probabilities Φ is also defined without logarithms

$$\Phi^{(m)}(r) = (N - m + 1)^{-1} \sum_{i=1}^{N-m+1} C_i^{(m)}(r). \quad (2.18)$$

Now SampEn is defined as

$$\text{SampEn}(m, r, N) = \ln(\Phi^{(m)}(r) / \Phi^{(m+1)}(r)). \quad (2.19)$$

The interpretation and use of SampEn remain exactly the same as for ApEn. However, the dependence on the tolerance parameter r and the number of data points N is different. ApEn reaches its maximum with a certain value of r , but SampEn decreases monotonically as r increases. SampEn is, in principle, also independent of the number of data points N , but with small values of N , its statistical reliability is naturally poor. When r and N are large enough, SampEn and ApEn yield the same result. SampEn provides a more reliable estimate of the complexity of a signal compared to ApEn. It may be used for considerably shorter time series than the ApEn, (<200 points).

Regularity and complexity are often interpreted as being contrary to each other: increased regularity means lower complexity and vice versa, but this is not always true. The degree of regularity can be quantified by evaluating the appearance of repetitive patterns and characterized by entropy measures. Complexity is, however, intuitively associated with *meaningful* structural richness, which can exhibit relatively high regularity. Entropy-based measures grow monotonically with the degree of randomness and they reach highest values from totally uncorrelated random data or white noise. Such data are unpredictable but not actually complex. Thus, entropy measures may lead to misleading results when they are applied to physiological time series such as the heart rate signal. For example, atrial fibrillation (AF) is associated with highly erratic fluctuations with statistical properties resembling uncorrelated noise. The entropy value of such

a signal is high. By contrast, healthy cardiac rhythms that are regulated by multiple interacting feedback mechanisms will yield lower entropy values. This inconsistency is obviously related to the fact that entropy measures are based on single-scale analysis, but many biological systems operate across multiple spatial and temporal scales and hence their complexity is also multiscaled.

To overcome the aforementioned difficulties in interpreting entropy measures, *multiscale entropy* (MSE) analysis has been introduced (Costa et al., 2002, 2005). In this method, the coarse-grained time series determined by the scale factor τ is defined as

$$y^{(\tau)}(j) = \frac{1}{\tau} \sum_{i=(j-1)\tau+1}^{j\tau} x(i), \quad (2.20)$$

where $x(i)$ is the original time series and $1 \leq j \leq N/\tau$. For a scale of 1, the time series $y(j)$ is simply the original time series. The length of $y(j)$ is equal to the length of the original time series divided by the scale factor. In the next step, the entropy of the coarse-grained time series is calculated as a function of the scale factor. In principle, the entropy can be calculated using any method that is reliable for a time series of variable length, and SampEn is a good choice when analyzing the RR interval time series. In order to have good statistical reliability at higher scales, the number of data points must be greater than 10,000. This limits the use of MSE in many clinical studies.

As an example, the MSE method has been applied to three different subjects: one healthy, one with congestive heart failure (CHF) and one with AF (see Figure 2.8). At the scale of 1, the healthy and CHF cases cannot be separated, but if the scale is 5 or 6, large separation can be obtained. Entropy of AF time series is highest at a scale of 1, but it decreases monotonically as the time scale increases, similar to white noise. At a very large time scale, CHF and AF time series cannot be separated any more. We conclude that MSE can distinguish these cases, but it needs computation of the entropy as a function of scale; no single entropy value at a fixed scale is enough.

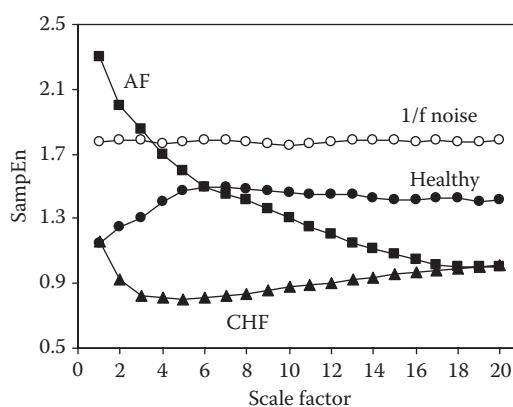


FIGURE 2.8

Multiscale entropy analysis of an RR interval time series derived from healthy subjects, congestive heart failure (CHF) subjects and subjects with atrial fibrillation (AF). As reference, the results of simulated $1/f$ noise are presented.

2.5.2 Scaling Exponents

2.5.2.1 Detrended Fluctuation Analysis

When analyzing a longer time series lasting several hours, identification of oscillatory components or repeated patterns are not the best approach for examining the HRV data. One method is to characterize the internal correlations of the signal. These correlations are expressed by scaling properties and fractal structures. Detrended fluctuation analysis (DFA) presents a possibility for characterizing this as a function of correlation distance (Peng et al., 1993, 1995; Iyengar et al., 1996).

To calculate DFA, we must first form an integrated version of the original time series $x(i)$, where $i = 1 \dots N$, which gives us

$$y(k) = \sum_{i=1}^k (x(i) - \langle x \rangle), \quad (2.21)$$

where $\langle x \rangle$ is the mean of the original time series and $k = 1 \dots N$. Next, we divide the time series $y(k)$ into equally spaced segments with length n as shown in Figure 2.9. For each segment, we calculate separately the local trend by fitting a regression line $y_n(k)$ to the segment. The RMS (root-mean-square) fluctuation of the integrated time series is calculated by removing the linear trend of each segment. Thus,

$$\text{DFA}(n) = \sqrt{\frac{1}{N} \sum_{k=1}^N [y(k) - y_n(k)]^2}. \quad (2.22)$$

In the summation, we must take into account that when the index k is stepped, $y_n(k)$ must be updated when moving into the next segment. DFA is calculated for several different segment lengths, that is, n values. Typically, DFA increases when the segment length increases. If $\log(\text{DFA})$ increases linearly as a function of $\log(n)$, the time series follows (fractal) scaling law, and in this case, the slope α of the linear change, the *scaling exponent*,

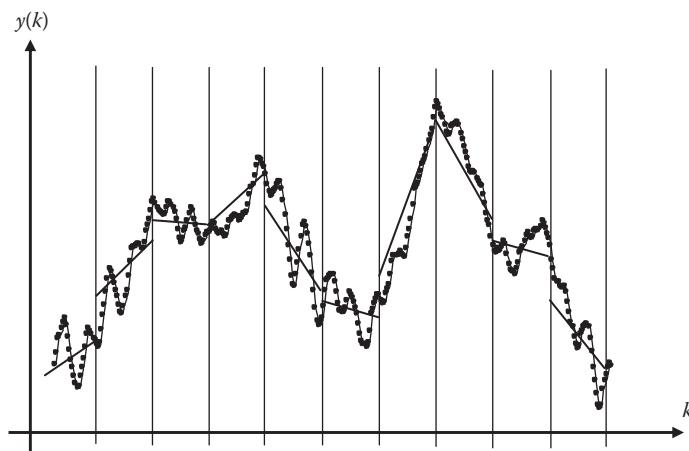


FIGURE 2.9

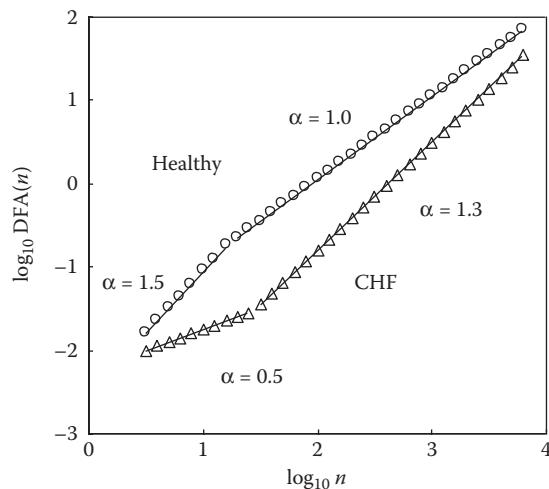
The integrated time series and the local trends.

TABLE 2.1Scaling Exponent α of Certain Type of Time Series

Scaling Exponent	Description of the Signal
$0 < \alpha < 0.5$	Small value followed most probably by a larger value and vice versa
$\alpha = 0.5$	Completely uncorrelated time series, that is, white noise
$0.5 < \alpha < 1.0$	Small value followed most likely by a small value and large value followed most likely by a large value (correlated)
$\alpha = 1.0$	$1/f$ type noise
$1.0 < \alpha < 1.5$	Noise of variable type
$\alpha = 1.5$	Brownian $1/f^2$ noise (integral of white noise)

defines the type of scaling. Different values of α correspond to specific types of time series as presented in Table 2.1.

A typical DFA of long RRI time series is shown in Figure 2.10. A heartbeat has short-range correlations reflecting the baroreflex mechanism, as well as long-range correlations, which are related to the efforts to keep the variation of the beat cycle within certain limits. The measurement of the long range correlations requires that the time series under investigation be preferably at least a few hours long so that the statistical reliability would be at least reasonable. The limit for short- and long-range correlations is set typically to 10 or 11 beats (corresponding to 2.4 on the logarithmic scale). The long-range scaling exponent α_L for a healthy patient is ≈ 1 , which corresponds to $1/f$ behavior. The short-range scaling exponent α_S may vary, but it is usually between 0.5 and 1.5. Many factors affect it, such as the functioning of the baroreflex mechanism, breathing modulation and so on. With a longer time series, there always exists the possibility that the measured correlations are not at all a characteristic of the system but rather reflect environmental effects.

**FIGURE 2.10**

DFA as a function of the number of segments for healthy and CHF subjects.

2.5.2.2 Spectrum Power Law Exponent

Long-range correlations of a time series may also be analyzed using the spectrum of the signal. In this case, we can study the lowest-frequency components of the spectrum and try to characterize its shape using simple exponential law. If we presume that for a certain frequency spectrum we have $1/f^\beta$, the scaling exponent β can be calculated by presenting the spectrum on a log-log scale and by fitting a line over the desired frequency range (Iyengar et al., 1996; Bigger et al., 1996). The slope of the line gives the spectrum power law exponent. The value of the exponent varies between 0 and 2. The border line case 0 corresponds to a flat spectrum, that is, white noise, and the value 2 corresponds to Brownian noise. Usually, the frequency range 0.0001–0.01 Hz of the spectrum is studied, and this corresponds to an oscillation period of 1 min to several hours. For the above definition to make sense, the HRV time series must be several hours long. The spectrum is calculated almost without exception using the FFT algorithm. Because the spectrum has a rather irregular form, especially at the lowest frequencies, the use of some smoothing method is desirable. Replacing the regression line with a less sensitive fitting method may also improve the reliability of the result.

2.5.3 Fractal Dimensions

2.5.3.1 Correlation Dimension

The dynamics of a system can be described by measuring its attractor (the path toward which the system converges) *dimension*. Especially for chaotic systems, the attractor can be fractal, in which case its dimension is not an integer. Knowing the dimension of the attractor may also help getting useful information about the characteristics of underlying systems. The correlation dimension (CD) is one of the simplest methods for estimating the attractor dimension (Grassberger and Procaccia, 1983; Kantz and Schreiber, 1995; Yum et al., 1999). The CD is sometimes referred to with the designation D_2 .

The basis for the calculations once again is in the reconstruction of time series in the multidimensional phase space $x(i)$, where $i = 1 \dots N$, by using the vectors of the pseudo phase space $u(i) = [x(i), x(i+1), x(i+2), \dots, x(i+m-1)]$, where m is the embedding dimension. Next, we calculate for each vector $u(i)$, how many attractor points are at a distance r as measured from the observation point

$$C_i^m(r) = \left\{ \text{the number of index } j \text{ for which, } j \leq N - m + 1, d[u(i), u(j)] \leq r \right\} / (N - m + 1), \quad (2.23)$$

where the distance d is defined (i.e., differing from the ApEn method) as the normal Euclidian distance

$$d[u(i), u(j)] = \left(\sum_{k=1}^m |u(i;k) - u(j;k)|^2 \right)^{1/2}. \quad (2.24)$$

Next, we calculate the mean of the quantities $C_i^m(r)$ over all vectors, from which we compute the so-called correlation integral

$$C^m(r) = \frac{1}{N - m + 1} \sum_{i=1}^{N-m+1} C_i^m(r). \quad (2.25)$$

CD is defined as a limit

$$\text{CD}(m) = \lim_{r \rightarrow 0} \lim_{N \rightarrow \infty} \frac{\log C^m(r)}{\log r}. \quad (2.26)$$

In practice, with limited data sets, these limits cannot be calculated with certainty and therefore the CD is defined as the slope of the regression line calculated from a log–log representation and over a range with the required linearity.

When calculating CD, the embedding dimension m must be selected so that it is at least $2D$, where D is the dimension of the system under study, that is, the number of real dynamical variables. In order for the correlation integral to describe the attractor accurately, the number of data points should exceed 10^m . For example, when studying the blood pressure regulation system, we may assume that the number of dynamical variables is >4 , which means that the time series must be very long. In addition, it is nearly impossible to find such a range of the distance r , in which $\log C^m(r)$ changes linearly as a function of $\log r$, because of the noise contained in the data and non-stationarity of the data. Due to these limitations, the calculation of the correct CD for biosignals is computationally not easily achieved. Despite this fact, computation of the correlation dimension may still be useful. Promising results have been achieved by using $m = 20$ and by searching for the mean slope within $0.01 < C^m(r) < 0.1$. The quantity calculated in the above fashion without forgetting the aforementioned limitations is called the *modified correlation dimension*. This quantity cannot accurately define the real dimension of the system, but nevertheless, it does give a measure of the complexity of the system, that is, when CD increases, the system becomes more complex.

2.5.3.2 Pointwise Correlation Dimension

Pointwise correlation dimension (CDi) is defined in a very similar way compared to CD, but instead of labeling the time series with a single value, it is calculated as a function of time (Farmer et al., 1983; Mayer-Kress et al., 1988). This gives us the possibility of evaluating changes in the system characteristics as a function of time, which is very important in non-stationary cases. CDi is sometimes referred to as D2i.

When searching for the regression line, we must once again select the range in which the relation is linear and use a high enough embedding dimension value. When calculating the CDi, we can set $m = 20$ (similar to computing the CD above) and select the area $0.01 < \text{CDi}(r) < 0.1$. In addition, we must note that even though CDi is calculated at each point and it can therefore in principle follow changes in data, the calculation of CDi at any point requires its calculation at all other points. For this reason, CDi is not applicable to non-stationary time series. Thus, in practice, it is advisable to use an additional condition that states that when calculating the regression line at each point in a log–log representation, the correlation factor of the achieved line must exceed a certain limit (e.g., 0.8), and if this criterion is not fulfilled, the CDi value at the point in question is not reliable.

2.5.3.3 Dispersion Analysis

Dimension analysis of a time series may also be performed by studying the curve describing the time series itself rather than the dynamical system behind the signal. This approach

toward analyzing RR intervals is similar to image analysis. Because complex behavior of the dynamical system manifests itself in complicated patterns in the measured time series, a study of the curve's fractal structure will also give information regarding the system itself.

In dispersion-based analysis, we first calculate from the time series, the standard deviation

$$\text{SD}(1) = \frac{1}{N} \sqrt{N \sum_{i=1}^N x^2(i) - \left(\sum_{i=1}^N x(i) \right)^2}, \quad (2.27)$$

where $x(i)$ is the time series having N data points. Next, we compute the mean of two consecutive data points, (for the entire time series) resulting in a new time series of $N/2$ data points. For this new time series, we again calculate the standard deviation $\text{SD}(2)$. This is continued with group sizes 4, 16, 32 and so on until there are less than 4 data points left in the time series. By repeating the above process, we have a series of standard deviation values $\text{SD}(m)$. When we plot $\log \text{SD}(m)$ as a function of $\log m$, a line can be plotted through the points if the original time series curve was fractal. For this fractal object, the dimension is $\text{FD-DA} = 1 - \text{slope of the line}$ (Bassingthwaite and Raymond, 1995; Yum et al., 1999). Fractal dimension defined in this way can have values between 1 and 1.5, where 1 represents the case of a steady-state signal and 1.5 represents maximal fractal characteristics.

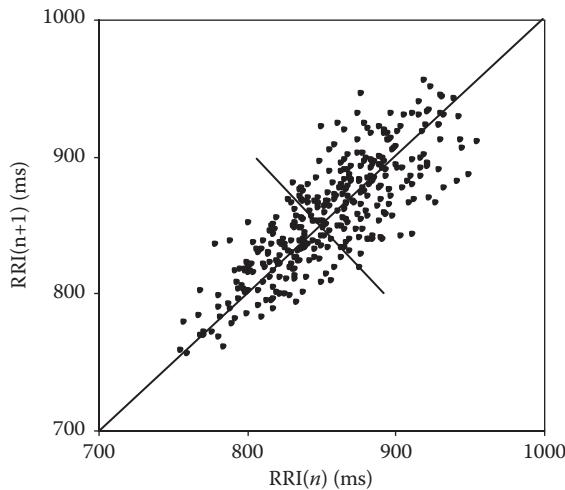
If the curve under study is not purely fractal, that is, it contains a sizeable amount of noise, the $\text{SD}(m)$ values do not exactly fit a line in log-log representation. For automated analysis when this line is not visually verified, one can set a minimal correlation of 0.8 as a measure of linearity.

2.5.4 Return Map

Dynamical systems are usually described by a group of differential equations. If the variables get values only at specific discrete moments in time, as is the case with the RR interval time series, the differential equations can be replaced with discrete equations, for example,

$$\begin{aligned} x_{i+1} &= F(x_i, y_i, z_i, \dots) \\ y_{i+1} &= G(x_i, y_i, z_i, \dots), \\ z_{i+1} &= H(x_i, y_i, z_i, \dots) \\ &\vdots \end{aligned} \quad (2.28)$$

where x, y, z and so on are dynamical variables of the system and F, G, H, \dots are functions that define the dynamics. Usually, these functions are not known, but we may try to solve for them by examining the measured time series. If there is only a single variable, the equation is expressed in a simpler form:

**FIGURE 2.11**

A return map made from an RR interval time series. Standard deviation along the diagonal ($SD_2 = 5$ ms), standard deviation perpendicular to the diagonal ($SD_1 = 18$ ms).

$$x_{i+1} = F(x_i). \quad (2.29)$$

Because this expression binds the new value x_{i+1} of the variable to its predecessor value x_i , we can solve function F in principle, by pairing successive values of the time series, (x_i, x_{i+1}) for $i = 1$ to $N - 1$, and plotting them on a two-dimensional graph. This kind of a graph is called a return map.* If the dynamics of x is wholly determined by function F and there are enough data points, the method should reveal the shape of the function F .

If the dynamical system behind the time series is not one dimensional, suggesting that more than one variable has an impact on the system, a return map formed on the basis of a single measured variable naturally cannot solve functions F , G and so on. Even in such cases, a single variable return map may prove to be useful, although it is a certain type of projection of the multidimensional system into a single dimension. Figure 2.11 shows the return map of an RR interval time series. The points are typically scattered to form an ellipsoid but can also form complex structures. When the return map is an ellipsoid, it can be characterized by two quantities: the SD in the direction of the diagonal SD_2 and the SD in a direction perpendicular to SD_2 , i.e., SD_1^{\dagger} (Huikuri et al., 1996; Woo et al., 1994). These deviations are, by nature, measures of variability, since they quantify the movement of the system in a phase space. However, when the return map has a complex shape, above parameters do not describe the variability very well.

* This is also called Poincaré or Lorenz plot or map.

[†] For RR interval, SD_1 is the same as RMSSD $\sqrt{2}$.

2.5.5 Other Approaches

2.5.5.1 Stationarity Test

An example of a simple stationarity test that mainly measures changes in the baseline signal is as follows: the signal is divided into segments of suitable length and for each segment, the signal average is calculated. When SD of these averages is divided by the SD of complete signal, we get a measure of stationarity (Palazzolo et al., 1998). This measure is small if the signal is stationary. The length of the segment should be chosen so that it is not too long in order for the local changes to be detectable, but it cannot be too short either in order to prevent the averages of the segments from varying too much. For an RR interval time series, a good choice is to use 20 beats/segment. If the measure is < 0.3 , the signal can be considered to be reasonably stationary.

2.5.5.2 Symbolic Dynamics

The basic idea of this method is to characterize the original time series with a much simpler and coarser symbolic notation which, however, retains the essential dynamic characteristics of the original time series. This is done by converting the time series into a string of symbols. By this, we reduce the study of dynamics into handling of a symbol string. Naturally we lose most of the information contained in the original time series, but nevertheless, we retain key dynamical features, in a *coarse-grained form* (Voss et al., 1995, 1996; Palazzolo et al., 1998).

The conversion of a time series into a symbol string may be done using several methods. One of them is described in Figure 2.12. The signal is divided into two or more value ranges, depending on how many symbols we wish to utilize. Value ranges may be absolute bands or based on signal averages or SD. For example, if we have four different symbols, we may use the following bands:

- A signal \leq average – SD
- B average – SD $<$ signal \leq average
- C average $<$ signal \leq average + SD
- D signal $>$ average + SD

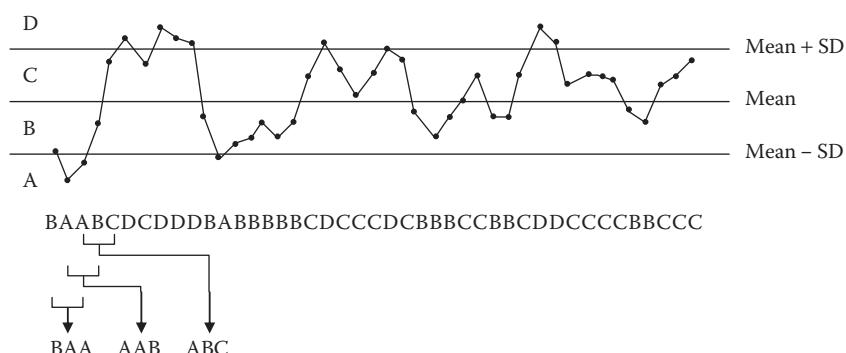


FIGURE 2.12

Conversion of the time series into a symbol row and grouping of the symbol row into words.

After the bands have been selected, the time series can be converted into a symbol string. The next step involves grouping the symbols in the string into *words*. A word is always formed by stepping forward one step in the symbol string. If we choose a word length of 3 and we have 4 different symbols, we get altogether $4 \times 4 \times 4 = 64$ different words. Each word corresponds to a specific graphical representation, which has at least a rough connection to the original dynamics. Different words do not have same probability because HRV dynamics favors certain words. The distribution of the words can thus be interpreted as a probability distribution. The shape of the distribution may itself act as a basis of further analysis, but it is also possible to measure the order related to the distribution in the terms of entropy. The simplest such measure is Shannon's entropy.

2.5.5.3 Multifractal Analysis

A monofractal signal can be described using just one scaling exponent α or Hurst exponent $h = \alpha - 1$, and in these situations, DFA, for example, is a valid method. If a signal is *multifractal*, a set or continuum of Hurst exponents is needed corresponding to a generalized fractal dimension $D(h)$ (Ivanov et al., 1999; Amaral et al., 2001). Multifractal analysis is based on the wavelet transform (Equation 2.11) and the scaling properties of its local maximums (see computational details in Muzy et al., 1991). As a result, we get the fractal dimension as a function of the Hurst exponent.

A typical multifractal analysis of an RR interval time series of 25,000 data points of a healthy subject and a CHF subject is shown in Figure 2.13. In the healthy subject, $D(h)$ has a peak at $h = 0.1$ ($\alpha = 1.1$), and in the CHF subject, $D(h)$ has a peak at $h = 0.2$ ($\alpha = 1.1$). Thus, there is only a minor difference, and both cases resemble a $1/f$ type of dynamics (see Table 2.1). However, $D(h)$ of the CHF subject has a very narrow span in h , corresponding almost to monofractal behavior, but the healthy subject has very wide $D(h)$, indicating true multifractal dynamics. This result clearly reflects the common belief that the complexity of the system decreases as heart rate control degenerates.

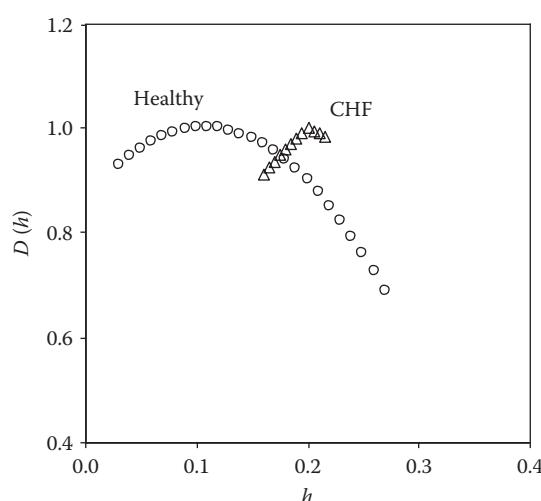


FIGURE 2.13
Fractal dimension $D(h)$ as a function of Hurst exponent h .

2.5.5.4 Stochastic Modeling

The unpredictable portion of the heart rate fluctuation can be due to chaotic dynamics, but there is an alternative explanation: the system includes a real stochastic component. The basic idea behind stochastic modeling is that the unpredictable component is not a perturbation but an essential part of the dynamical behavior of the system. The source of this true noise can be physiological, or it may be a reflection of external disturbances. If the system is truly stochastic, it cannot be described by a deterministic model; rather a stochastic one is needed. Many stochastic systems can be described by the *Langevin* equation

$$\frac{dX(t)}{dt} = g(X(t)) + h(X(t))\Gamma(t), \quad (2.30)$$

where $X(t)$ is the state of the system at moment t , and functions g and h represent the deterministic and stochastic parts of the time evolution. $\Gamma(t)$ is the uncorrelated white noise with zero mean and Gaussian distribution. It has been shown that the *difference version* of Equation 2.30,

$$X(t+\tau) = X(t) + g(X(t)) + h(X(t))\Gamma(t), \quad (2.31)$$

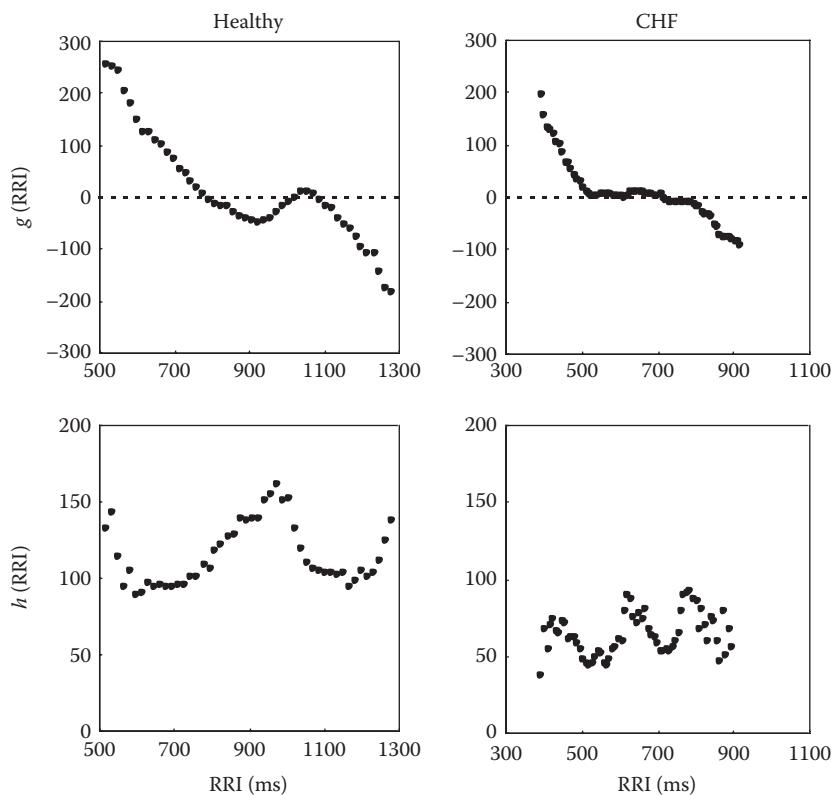
where τ is a finite delay parameter (2–20 min), can model the long-term RR interval time series (Kuusela, 2004; Kuusela et al., 2003). The control functions g and h can be extracted from the data by computing conditional probability distributions. In practice, 50,000–100,000 data points, that is, 12–24 h of RR intervals, are needed in order to determine these distributions reliably. Results from an analysis of 24 h recordings of RR interval are shown in Figure 2.14. At small (large) RR interval values, the deterministic part g is clearly positive (negative); this guarantees that the RR interval is kept within certain limits.* In the case of the healthy subject, typical g function has three zero-crossings (two stable fixed points and one unstable fixed point†) in the middle, but with the CHF subject, g function is flat, indicating a less complex dynamical control. The stochastic parts h have a complicated structure in both cases, but the mean level of the h function is smaller in the CHF subject, which can be interpreted as a lower stochasticity of the system.

2.6 Conclusions

Heart rate fluctuations can be analyzed using many different methods and approaches. No single method described here is clearly superior to other techniques, and therefore, it

* When the RR interval is small, the g function and also the derivative in Equation 2.30 are positive; thus, the RR interval increases. Similarly, when the RR interval is large, the g function and the derivative are negative; thus, the RR interval decreases.

† If we omit the stochastic part in Equation 2.30, the zeros of the g function correspond to the fixed points of the system. At the fixed points, the derivative is zero and the system has no tendency to change. Fixed points can be either stable and attract all nearby states or unstable and repel nearby states.

**FIGURE 2.14**

The deterministic control function g and the stochastic control function h for healthy and CHF subjects.

is recommended that researchers use several techniques in combination. The physiological interpretation of results is often difficult, especially in the case of non-linear methods and further investigation is needed. However, the time series analysis of RR interval data has proven to be useful and it has already gained significant clinical relevance. It would be very useful to agree on common rules or guidelines about when to use each method, the length of the time series needed, normative values and the kind of editing or filtering operations, so that the results from different laboratories can be compared.

Abbreviations

AF	Atrial fibrillation
AIC	Akaike information criteria
ApEn	Approximate entropy
AR	Autoregressive
CD	Correlation dimension
CDi	Pointwise correlation dimension
CDM	Complex demodulation

CHF	Congestive heart failure
CWT	Continuous wavelet transform
DFA	Detrended fluctuation analysis
FFT	Fast fourier transform
FPE	Final prediction error
HF	High frequency
HRV	Heart rate variability
LF	Low frequency
MDL	Minimum description length
MSE	Multiscale entropy
NN50	Number of pairs of adjacent RR intervals differing by more than 50 ms
pNN50	Ratio of NN50 count to the count of all RR intervals expressed as a percentage
PSD	Power spectral density
RMSSD	Root mean square of successive differences of RR intervals
SampEn	Sample entropy
SD	Standard deviation
SDA	Selective discrete Fourier transform algorithm
SDANN	Normal-to-normal standard deviation of all 5 minute segments averaged over 24 hours
SDNN	Normal-to-normal standard deviation
STFT	Short-time Fourier transform
TP	Total power
ULF	Ultralow frequency
VLF	Very low frequency
WFT	Windowed fourier transform
WVD	Wigner–Ville distribution

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3

Methodological Aspects of Baroreflex Sensitivity Analysis

Tom Kuusela

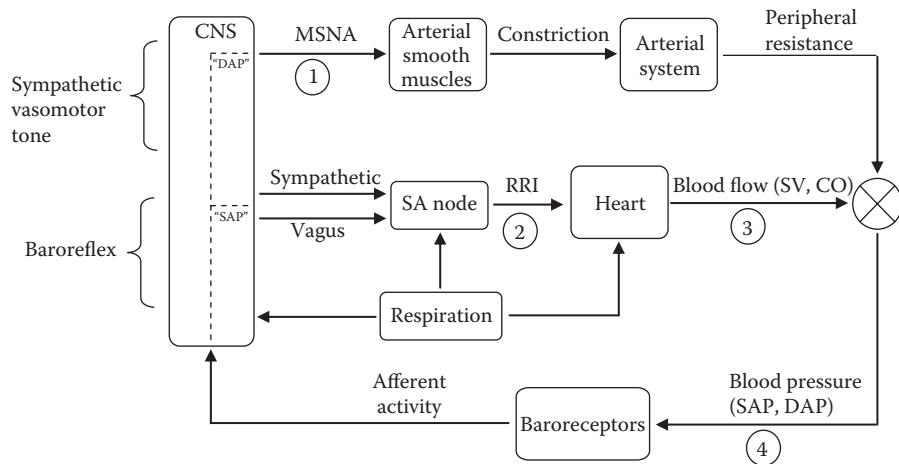
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3.1 Introduction

The essential task of the cardiovascular blood pressure control system is to deliver sufficiently high blood pressure to maintain various functions of the body and its organs. If the blood pressure is too low or too high, blood flow cannot be maintained. For example, when a person stands up, blood tends to stay in the lower body due to gravity and the blood pressure regulatory system must respond quickly in order to maintain sufficient blood flow to the brain. If response of the hemodynamic system is not quick, the person would faint almost immediately. The body must also adapt to a wide range of physical workloads in which muscles must receive a sufficient supply of oxygen-rich blood. Thus, a blood pressure control system that can maintain stable blood pressure in the face of rapidly changing demands is a fundamental requirement for our health.

The blood pressure regulatory system can be considered to be a feedback system, consisting of sensors (the baroreceptors that measure blood pressure at select locations in the body), a processing unit (residing in the central nervous system) and an output unit (the autonomic nervous system, which adjusts blood pressure by changing heart rate, cardiac contractility and resistance of the peripheral blood vessels). A diagram of this system is shown in Figure 3.1. Baroreceptors are specialized nerve cells, which measure blood pressure indirectly by sensing the stretch of blood vessels. Baroreceptors are abundant in aorta and carotid arteries and can also be found in larger veins. Put simply, blood pressure is regulated by adjusting heart rate and peripheral resistance according to the input from pressure-sensing baroreceptors. This system can compensate, within

**FIGURE 3.1**

Simplified model of the blood pressure regulation system. CNS, central nervous system; MSNA, muscle sympathetic nervous activity; SA, sinoatrial; RRI, RR interval; SV, stroke volume; CO, cardiac output; SAP, systolic arterial pressure; DAP, diastolic arterial pressure. The signals 1–4 are, in practice, measurable. In the linear model, the natural pairs of signals are DAP (input)–MSNA (output) and SAP (input)–RRI (output).

certain limits and conditions, including changes in blood pressure imposed upon the body due to positional changes and exercise loads caused by different activities. In reality, the situation is certainly much more complex because both sympathetic and parasympathetic parts of the central nervous system adjust the overall system in many different ways. In addition, time scales of adjustments range from two consecutive heartbeats to several hours and even days. This chapter will focus on those parts of the blood pressure control system in which the response may be measured within few tens of seconds.

Baroreflexes operate not only to control abrupt changes in the arterial pressure but also to maintain different levels of steady-state pressure. Baroreflex activity can be studied in one of the two ways: either by studying heart rate responses to external perturbations, such as mechanical (e.g., using lower body negative pressure or neck suction) or pharmacological manipulations (e.g., vasoactive drugs) that produce sudden and large changes in blood pressure or by studying heart rate responses to spontaneous fluctuations in blood pressure. The difference between these two approaches is significant. When a strong external input is applied to baroreceptors by forcing a rapid change in the arterial pressure, changes in blood pressure are mainly determined by the external stimulus. In this situation, the relationship between blood pressure and heart rate are approximated by an *open-loop* model. By contrast, under conditions of spontaneous fluctuations in arterial pressure, all control mechanisms and feedback loops are fully active and an estimation of the baroreflex gain is based on a *closed-loop* model. Another difference is that in the first approach, full dynamic range of the system can be explored, while in the second approach, responses are limited to a smaller range around baseline conditions.

A measure of the capability of baroreflex to adjust heart rate to changing conditions is called baroreflexivity or baroreflex sensitivity (BRS). BRS is commonly measured as a ratio of the change in heart rate (quantified by its reciprocal, the RR interval) in response to a

fixed change in the blood pressure. Its unit is “ms/mmHg,” and is usually positive.* A higher BRS value indicates that the system strongly reacts to pressure changes, that is, the system is more sensitive. The idea behind BRS is to try to characterize the quality of operation of the entire blood pressure regulatory system with a single numerical value, which, by itself, is a tall order. Nevertheless, the BRS has been found to be a useful measure with clear diagnostic relevance. The goal of this chapter is to describe techniques used to measure the BRS.

3.2 Slope Method

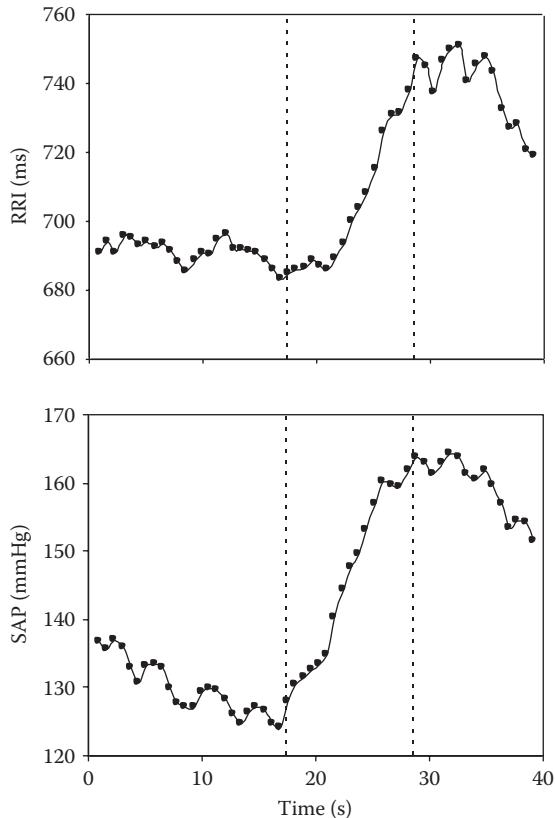
This is the most traditional method used for measuring BRS and is used routinely in clinical medicine. The basic idea of this method is to perturb the blood pressure control system and measure the response to such a perturbation. The most common technique is to give an intravenous bolus of phenylephrine to raise the blood pressure or nitroprusside to lower the blood pressure, while simultaneously recording electrocardiogram and blood pressure waveforms.

Figure 3.2 shows the results of a typical phenylephrine test (the subject was a 56-year-old male). The systolic pressure increases and the heart rate correspondingly decreases, that is, the RR interval becomes longer. From an analytical point of view, the problem is how to select an area of interest, because exact moments of pressure rise and heart rate slowing may be difficult to define. Unfortunately, the estimated BRS value is sensitive to these choices.

The simplest way of calculating BRS would be to measure absolute changes in the systolic arterial pressure (SAP) and RR interval from a baseline, but the difficulty lies in defining the baseline. Instead, BRS is calculated by plotting the SAP and the corresponding RR interval as (x, y) value pairs and fitting a regression line. BRS is then defined as the slope of this regression line. Figure 3.3a shows such an (x, y) pair with a BRS of 1.46 ms/mmHg and a correlation coefficient of 0.947, which indicates a rather good fit. This method does, however, make a basic assumption. When the (x, y) pair is formed using simultaneous SAP and RR interval values, it is assumed that the system has no delay or that the delay is extremely short, that is, a change in the pressure would cause an immediate change in heart rate. Many studies have shown that the above assumption is not true.

Figures 3.3b, 3.3c and 3.3d show corresponding curves when the RR interval time series is shifted by two, four or six beats from the beat at which the blood pressure (BP) value was obtained. In this example, we can see that the correlation depends on the delay and has the highest value when the delay is four beats and is actually better than that with no delay. In this particular case, a delay of four beats corresponds to a delay of more than 3 s. It is unknown whether such a delay is due to an internal delay of the control system. On the other hand, different patients may have large differences in their response times, and

* Positive BRS means that the RR intervals lengthen when the blood pressure rises and vice versa. Under certain circumstances where the baroreflex system is not properly working, apparent BRS can momentarily be negative. When analyzing spontaneous *small fluctuations* of the RR intervals and SAP, it is not uncommon to see sequences of beats with lengthening (shortening) RR intervals and decreasing (increasing) SAP. These *non-baroreflex* influences can be important when characterizing the overall effectiveness of cardiac control.

**FIGURE 3.2**

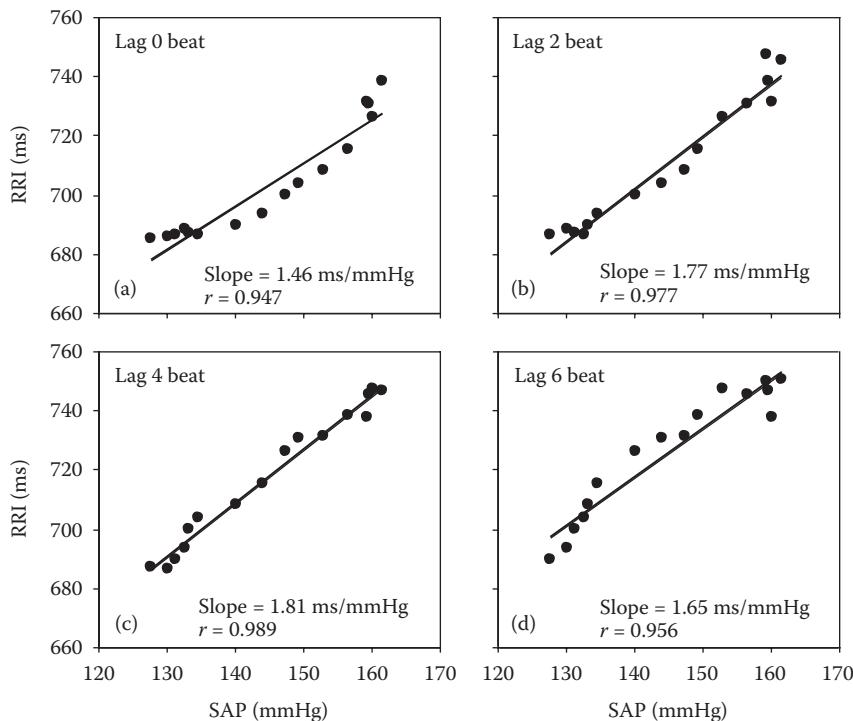
RR interval and SAP time series from a phenylephrine test. The rise of systolic blood pressure and the lengthening of RR interval appear in the time range between dotted lines.

therefore, analyzing the delay makes sense. As we can see from Figure 3.3, different delays produce varying values of the BRS.

3.3 Advanced Slope Method

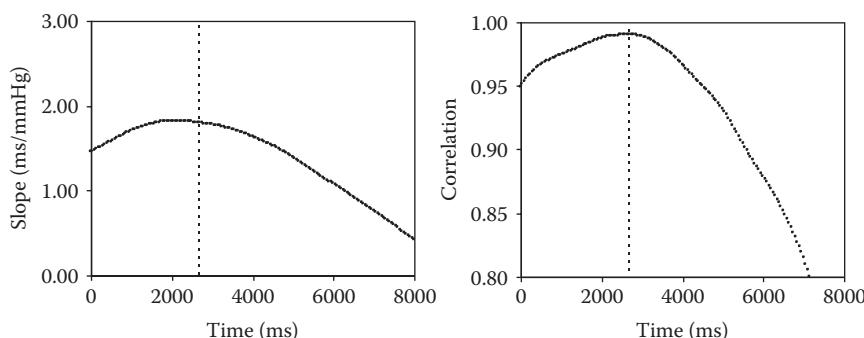
The slope method described in the previous section may be used to estimate the delay at which the best fit between the SAP and RR interval values can be achieved, but such a delay cannot be measured in steps that are smaller than one beat. An improvement may be achieved by interpolating both time series and resampling them at a higher frequency and study the effects of smaller delays. However, this method also has its drawbacks because effects of interpolation are difficult to estimate. Since both RR intervals and SAP values are basically time series without underlying continuous signals, corresponding phase may not be preserved between them.

After interpolation and resampling, one could use (x, y) pairs to compute the BRS with different delays. But the search for an optimal delay that produces the highest correlation factor of the regression line would be tedious using manual methods. Instead, the analysis can be automated by calculating both the slope of the regression line and the correlation

**FIGURE 3.3**

The SAP and RR interval values from Figure 3.2 as (x, y) pairs. (a–d) The beat lag was 0, 2, 4 or 6 beats. The slope and correlation coefficient of the regression lines at these lags are indicated in each panel.

coefficient as a function of delay. Figure 3.4 represents an example using such an approach. Both signals have been sampled at 20 Hz, in which case the delay may be adjusted in 50 ms steps. The result shows that the BRS (left panel) changes as a function of the delay and has a maximum between 2000 and 3000 ms. In practice, the shape of the function varies from one patient to another but often has a maximum.

**FIGURE 3.4**

The slope of the regression line and correlation coefficient as a function of the delay between the SAP and RR interval calculated for a phenylephrine test and for a rising of blood pressure. Maximum correlation of 0.990 (marked by a dotted line) is reached at a delay of 2650 ms and the corresponding slope value is 1.80 ms/mmHg.

The correlation coefficient in our example (right panel) has a maximum value at 2650 ms, where the BRS is 1.80 ms/mmHg. In this case, the BRS value would not change much even if we were to increase the delay; but this is not always the case and a maximum may lie in the part where the slope changes drastically, resulting in a strong dependence of the BRS on the delay. Even though an optimal delay between RR intervals and BP values defined earlier cannot be directly linked to a physiological mechanism, the method does present a unique way defining the delay and a corresponding BRS value. One should note that the selection of the area of interest in recorded waveforms still affects the final result. One may be able to further improve the method by optimizing (e.g., in terms of correlation) the starting and ending time points. However, it is not clear whether the maximum correlation would then correspond to a physiologically meaningful situation.

3.4 Sequence Method

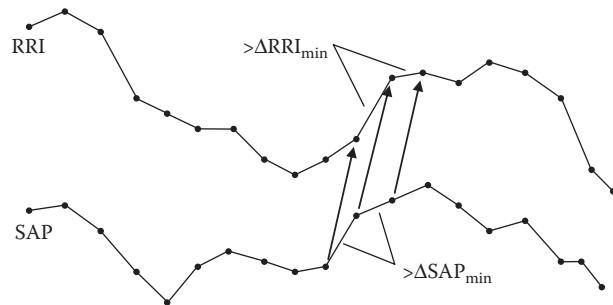
In the sequence method, BRS is evaluated as described in the slope method in Section 3.2, but instead of concentrating on a singular pressure rise or fall, the calculation is performed multiple times during a recording (Bertinieri et al., 1988; Parati et al., 1988; Hughson et al., 1993; Parlow et al., 1995). In this case, the pressure rise and fall are not externally induced. Instead, naturally occurring fluctuations of these signals are utilized.

There are certain conditions that must be satisfied before we accept a sequence for BRS calculations. First, in the sequence to be used, both SAP and RR interval signals must rise or fall monotonically in the same direction for at least three beats. Normally, one uses RR intervals that have been advanced by a beat in order to compensate for an assumed adjustment delay between the blood pressure and the corresponding RR interval. Second, each consecutive change of SAP and RR intervals must exceed a certain preset value. This condition acts as a filter, which removes random noise related changes and affects how many acceptable sequences are found. The preset value is chosen empirically on a case-by-case basis.* A minimum change of 0.5 mmHg in SAP and a change of 1 ms in RR interval may be used to begin with. These values correspond to typical resolution in the measurement of these signals. In the sequence method, one usually analyzes the rising (BRS Up-Up) and falling (BRS Down-Down) sequences separately, since underlying physiological mechanisms are assumed to be different, mainly because of asymmetry between baroreceptor stimulation and deactivation.

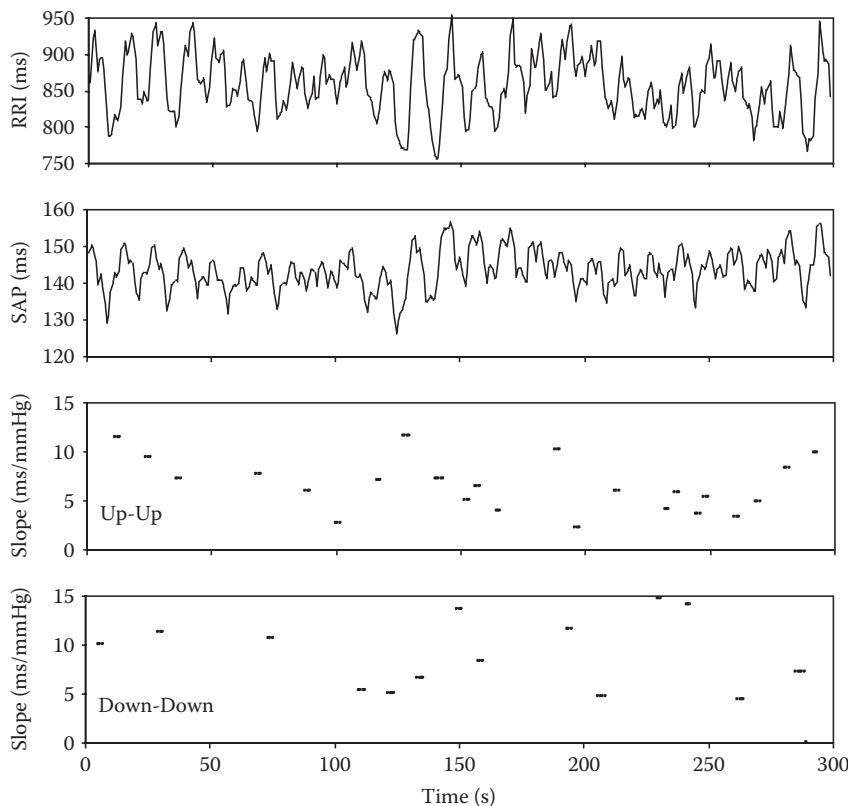
Figure 3.5 contains a short stretch of simultaneously recorded SAP and RR intervals with a rising sequence that fulfills above requirements. A regression line is fitted to the SAP (x) and RR interval (y) values belonging to the sequence. The slope of the regression line gives the BRS value. When the whole time series is analyzed in a similar fashion, often acceptable sequences are found only intermittently, as shown in Figure 3.6.[†] In this example, the length of almost all valid sequences is three beats and only a few have a length of four beats. BRS values calculated using the sequence method typically have a

* The minimum acceptable change of RR interval and SAP should be as small as possible in order to get the maximal number of regression lines, but the limits should not be too small, because false sequences may be generated due to noise within the signals. Limits close to the resolution of the signals are normally a good starting point.

[†] BRS by the sequence method is not continuous in such a sense that it cannot be determined for each heartbeat.

**FIGURE 3.5**

In the sequence method, sequences with a minimum of three consecutive rising (or falling) values in SAP and RR interval values are identified. To be considered valid, the consecutive values must exceed a present limit of ΔSAP_{min} and ΔRRI_{min} . For each sequence, SAP[n] and RR[n + 1] interval values are interpreted as an (x, y) pair data to which a regression line is fitted. The slope of the line is the BRS value at that time point.

**FIGURE 3.6**

SAP and RR interval signals and the baroreflex sequences acquired using the sequence method. Analysis is performed separately for ascending (Up-Up) and descending (Down-Down) sequences. Average Up-Up BRS = 6.5 (20.6% of all beats) and Down-Down BRS = 9.1 (14.9% of all beats).

large standard deviation. Only 15%–20% of all heartbeats may yield acceptable sequences for estimating the BRS, although other beats may contain useful information. The percentage of acceptable sequences of all heartbeats, typically 15%–20%, may also contain useful information.

The BRS values acquired using the sequence method differ from BRS values acquired using phenylephrine-based tests because both definitions and methods of computation are significantly different. During intravenous drug challenge, blood pressure is strongly perturbed and the system may be considered to have shifted, albeit temporarily, to a different operating point. By contrast, for the sequence method, the system is allowed to oscillate freely around a stable operating point. Another issue to consider is the source of these naturally occurring fluctuations. Detailed research suggests that most of these oscillations are caused by breathing, which modulates both blood pressure and heartbeat signals. An example of a BRS computation (Up-Up sequence of heartbeats) and the corresponding respiratory flow (to a metronomic breathing set at 15 breaths/min) signal are shown in Figure 3.7. The beginning of each valid sequence marked by a vertical dotted line coincides with the peak flow of the expiratory phase (positive values of the flow signal). Consequently, results acquired using the sequence method may depend on the depth of breathing and the breathing frequency. The number of valid sequences is affected by both these respiratory variables. If the heart rate is low, the RR interval is >1 s and breathing occurs in phase with a metronome (e.g., in this instance, set to 4 s intervals), sometimes sequences in practice do not contain three consecutive rising data values, in which case an evaluation of BRS is not possible.

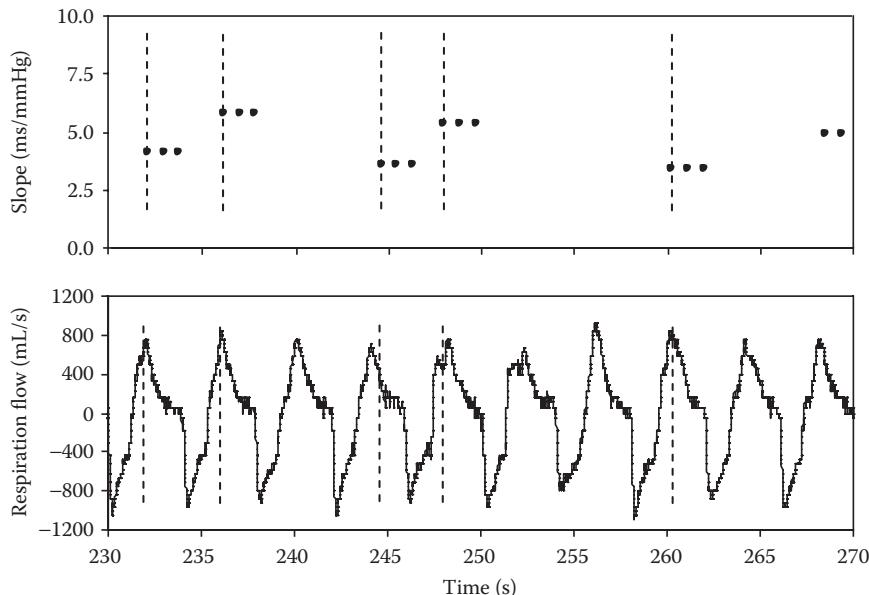


FIGURE 3.7

Part of Up-Up BRS sequences from Figure 3.6 and the respiratory flow signal. Positive flow values indicate expiration, and negative flow values indicate the inspiration phase. The start of the Up-Up sequences (all of them are three beats long) coincides with the peak flow of the expiration phase.

3.5 Spectral Methods

The baroreflex mechanism may also be studied using the power spectra of both RR interval and SAP signals (de Boer et al., 1985, 1987; Robbe et al., 1987; Airaksinen et al., 1997; Herpin and Ragot, 1997). Figure 3.8 shows the spectra of both signals computed using fast Fourier transform (FFT). Both spectra consist of two major frequency bands. The first is modulated by breathing (HF), which, in this example, was set at 0.25 Hz (corresponding to a 4 s time period) using a metronome. The second frequency band is due to an oscillation related to the pressure regulatory mechanism, with a frequency of about 0.1 Hz (corresponding to a 10 s time period). In addition, it is also possible to observe oscillations with a period of 1–2 min (frequency band around 0.0167 Hz), which may be correlated with the body's temperature regulation system or other hormonal control mechanisms (Kitney and Rompelman, 1977).

Power spectrum of the heart rate and blood pressure signal is divided into different bands according to physiological mechanisms and experimental evidence. Researchers have assigned fast, mainly breathing-related components to the HF band (0.15–0.4 Hz). Adjustments primarily related to the sympathetic nervous system are thought to be reflected in the LF band (0.04–0.15 Hz). The rest of the power relates to slow changes occurring in the VLF band (0.003–0.04 Hz). If the recording time is long (>30 min), it is also possible to define frequency components belonging to the ULF band (<0.003 Hz). The condition of whether the breathing component actually lies in the HF band depends on the test setup. Without a metronome, the natural frequency of breathing may be low (~6/min or at 0.1 Hz), causing the respiratory component to shift to the LF band.

Because the power spectrum reflects the strength of different frequency components in a signal, the absolute height of a specific peak might be used as a measure of particular

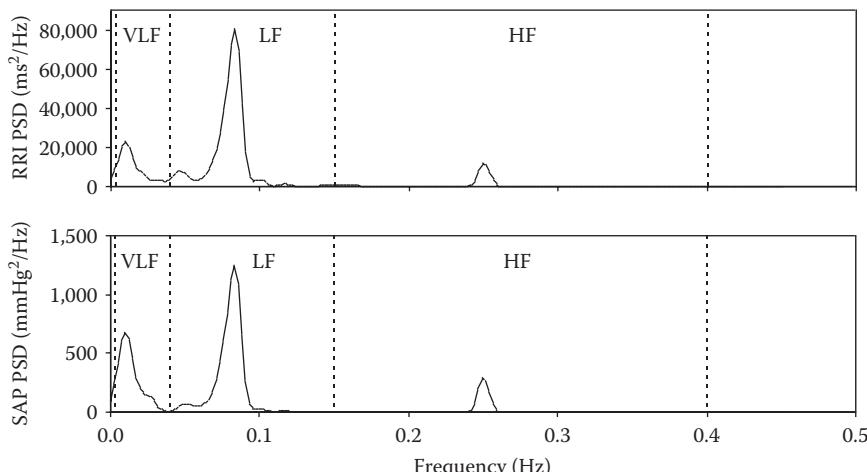


FIGURE 3.8

The power spectral density (PSD) of RR interval and SAP signals computed using the FFT method. Recording time of signals was 5 min. The spectral peaks related to breathing (0.25 Hz) and blood pressure regulation (0.1 Hz) are clearly visible. The VLF band is likely due to temperature and hormonal control mechanisms.

components; but, in practice, this is not recommended.* One reason could be that the absolute height of the peak may vary depending on the algorithm used for calculating the power spectral density. It is also possible that the desired band may contain more than a single peak. A better way of assessing the relative effect of a certain frequency component in a signal is to calculate the integral of the spectrum over a certain frequency band. This is a natural approach as the integral over the whole spectrum gives variance, and its square root corresponds to the standard deviation of the signal under consideration, in time domain.

Spectral BRS may be defined in many ways. A possible choice is to use the power in LF band:

$$\text{BRS}_{\text{LF}} = \sqrt{\frac{\text{RRI power in LF band}}{\text{SAP power in LF band}}} \quad (3.1)$$

If we assume that the blood pressure is regulated mainly by LF band oscillations, this definition is intuitive. Because spectral power of RRI is represented by ms^2 and that of SAP is measured in mmHg^2 , the BRS_{LF} is represented as ms/mmHg . In the example provided in Figure 3.8, $\text{BRS}_{\text{LF}} = 8.2 \text{ ms/mmHg}$.

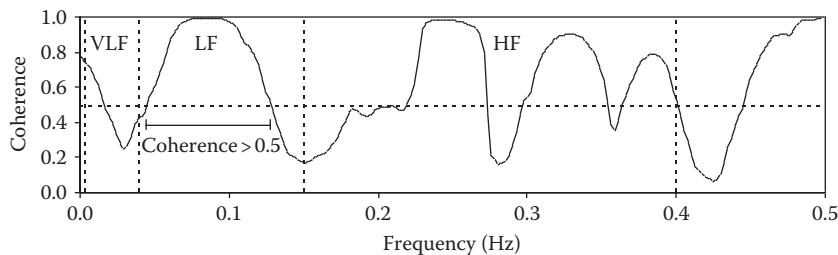
The approach described above does not guarantee that the oscillations in the RR interval and SAP signals would in any way be *synchronized* or are even correlated with each other. For example, if during a recording, a "real" oscillation appears at the beginning in the RR interval but not in the SAP and the opposite occurs at the end of the recording, the BRS calculation described above will give a spurious estimate. In order to ascertain that both the signals have same frequency components and that their phase relationships are taken into consideration, we need to calculate both coherence and phase difference as a function of frequency between the two signals. Figure 3.9 shows the coherence between SAP and RR interval signals. Coherence indicates how two signals correlate at a certain frequency. Coherence values range from 0 to 1. A coherence value of 1 indicates that the signals behave more coherently in that frequency band. In the example shown in Figure 3.9, coherence is high corresponding to the 10 s oscillation period (0.1 Hz) and also at the breathing frequency. From these results, one can conclude that at these frequencies both the SAP and RR interval signals oscillate similar to each other.[†] It must be noted that the coherence does not indicate how strong the oscillations are but merely measures their similarity. For example, high values of coherence can be observed on the right of the HF peak, but the spectra in Figure 3.8 show that there are no significant components at these frequency bands. We can now redefine BRS as

$$\text{BRS}_C = \sqrt{\frac{\text{RRI power in LF band over those frequencies where coherence} > 0.5}{\text{SAP power in LF band over those frequencies where coherence} > 0.5}} \quad (3.2)$$

The basic idea of this definition is to integrate spectral density only over those frequency bands in which coherence exceeds a certain limit, usually 0.5. This guarantees that the integral will not contain bands in which oscillations are not synchronized.

* See details of spectral calculations in Chapter 2.

[†] When two signals oscillate coherently on a certain frequency band, it means that the amplitudes of both signals have the same time dependence and the phase difference is constant. It does not mean that both signals have the same phase.

**FIGURE 3.9**

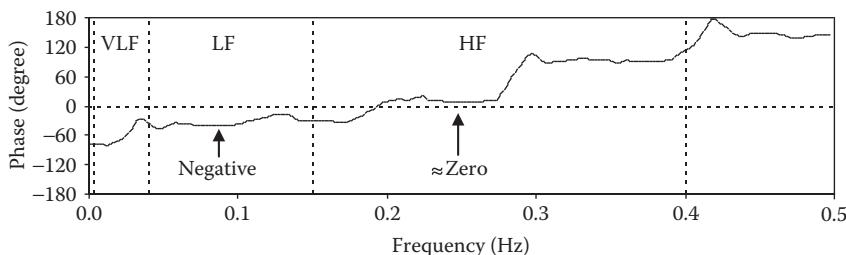
Coherence between SAP and RR interval signals as a function of frequency.

The use of coherence greater than 0.5 does not guarantee that changes in the SAP would occur before changes in RR interval, although that is what we would expect on the basis of general principles of blood pressure control system. A plot of phase differences between the two signals as a function of frequency is shown in Figure 3.10. We can observe that the phase difference is negative in the LF band. This implies that changes in the SAP preceded changes in the RR interval as expected. On the other hand, the phase difference at the breathing frequency is nearly 0, from which we can conclude that oscillations of the SAP and RR interval signals are in phase. We can further conclude that breathing seems to affect both signals simultaneously. These observations give clear indications regarding the nature of the blood pressure regulation system. Now we can define a new BRS parameter:

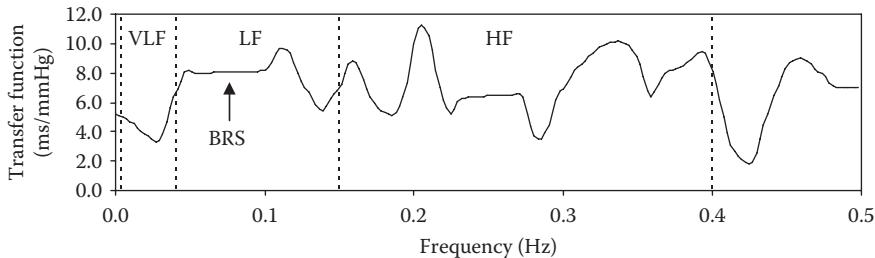
$$\text{BRS}_{\text{CP}} = \sqrt{\frac{\text{RRI power in LF band where coherence} > 0.5 \text{ and phase} < 0}{\text{SAP power in LF band where coherence} > 0.5 \text{ and phase} < 0}} \quad (3.3)$$

Nevertheless, it should be noted that even these improved spectral methods used for the calculation of BRS do not guarantee that there is any *causality* between the SAP and RR interval signals, because a phase difference defines only the phase relationship between the two signals and not which signal leads the other. In practice, this is not a major limitation, since based on our knowledge of cardiac physiology, the SAP signal is the independent variable.

BRS may also be defined as a function of frequency without calculating the power spectra but using the transfer function. The basic assumption in transfer function-based analysis is that the system under investigation may be modeled as a linear system in which

**FIGURE 3.10**

Phase difference of SAP and RR interval signals as a function of frequency. If the phase difference is negative, a change in SAP occurs before a change in RR interval.

**FIGURE 3.11**

The transfer function between the SAP and the RR interval as a function of frequency.

the SAP signal is the input and the RR interval signal is the output. Then, the transfer function indicates the gain of the system at each frequency. It indicates the strength of the output signal (RR interval) when a specific change occurs in the input signal (SAP). The transfer function, therefore, is mathematically equivalent to BRS and has the same unit as BRS (ms/mmHg). Figure 3.11 is an example of a typical transfer function. The transfer function does contain useful information about the system, from an engineering perspective, but to gain any clinical use one must somehow specify a reduced set of easily comparable quantities. The best method is probably to calculate the mean value of the transfer function over those frequencies (within the LF band) where the coherence value exceeds 0.5.

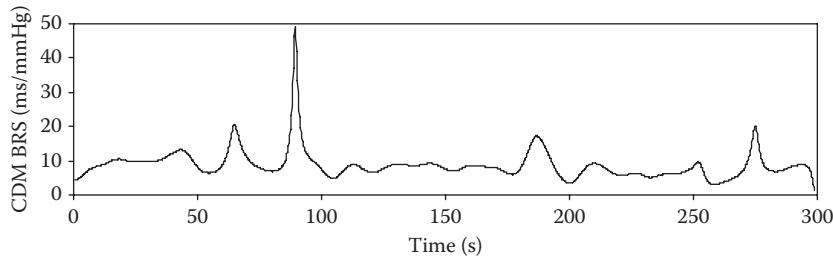
3.6 Complex Demodulation Method

Complex demodulation (CDM) method is a non-linear method used to define the amplitude of a time series as a function of frequency or a frequency band (Hayano et al., 1993; Kim and Euler, 1997). In other words, if the signal to be studied is given by the equation,

$$x(t) = A(t) \cos(\omega t + \phi(t)) + z(t), \quad (3.4)$$

we must determine the time-dependent amplitude A and phase ϕ . The term $z(t)$ contains all other oscillating components (having a frequency different from ω) and possible noise. The computational method for determining the amplitude A by CDM is described in Chapter 2. By varying the parameter ω and the cutoff frequency of the low-pass filter, we can estimate the amplitude of any frequency component or a frequency band, as a function of time from the signal to be analyzed.

When the CDM method is applied to RR interval and SAP signals with a center frequency $\omega = 0.09$ Hz and a cutoff frequency of the low-pass filter set at $\Delta\omega = 0.05$ Hz, the CDM method chooses the LF band components. When the amplitude of the RR interval signal estimated in this way is divided by the amplitude of the SAP signal, it results in a novel method of calculating BRS. Figure 3.12 shows an example of results based on such an analysis. The BRS values computed using CDM are quite stable, with values around 10 ms/mmHg. There are occasional high BRS values. If the amplitude of the SAP signal

**FIGURE 3.12**

BRS as a function of time as calculated using the CDM method for the RR interval and SAP time series shown in Figure 3.6.

drops in the LF band, it usually causes a peak in the BRS since the SAP amplitude is the denominator in the BRS formula. In this method there is no control over whether the signals are coherent with respect to each other or whether a change in the SAP signal precedes a change in the RR interval. The essential idea is that the amplitude of both signals at low frequencies are compared at each specific moment in time. An advantage of this method is that it has a high temporal resolution of about 15 s. This is better than the resolution that can be achieved using any of the spectral methods described in Section 3.5.

3.7 Autoregressive Moving Average Analysis

If one wants to analyze the baroreflex mechanism in more detail than provided by previous methods, another option is to model the blood pressure regulatory system. Because a realistic physiological model is inevitably very complex, one must make certain assumptions and simplifications. A natural starting point in such a case is a linear model referred to as the autoregressive moving average (ARMA) approach (O'Leary et al., 1999; Patton et al., 1996). This section describes such a model consisting of two input signals, SAP and RSP (respiratory) time series, and one output signal, which is the RR interval time series. We can generalize this as

$$\text{RRI}_k = \sum_{i=1}^L a_i \text{RRI}_{k-i} + \sum_{i=M_0}^M b_i \text{SAP}_{k-i} + \sum_{i=N_0}^N c_i \text{RSP}_{k-i} + e(k). \quad (3.5)$$

The first term on the right side of the equation is the autoregressive (AR) component and the next two terms form the MA (moving average) components. The basic idea of the model is that the new RR interval depends linearly on the previous RR intervals, SAP and RSP values. The last term represents the noise, which is uncorrelated with the signal. The fundamental purpose of the ARMA analysis is to fit the model with the data under investigation. If the *model order* parameters L , M and N and *delays* M_0 and N_0 are fixed, the calculations can be easily performed using, for example, the method of least squares, in which case one gets the best values for the *coefficients* a_i , b_i and c_i . In general, those model orders and delays are not known in advance. Several different strategies have been

proposed for determining the optimal set of parameters (Perrot and Cohen, 1996), but details of these methods are beyond the scope of this chapter. It suffices to say that, in general, the problem is quite complex. One option is simply to fix the model orders and delays and use the same basic model for all analyses. In such a case, that the model may deemed to be too simple to explain the signal under investigation. On the other hand, if the model order is very high, it may erroneously try to model the noise contained within the signal. The basic idea is to try to determine a model that is as simple as possible and yet will explain the signal under investigation as completely as possible. Under such conditions, the term $e(k)$ in Equation 3.5 will contain only white noise. It should be noted that if the real system is, in fact, non-linear, even the best ARMA model would not be able to describe output signal adequately.

After estimating the order of AR and MA terms and corresponding delays and coefficients, the model may also be used to evaluate BRS. In principle, the factor b_1 corresponds to the relationship between RR interval and SAP signals, thus representing an estimate of the BRS. In reality, however, coefficients of the model may vary significantly, although signals themselves might not. Because of such variations, a better approach is to investigate the system impulse response. The impulse response is not easily affected by minor variations in various signals. When calculating the impulse response, the SAP signal is set as a pressure pulse of 1 mmHg, with a length of one beat, after which the response in the RR interval signal is calculated using the ARMA model. This type of impulse response investigation actually corresponds to a simulated phenylephrine test. Figure 3.13 is an example of an impulse response. In Equation 3.5, model order for the AR component was set at 8. The model was unstable for higher model orders and significantly lower model orders could not generate any clear response. The model order for the SAP component was increased until no change in the output was observed and the final value was 18. The model order for respiration volume did not affect the output much and it was fixed at 4. The delays M_0 and N_0 were 1. Figure 3.13 shows that the RR interval increases immediately after the pressure pulse is applied. It reaches a maximum after a delay of approximately 2 s and then decays gradually. BRS is defined as the maximum value reached following the application of impulse input. Another method of calculating the BRS using the ARMA

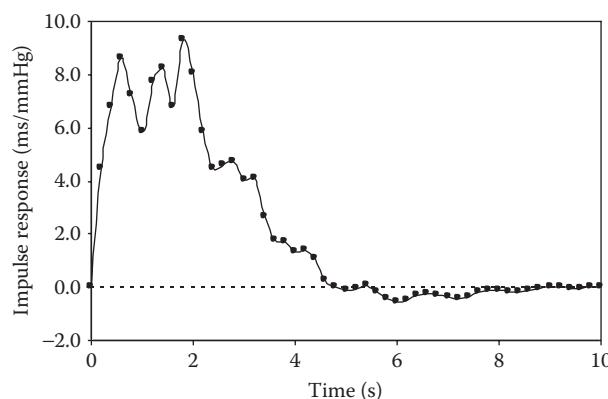


FIGURE 3.13

Impulse response calculated using ARMA analysis with RR interval as output signal with SAP and breathing volume as input signals. The maximum value that the impulse response reaches after the impulse is applied is an approximation of BRS, which in this case would be 9.3 ms/mmHg.

model is to calculate the response to a step pulse, which is, in fact, the time integral of the impulse response.

The ARMA model is, in principle, perhaps an optimal method to estimate the BRS because, on one hand, the model takes into account time-related delays and causality and on the other hand, it may well be sensitive to the selection of model order and delays. In addition, the usability of a model requires that the system explores its phase space, in order for the linear model to quantitatively describe the characteristics of the system. This requirement may be better fulfilled by regulating the breathing rate such that the breathing frequency spectrum resembles a white noise distribution. In practice, breathing at widely varying frequencies in a controlled manner is rather difficult and which by itself may fundamentally alter the system under investigation. It is also possible to use spontaneous variation of an individual subject's breathing pattern, but in such an instance, inter-subject variability could pose problems.

3.8 Conclusions

Physiological and clinical significance of assessing BRS has been demonstrated in many studies on cardiovascular homeostasis in health and in disease. BRS can be quantified in many ways, such as measuring the response to an external stimuli or by utilizing spontaneous fluctuations in RR interval and instantaneous arterial blood pressure signals. These methods are not mutually exclusive but should be used together to study the autonomic regulation of blood pressure. Results of computing BRS based on either time or frequency domain are not directly comparable to each other. In summary, one may state that they represent two distinct methods used to study the regulation of blood pressure in clinical medicine.

Abbreviations

AR	Autoregressive
ARMA	Autoregressive moving average
BP	Blood pressure
BRS	Baroreflex sensitivity
CDM	Complex demodulation
CO	Cardiac output
DAP	Diastolic arterial pressure
FFT	Fast fourier transform
HF	High frequency
LF	Low frequency
MA	Moving average
MSNA	Muscle sympathetic nervous activity
PSD	Power spectral density
RRI	RR interval

RSP	Respiratory
SA	Sinoatrial
SAP	Systolic arterial pressure
SV	Stroke volume
ULF	Ultralow frequency
VLF	Very low frequency

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4

*Arterial Blood Pressure Waveform Analysis and Its Applications in the Assessment of Vasovagal Syncope**

Juan Carlos Perfetto, Ricardo O. Sirne, Aurora Ruiz and Carlos E. D'Attellis

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4.1 Arterial Blood Pressure

The arterial blood pressure (ABP) is a measure of the pressure (force per unit area) of blood against the walls of arteries. It is commonly expressed as two numerical values: the maximum pressure measured during contraction of ventricles, that is, systole (systolic blood pressure [SBP]), and the minimum pressure measured during relaxation of ventricles, that is, diastole (diastolic blood pressure [DBP]). Pulse pressure (PP) is the difference between SBP and DBP.

$$\text{PP} = \text{SBP} - \text{DBP}.$$

4.1.1 Measuring ABP: Continuous and Non-Continuous Methods—Invasive versus Non-Invasive Methods

For most of our history, we have only been able to obtain discrete values of ABP, namely, SBP and DBP, using the non-invasive method of auscultation (the Riva-Rocci method) that we are all familiar with (Guyton and Hall, 2000). The oscillometric method (Webster, 1997) is also non-invasive and produces discrete ABP measurements. Conversely, continuous measurement of ABP has been undoubtedly associated with invasiveness, because insertion of a pressure sensor inside the blood vessel by way of arterial catheterization was the only method available for obtaining continuous ABP measurement until almost the end of twentieth century.

4.1.2 Traditional Clinical Assessment of the Arterial Pressure

Although the shape of continuous peripheral arterial waveform was described toward the end of the nineteenth century (Mahomed, 1872; Roy, 1881; Guyton and Hall, 2000) and was expected to provide diagnostic information, physicians have paid little, if any, attention to the morphology of blood pressure waveform. This is likely due to the development of the auscultation method by Korotkov in 1905, which measures only the maximum (SBP) and minimum (DBP) values of the arterial pressure in brachial artery. It has advantages of being easy, reliable, non-invasive and cheap. The auscultation method assumes that the measured signal is quasi-stationary, which is only true if the subject is at rest and not perturbed during examination. SBP and DBP can be used to estimate a third hemodynamic parameter, the mean arterial pressure (MAP), which is defined as the average arterial pressure during a cardiac cycle. MAP is computed from the normalized area below the continuous arterial pressure waveform. One approximation of MAP uses the following formula:

$$\text{MAP} = \text{DBP} + (\text{SBP} - \text{DBP})/3.$$

This estimation utilizes SBP and DBP values and assumes that the arterial pressure waveform is the typical waveform of a young subject. The error (Michael, 1999) in using this formula is higher in older and very young subjects. Therefore, it is recommended that the MAP be computed from mathematical integration of the ABP waveform, whenever it is available. In 1970s, non-invasive devices for measuring continuous ABP appeared on the market. While invasive intra-arterial BP measurement

is considered to be more reliable and remains the gold standard, non-invasive blood pressure (NIBP) monitoring is recommended whenever the invasive technique is not justified. An example where invasive ABP monitoring is justified is in the intensive care unit, where indwelling arterial catheters are necessary for frequent drawing of arterial blood for blood gas monitoring and where it is useful to monitor ABP continuously so that sudden drops in ABP can be detected and acted upon immediately. In all other situations, invasive ABP measurement is best avoided because of the risk of complications such as thromboses, hematomas and infections. The main drawback of non-invasive monitors is that they need frequent calibration, which can lead to signal loss. Also, as with any indirect measurement, a scale factor needs to be computed to obtain the SBP, which is then used for calibration.

4.1.3 Variations in Waveform Morphology Depending on the Site of Recording

Depending on the site where the continuous blood pressure (CBP) signal is acquired, the waveform morphology varies (Bruner, 1979). Blood pressure waveforms vary between the aorta and locations further from the heart, such as brachial, radial and femoral arteries. The dicrotic notch, in particular, appears to be rather sensitive to the recording location. Figure 4.1 demonstrates the difference in morphology between the aortic and radial pressure waveforms. Portable tonometers allow blood pressure measurement at the carotid sinus, which is close to the aortic arch. However, since this instrument must be held manually, it is not practical in a study lasting more than several minutes. Radial ABP recording is much more common in practice. Hence, the algorithm that we present was developed mainly for radial pressure waveform, but minor changes can be made to analyze ABP signals recorded from other sites.

4.1.4 Morphological Analysis of ABP Waves and Arterial Stiffness Assessment

Recently, parameters obtained from blood pressure waveform analysis were found to be associated with cardiovascular risk in hypertension (Agabiti-Rosei et al., 2007) and other cardiac pathologies, such as orthostatic intolerance, diabetes and syncope (Romano et al., 2004; Simek et al., 2005; Laurent et al., 2006). It is known that arterial stiffness and wave reflections are responsible for increased systolic pressure. As the body ages, increased arterial stiffness leads to an increased velocity of the reflected wave across the artery (Roy, 1881).

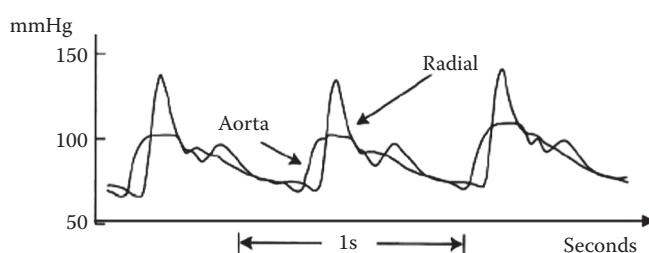


FIGURE 4.1

Two records of ABP were superimposed to highlight differences in blood pressure waveform, due to recording location—one from the aorta and the other from the radial artery.

Another important fact about arterial pressure is the so-called pressure wave amplification. Typically, diastolic and mean pressures change little across the arterial tree, but peak SBP increases as distance from the heart increases. An example of this is shown in Figure 4.1. The SBP in the aorta may be less than that in the brachial artery by more than 20 mmHg (Wilkinson et al., 2000) and the relationship between them is not always constant.

In addition, antihypertensive drugs may affect SBP differently at different sites. Despite similar reduction in brachial blood pressure, the reduction in pressure at the aorta may be different. The Windkessel model (Finkelstein and Cohn, 1992) and arterial wave propagation theory (O'Rourke and Avolio, 1980) have been used to model these phenomena extensively. The arterial pressure wave generated in the left ventricle, also known as the incident wave, travels through the arterial tree and when a bifurcation or another obstacle is found, a reflected wave is generated and propagated in the opposite direction. As a consequence, at any point in time, recorded pressure is the sum of incident and reflected waves. Both waves (incident and reflected) travel at the same velocity, known as pulse wave velocity (PWV). Large arteries are more sensitive to the loss of elasticity with age and this reduced elasticity is accompanied by an increased wave velocity. The aorta of a young subject can absorb almost all the energy from the contraction of the left ventricle, but the aorta of an older subject will reflect a large proportion of the waveform.

In the younger age group, the reflected wave appears during diastole, which promotes coronary perfusion. However, in older subjects, where increased PWV is expected, the reflected wave can appear during systole, resulting in increased systolic pressure.

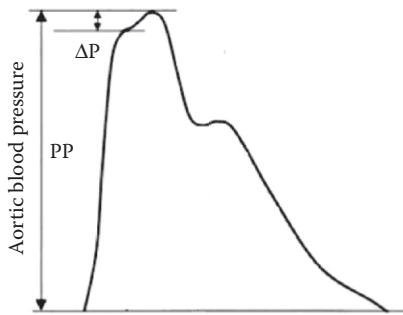
The augmentation index (AI) is used to quantify the magnitude of the reflected wave and is defined as the pressure increment due to the reflected wave as a percentage of the PP. It can be measured at central (carotid) or distal (radial) sites, but due to differences in morphology, procedures are different. Despite the fact that the magnitude of the wave reflection depends not only on arterial stiffness but also on arterial tone, it is considered an indicator of arterial stiffness and is used as a risk predictor (Weber et al., 2004).

Another index related to PWV is the delay time (DT), which is the time elapsed between the peak of the incident wave and the peak of the reflected wave. A lower DT indicates a higher PWV and arterial stiffness.

The PWV along an arterial segment is calculated as the estimated length of the arterial segment divided by the foot-to-foot time of the arterial pressure at the beginning and end of the arterial segment in question. A typical arterial segment analyzed is between the carotid and femoral arteries, and the carotid–femoral PWV is considered to be the “gold standard” measurement of arterial stiffness (Laurent et al., 2006).

The carotid pressure waveform closely resembles the waveform recorded in the ascending aorta and is therefore believed to provide better information about cardiovascular risk (London et al., 2001; Wang et al., 2010). However, carotid measurements have some problems inherent to the method used. For example, sensors that are used to record the carotid pressure are handheld and are therefore susceptible to movement. Furthermore, since the position of sensor can shift, the waveform is prone to error due to a shift in the position (misalignment between the sensor and artery), and the recording duration is limited due to muscular fatigue experienced by the operator. On the other hand, pressure waveforms recorded at distal sites allow longer periods of measurement, since they are provided with elements to fix the sensor firmly in the right position. We note that reflection waves are present regardless of the site of measurement, allowing AI and DT to be computed with waveforms obtained at any site.

Computing central indices: In the case of central pressures, systolic peak can be detected from the first inflection point in the arterial pressure waveform (at height $PP - \Delta P$ in

**FIGURE 4.2**

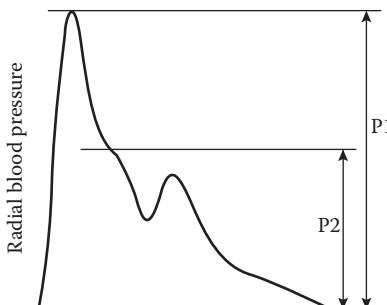
One cardiac cycle from a typical aortic blood pressure trace. Aortic AI is computed as $\Delta P/PP$.

Figure 4.2). This location marks the beginning of the upstroke of the reflected wave. The maximum of the waveform that corresponds to the SBP (PP in Figure 4.2) includes contribution from the reflected wave peak. The inflection point after the systolic pressure peak corresponds to the dicrotic notch. To compute the PP, the DBP that corresponds to the nadir of the waveform must be known.

Computing distal indices: The phenomenon of reflected pressure wave is present at all sites, including distal sites such as the radial, brachial and femoral locations, as described earlier. However, distances that the pressure wave has to travel are different, as is the corresponding time taken by the reflected wave to arrive and join the incident wave. In this case, the reflected wave can only appear after the systolic pressure peak and is located at the first inflection point found after the peak (at height P2 in Figure 4.3).

As has been stated, the central blood pressure contributes useful information towards the assessment of cardiovascular diseases. The AI can be obtained either by registering pressure waveforms at the carotid artery or by using mathematical methods to estimate central values from radial pressure records. The aortic waveform is then reconstructed by means of a generalized transfer function (Karamanoglu et al., 1993; Chen et al., 1997; Sharman et al., 2006). There is also a medical device that has incorporated this algorithm in its hardware (SphygmoCor from Atcor Medical, Itasca, IL, USA).

However, recent studies have demonstrated that radial AI is strongly and positively correlated with carotid AI in medicated hypertensive patients as well as in healthy controls (Millasseau et al., 2003; Sugawara et al., 2008). These results suggest that radial AI may provide information similar to that obtained using carotid AI.

**FIGURE 4.3**

One cardiac cycle from a radial ABP trace. Radial AI is computed as $P2/P1$.

4.2 Multi-Resolution Analysis

In the past, methods based on time–frequency analysis have been used for processing various biomedical signals, such as electrocardiogram (ECG), electroencephalogram (EEG) and others. In particular, multi-resolution analysis (MRA) algorithms based on wavelet theory (Daubechies, 1992) allow a simultaneous localization in time and frequency, helping to characterize the shape of different parts of a complex signal.

MRA (Daubechies, 1992; Unser et al., 1993; Unser, 1996) is defined as a sequence of nested subspaces $\{V_j, j \in \mathbb{Z}\}$ such that $V_{j+1} \subset V_j$ and a *scaling function* ϕ such that the family $\{\phi_{j,k}, k \in \mathbb{Z}\}$ is a basis for V_j , where

$$\phi_{j,k}(t) = 2^{-j/2} \phi(2^{-j}t - k)$$

and \mathbb{Z} is the set of integer numbers.

If we denote W_j as the complement subspace of V_j with respect to V_{j-1} , the *wavelet function* ψ defines the family of functions $\{\psi_{j,k}, k \in \mathbb{Z}\}$; this set is a basis for W_j , where

$$\psi_{j,k}(t) = 2^{-j/2} \psi(2^{-j}t - k).$$

Every signal $s_j \in V_j$ has a unique decomposition

$$s_j = r_{j+1} + s_{j+1}, \text{ with } r_{j+1} \in W_{j+1} \text{ and } s_{j+1} \in V_{j+1},$$

where r_{j+1} is the $j + 1$ *residual*. Repeating this process, it is possible to decompose a signal as a sum of signals at different resolution levels. In this way, different types of events, such as R-waves in ECG (Tanaka and Hargens, 1994), spikes and waves in EEG (D'Attellis et al., 1997), interictal epileptiform activity (Sirne et al., 1999) and epileptic seizures (Gigola et al., 2004), can be detected. In each case, the MRA is the basic tool, but a specific application requires the use of selected wavelet coefficients from different multi-resolution levels, which may be combined with appropriate thresholds in order to separate different types of features present in a signal.

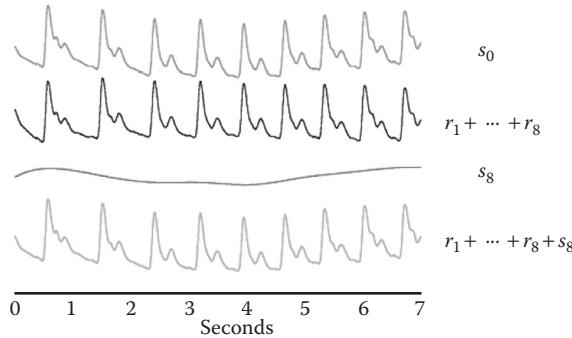
Such analysis is an interesting and general tool that has been applied to different problems in biomedical engineering (Akay, 1997), electrical engineering, radar application and other fields. However, adaptation of a general method to a particular problem requires more calculations in the algorithm than those needed for multi-resolution. Thus, by and large, false positives and negatives may show up (D'Attellis and Fernandez-Berdaguer, 1997).

If $s_0(t)$ is the signal, the decomposition is

$$s_0 = r_1 + \dots + r_j + s_j,$$

where

$$r_j(t) = \sum_{k \in \mathbb{Z}} d_j(k) \psi_{j,k}(t) \text{ with } j = 1, \dots, J$$

**FIGURE 4.4**

A blood pressure signal s_0 (previously downsampled to 300 samples/s) is reproduced by the sum of the first eight residual signals of the MRA with compactly supported cubic spline wavelet. (Reprinted with permission from Perfetto, J.C., Ruiz, A.G., Sirne, R.O. and D'Attellis, C.E., *IEEE Eng. Med. Biol. Mag.*, 28, 35–40 © 2009 IEEE.)

and

$$s_J(t) = \sum_{k \in \mathbb{Z}} c_J(k) \phi_{J,k}(t).$$

An example of the decomposition applied to a blood pressure signal s_0 (previously downsampled to 300 samples/s) can be seen in Figure 4.4. This plot shows that the sum of the first eight residual signals $r_1 + \dots + r_8$ reproduces the signal under analysis.

The wavelet function ψ selected is compactly supported (i.e., $\psi(t) = 0$, if $t \notin [a, b]$, where $-\infty < a < b < \infty$). Particularly, we use the compactly supported cubic spline wavelet

$$\begin{aligned} \psi(t) = & \frac{1}{40320} \left[-\phi(2t+6) + 124\phi(2t+5) - 1677\phi(2t+4) \right. \\ & + 7904\phi(2t+3) - 18482\phi(2t+2) + 24264\phi(2t+1) \\ & - 18482\phi(2t) + 7904\phi(2t-1) - 1677\phi(2t-2) \\ & \left. + 124\phi(2t-3) - \phi(2t-4) \right], \end{aligned}$$

where

$$\phi(t) = \begin{cases} \frac{1}{6} (3|t|^3 - 6t^2 + 4), & |t| \leq 1, \\ \frac{1}{6} (2 - |t|)^3, & 1 < |t| \leq 2, \\ 0, & \text{otherwise} \end{cases}$$

is the scaling function of the MRA; it is the convolution ($\phi = u \times u \times u \times u$) of the characteristic function

$$u(t) = \begin{cases} 1, & -1/2 \leq t < 1/2, \\ 0, & \text{otherwise.} \end{cases}$$

TABLE 4.1Wavelet ψ Characteristics

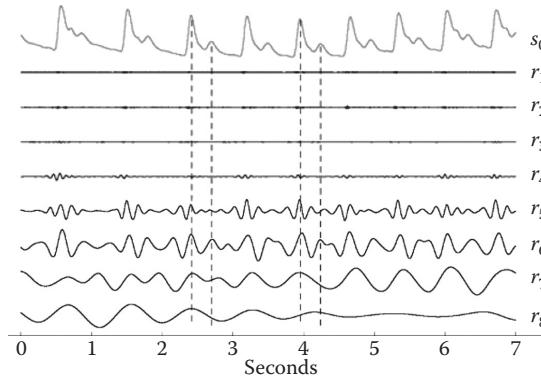
	Center	Radius	
Time window	$= -0.5$	$\cong 0.542$	Time–frequency window area
Frequency window (for $f > 0$)	$\cong 0.822$	$\cong 0.148$	$\cong 1.01\pi^{-1}$ (minimum is π^{-1})

Source: Reprinted with permission from Perfetto, J.C., Ruiz, A.G., Sirne, R.O. and D'Attellis, C.E., *IEEE Eng. Med. Biol. Mag.*, 28, 35–40 © 2009 IEEE.

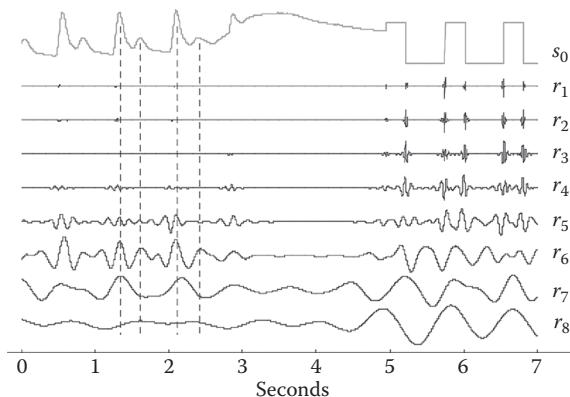
This wavelet ψ has the characteristics found in Table 4.1.

The area of the time–frequency window of this wavelet is very close to the theoretical minimum. This is an important feature for detecting events using wavelets. The signal s_0 and the residuals r_1 to r_8 are depicted in Figure 4.5.

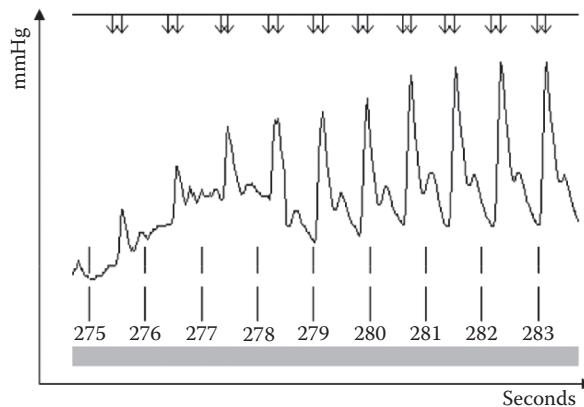
In Figure 4.6, a signal including blood pressure and the calibration signal are shown. Both signals have components in the same multi-resolution levels r_5 , r_6 and r_7 . The calibration

**FIGURE 4.5**

We can see that different maxima have similar magnitude at scales r_5 , r_6 and r_7 which are the only scales where they are detected. (Reprinted with permission from Perfetto, J.C., Ruiz, A.G., Sirne, R.O. and D'Attellis, C.E., *IEEE Eng. Med. Biol. Mag.*, 28, 35–40 © 2009 IEEE.)

**FIGURE 4.6**

Blood pressure (0–2.5 s) and calibration signal (5–7 s). We can see that residuals show similar magnitudes for blood pressure and calibration signal. (Reprinted with permission from Perfetto, J.C., Ruiz, A.G., Sirne, R.O. and D'Attellis, C.E., *IEEE Eng. Med. Biol. Mag.*, 28, 35–40 © 2009 IEEE.)

**FIGURE 4.7**

Screen capture from the software that we developed. The arrows show time of occurrence of diastolic nadir and systolic peaks for each beat. (Reprinted with permission from Perfetto, J.C., Ruiz, A.G., Sirne, R.O. and D'Attellis, C.E., *IEEE Eng. Med. Biol.*, 28, 35–40 © 2009 IEEE.)

signal can be detected in r_1 , r_2 and r_3 levels, but this fact complicates the design of the detection algorithm. One must consider whether to use a general tool and adapt it for the specific application or develop a specific algorithm.

Problems arising from the use of wavelet transformations are mentioned next. ABP signals, such as those in Figure 4.7, have special characteristics that make the use of generalized wavelet algorithms difficult.

Consequently, we developed the algorithm described in the next section, for this application (Perfetto et al., 2009).

4.3 Requirements of an Algorithm to Analyze the Blood Pressure Waveform

In the previous section, we stated that arterial stiffness was the main variable that controls wave reflections and waveform morphology and that arterial stiffness can be assessed by measuring magnitudes of incident and reflected waves and the delay of the reflected wave. The requirements for the algorithm to compute AI and other indices are not very demanding, because, in general, with the patient at rest, only a few beats are needed to obtain a steady-state signal. All beats are averaged and then characteristic points are extracted from the averaged waveform of arterial pressure. In some cases, it can be done by manual inspection.

With the availability of A/D converters combined with computational tools with large storage capacity, continuous monitoring of blood pressure is now feasible. In combination with advanced algorithms, one can detect the characteristic points from the ABP waveforms, even in non-stationary environments.

4.3.1 Characterization of the Radial Arterial Pressure Waveform

Consider the following three segments of the pressure waveform:

1. *Rising phase*: It corresponds to the rise due to ventricular contraction following the opening of the atrioventricular valve. Mathematically, it can be represented as an increasing monotonic function. The maximum pressure is known as systolic pressure.

2. *Dicrotic notch and reflected waves:* Due to reflections in the arterial tree, we can have one or more local maxima. Reflected waves can also mask dicrotic notch. These factors may result in more than one maximum or none at all. For this reason, we decided not to use any features from this zone.
3. *Final relaxation:* The final part of the waveform corresponds to relaxation of ventricles, which, mathematically, can be viewed as a monotonic decay.

4.3.2 Determination of Invariant Feature Detectors

Blood pressure magnitude and heart rate vary beat-to-beat and in addition, one can expect periods of asystole. They could lead to difficulties in designing algorithms suitable for evaluating syncope. However, there are certain characteristics of a pressure waveform that are invariant. All arterial pressure waveforms have a rising phase and a decaying phase, with a dicrotic notch in between, in addition to one or more reflected waves. The algorithm checks the first and the third zone and finds the maximum associated with the first zone. The second zone, the duration of which is specified in the program and which contains the dicrotic notch, is ignored. Only if all these conditions are fulfilled, the peak value is recognized as the SBP.

4.4 Algorithm Design

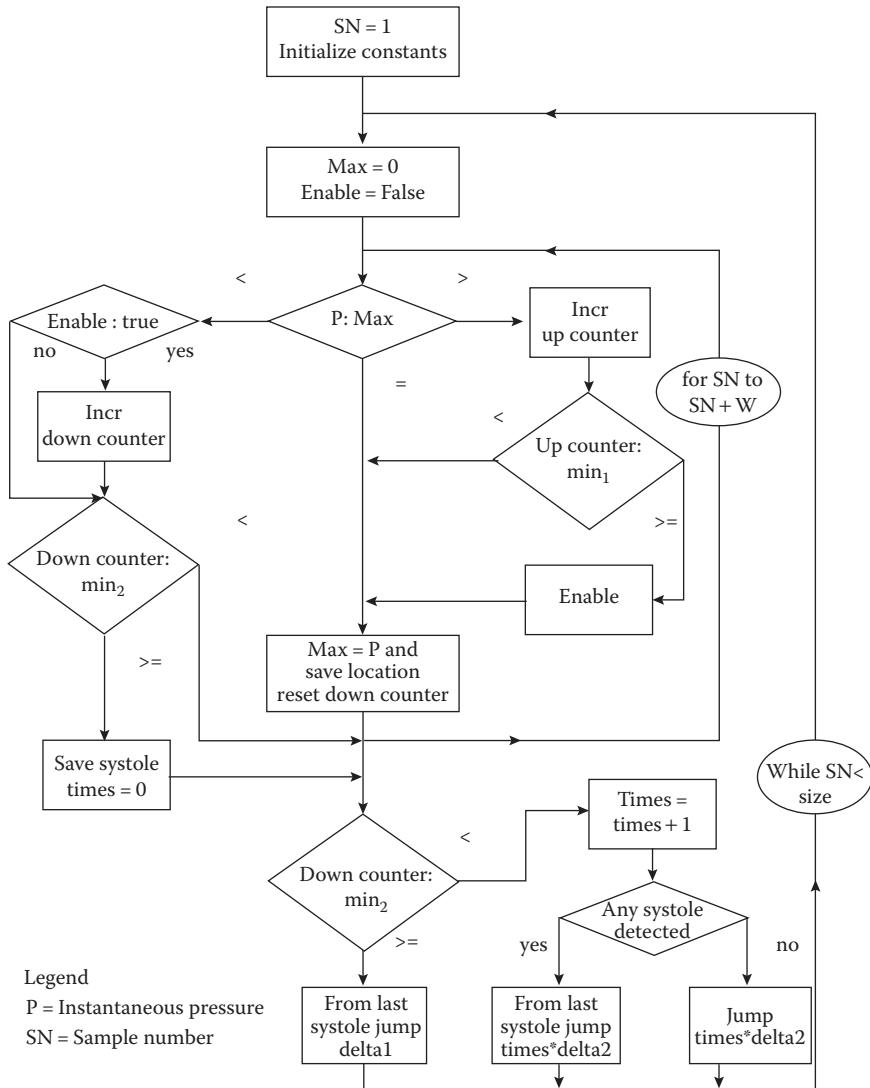
When the sampled signal is plotted as a function of time, each representative point appears in black against a white background, thus offering a binary image. The y -axis represents pressure and the horizontal axis represents the time (sample number). The contour follower (Jain, 1989) is employed for linking points that fulfill one or more conditions.

4.4.1 Contour Follower

With this tool, we can identify signal segments associated with different portions of the pressure record (Figure 4.8). Starting at any point of the signal, rising or falling phase segments are identified. Each segment is formed by a group of points. To be recognized as belonging to the first group, each point is compared with its neighbor ahead. If the y -coordinate is bigger than that of the previous point, the point is accepted. In this case, a counter denoted as Up Counter (UC), increases its count in one unit, and the point is added to the segment. The value of the counter is associated with the time when the blood pressure increases, as part of the rising phase.

A point without increment can be tolerated due to digitization errors and it does not increment the counter. In the end, traces grow in size. Some will grow until the counter reaches a predetermined threshold level, min_1 .

However, in case a difference is negative and the counter does not reach the threshold level, not only the point but also the whole segment gets rejected. When such a limit is reached, a flag is set and the relative maxima are stored together with their corresponding occurrence time of and the segment will continue to grow until the maximum is found. The other segment, part of the diastolic runoff, must have reached the minimum min_2 , associated with a counter called Down Counter (DC2), in order for such a maximum to be accepted as a valid systolic pressure.

**FIGURE 4.8**

Flowchart of the systolic detection algorithm. The upper part presents two branches. The right one is responsible for detecting the raising edge and the left for detecting the decaying edge. The bottom part ensures not to be trapped by an infinite loop. (Reprinted with permission from Perfetto, J.C., Ruiz, A.G., Sirne, R.O. and D'Attellis, C.E., *IEEE Eng. Med. Biol. Mag.*, 28, 35–40 © 2009 IEEE.)

4.4.2 Invariant Property

The fact that the magnitude of the increment is not to be taken into account leads to an invariant property with respect to the magnitude of the signal. For example, if the algorithm is searching for the rising edge, it only compares current and successive values to verify that they are increasing. But the difference between them is not used. In this way, signals with different increasing rates are indistinguishable for the algorithm.

4.4.3 Filtering Noise and Correcting the Digitization Error

There are two sources of error: the first being due to the noise in signal acquisition and the second due to finite number of pixels in a sampled data segment. The proposed algorithm is very sensitive to noise, requiring application of a smoothing zero-phase FIR filter of the order 100 with a cutoff frequency of 30 Hz, to the pressure waveform. The second error occurring due to finite number of pixels cannot be corrected readily and has to be compensated subsequently.

4.4.4 Flowchart

The algorithm uses a sliding time window to search for and identify the characteristic parts of the blood pressure signal. To do this task, it uses a contour follower. The right part of the flowchart (Figure 4.8) checks for the presence of the rising edge and the left part checks for the subsequent falling edge. The center loop allows continued searching for the rising edge when no increment is found and is included to consider the digitization error. Finally, the lower part of the flowchart prevents the algorithm from entering an infinite loop when no blood pressure signal is detected; for example, during calibration or during prolonged asystole. It seldom occurs during positive tilt tests.

The following criteria are used by the algorithm:

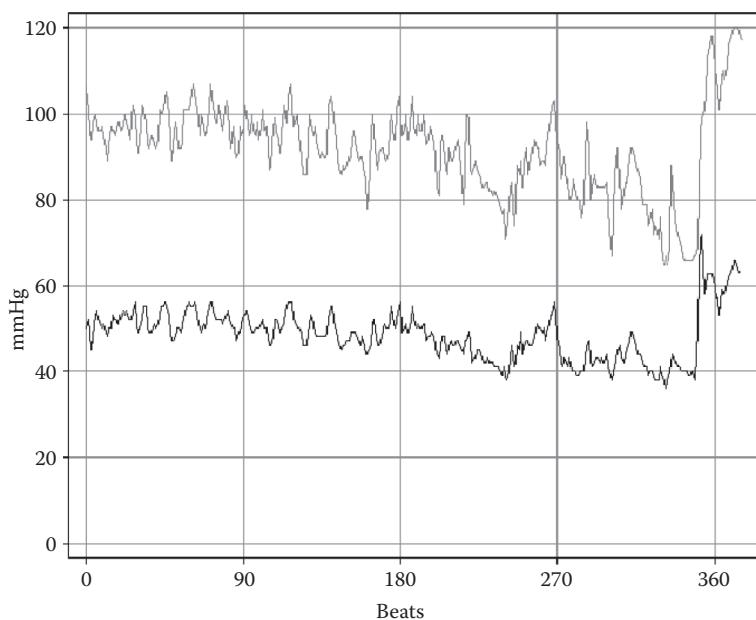
1. The time window must be wide enough to include at least one cardiac cycle.
2. The contour is followed while the blood pressure rises, and the relative maximum has to be stored until it identifies a peak, which must exceed a threshold (defined as min_1).
3. It accepts a maximum as systole when both counters in Figure 4.8 (UC and DC) reach pre-determined levels (min_1 and min_2) in the appropriate sequence.
4. When aforementioned conditions are fulfilled, the location and magnitude values are stored.
5. To avoid the reflected wave region, when the peak is found, the time window is shifted ($\text{delta}2$ in Figure 4.8), and the algorithm proceeds from that new position.
6. If the entire window is unsuccessfully explored, it is shifted again ($\text{delta}1$ in Figure 4.8), proceeding thereafter as before.
7. The whole process is repeated until there is success and/or until all data are exhausted.

Diastolic values are detected by exploring the blood pressure trace in the reverse order, starting at each systole and storing the first minimum, both in magnitude and location.

4.4.5 Choosing Parameters

The constants min_1 and min_2 are related to the elapsed time of the rising and falling edges, respectively, and their values depend on the sampling rate. If they are set too high, there can be failure in the detection of some systoles; if they are set too low, false positives are likely to occur. Threshold₁ and Threshold₂ are set at 10 and 20 ms, respectively, which are not modified during signal processing.

The constant delta1 corresponds to the period where wave reflections are expected and is set at 10 ms. Similarly, delta2 is set according to the minimum interval between pulses expected in human tachycardia. It is set at 15 ms in our laboratory.

**FIGURE 4.9**

Example of the algorithm detection: graph of the numerical series built from consecutive systolic BP (upper trace) and diastolic BP values (lower trace). These results are extracted from one of our records. (Reprinted with permission from Perfetto, J.C., Ruiz, A.G., Sirne, R.O. and D'Attellis, C.E., *IEEE Eng. Med. Biol. Mag.*, 28, 35–40 © 2009 IEEE.)

4.5 Results

Signals recorded during tilt test are processed offline. The time point at which the algorithm starts the computation is identified by the user, and it is best not to use the maximum value of the signal for this purpose. The algorithm presented herein is used for the calculation of beat-to-beat values of SBP and DBP. Figure 4.7 shows an example of the time points identified by the computer as locations of the peak systolic and diastolic pressure values for an 8 s stretch. Pressure values obtained in this manner are plotted against the beat number (X-axis), as shown in Figure 4.9 for a 5 min interval. The results obtained from our algorithms were verified by an independent researcher.

4.6 Application: Vasovagal Syncope Assessment

Tilt table testing (Kenny et al., 1986) is a tool used to reproduce syncope or pre-syncope in controlled conditions with continuous monitoring of cardiac parameters. In particular, an ECG channel and continuous radial ABP are commonly recorded. In the first part of the study, the subjects remain supine for 20 min to adjust to the laboratory environment, and baseline values of the hemodynamic variables are subsequently recorded over the next

5 min. Then the table is tilted up to 70° to evaluate the patient's susceptibility to a syncope episode or for a duration determined by the researcher, usually lasting 45 min.

4.6.1 Signal Processing

The blood pressure measurements were determined using a non-invasive monitor (Colin Medical Instruments, San Antonio, TX, USA) that uses the tonometer technique associated with a cuff for calibration purpose. The ECG is recorded using a precordial lead.

ECG signals and blood pressure are digitized at 1200 samples/s, with a resolution of 12 bits, and stored in digital format on a PC. The continuous ABP was obtained by means of an NIBP monitor from Colin Medical Instruments. The waveforms were digitized and processed to extract the characteristic points, namely, SBP, DBP and the peak of the reflected wave. For each of these points, the corresponding magnitude and time stamp were recorded.

For this task, the proposed algorithm was used. It was modified to include the last characteristic point. After processing the CBP signal, values for each characteristic point are made available to the researcher.

4.6.2 Variability of AI and DT during Head-Up Test

Recently, the indices AI and DT, frequently used as early markers of increased arterial stiffness, have also been proposed to be useful as markers for discriminating subjects susceptible to vasovagal syncope (VVS) from healthy controls.

According to Chen et al. (2000), AI measurement at baseline of patients with VVS could confirm the diagnosis, making the tilt test, which thus far is the only recognized test for that purpose, sometimes unnecessary.

Simek et al. (2005) suggested that DT (time delay between systolic and diastolic peaks) could be used in the diagnosis of VVS even when recorded at supine rest.

In both papers, pressure waveforms are synchronously averaged, from which both values (AI and DT) are calculated. In our proposed approach, we first obtain these parameters for each cardiac cycle and then compute the mean for each series.

4.6.3 Study Population

Nineteen patients (10 males, 9 females; age: 22.21 ± 5.2) with a history of recurrent syncope but without a history of heart disease and a control group (5 males, 5 females; age: 22.6 ± 4.04) were evaluated. All underwent the tilt table test. Patients with syncope were classified either as positive responders (Group +) and others were negative responders (Group -), as shown in Table 4.2.

4.6.4 Results Observed from Variability of AI and DT

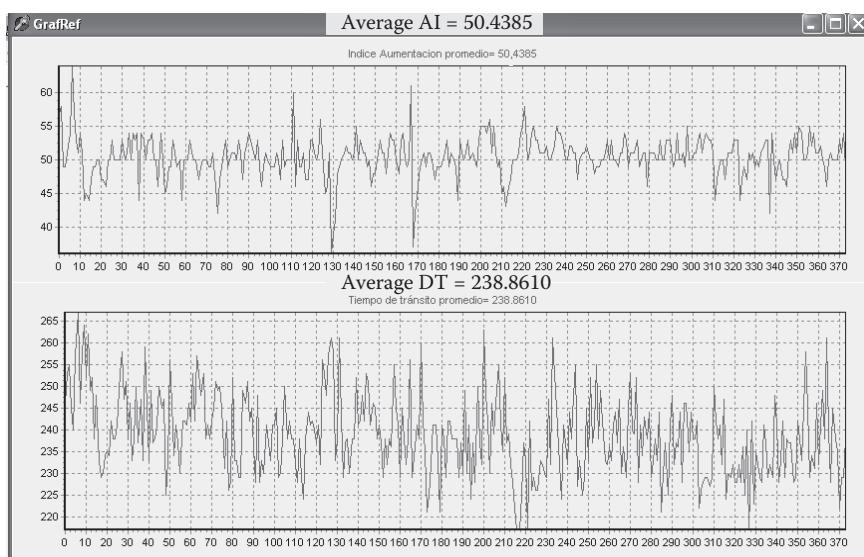
The results shown in Table 4.2 were obtained from studies conducted in our laboratory. In Figure 4.10, both indices are plotted as a function of the beat number. They show a behavior far from stationary, demonstrating that our approach is more suitable than computing these values from a single averaged signal.

TABLE 4.2

Augmentation Index (AI) and Delay Time (DT) for Patients with Vasovagal Syncope and Controls

	Value	Group +	Group -	Control Group	ANOVA (F,p)
Supine	AI	61.25 ± 5.80	58.85 ± 10.61	59.69 ± 7.53	0.244 0.785
	DT	312.84 ± 27.46	316.31 ± 18.06	314.11 ± 25.75	0.039 0.962
Orthostatic	AI	58.02 ± 5.77	58.60 ± 6.81	55.31 ± 5.87	1.130 0.338
	DT	251.11 ± 20.87	250.15 ± 23.58	235.25 ± 20.64	1.686 0.205

The results are expressed as mean \pm standard deviation.

**FIGURE 4.10**

An example of AI (top panel) and DT (lower panel) time series in a control subject, shown against the beat number (X-axis).

4.7 Discussion

Conventional algorithms for detecting SBP and DBP from CBP signals usually rely on statistical properties (Zong et al., 2003; Treo et al., 2005). These algorithms were developed under the assumption of quasi-stationarity of the signal under consideration. The proposed method is designed to be applied to tilt table test studies. The methodology described herein enables us to examine offline records for checking visually whether the algorithm accurately accomplishes detection of systole or diastole. As stated earlier, accuracy of the blood pressure values relies on precise detection along the time axis.

The hypothesis that we could discriminate between patients with VVS and normal subjects based solely on these values, and without the need for a tilt table test, could not be proved, because values of both parameters in all population groups were not significantly different. We found no significant differences between various groups. However, for orthostatic position, there was a tendency toward lower values of DT ($p = .08$) in the

control population, compared to other groups. This score was achieved using orthogonal contrasts technique to increase the sensitivity of the analysis of variance (ANOVA). Our results suggest that the magnitude and timing of the reflected wave in the arterial tree of patients with a history of syncope may be different from those of normal group, and it occurs during tilt table test. A larger sample size may be needed to confirm our results.

4.8 Conclusions

The algorithm described in this chapter allows accurate detection of SBP and DBP from a continuous pressure curve. It can be used with non-stationary signals, because it does not rely on the history of the signal but takes advantage of known features within the signal. Low computational cost is an additional feature of the algorithm. We have demonstrated that variability of AI and DT can also be computed. Furthermore, our study suggests that the algorithm can be extended to other cardiac parameters, such as pulse photoplethysmography or arterial diameter measurements. It also opens the possibility of studying spontaneous changes in cardiac dynamics without external intervention.

Acknowledgment

The authors are grateful to Universidad de Buenos Aires for partial financial support by UBACYT project I001 and I421.

Abbreviations

ABF	Arterial blood flow
ABP	Arterial blood pressure
AI	Augmentation index
AV	Atrioventricular
CBP	Continuous blood pressure
DBP	Diastolic blood pressure
DC2	Down counter
DT	Delay time
ECG	Electrocardiogram
EEG	Electroencephalogram
MAP	Mean arterial pressure
MRA	Multi-resolution analysis
NIBP	Non-invasive blood pressure
PP	Pulse pressure

PWV	Pulse wave velocity
SBP	Systolic blood pressure
UC	Up counter
VVS	Vasovagal syncope

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5

Heart Rate Turbulence

Mari A. Watanabe and Georg Schmidt

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5.1 Introduction

Heart rate turbulence (HRT) is a phenomenon discovered during the mid- to late 1990s by Georg Schmidt's group in Munich (Schmidt et al., 1999). Their study of sinus rhythm following ventricular premature beats (often abbreviated as VPC, where C stands for complex or contraction) using signal averaging techniques historically applied to the study of electrocardiographic late potentials revealed that after a single arrhythmic ventricular beat, the heart rate increased* and then decreased before returning to baseline. Clinical research revealed that patients in whom this fluctuation of sinus rhythm was absent had a higher likelihood of dying (Schmidt et al., 1999).

Since its initial publication, many large-scale studies with thousands of patients have confirmed the utility of HRT in predicting mortality, cardiac mortality and, in some studies, arrhythmic mortality (Ghuran et al., 2002; Barthel et al., 2003; Hallstrom et al., 2005; Exner et al., 2007; Mäkipallio et al., 2005). Broadly speaking, its predictive capabilities rank with, or often exceed, that of conventional linear heart rate variability (HRV) measures. In 2008, the International Society for Holter and Noninvasive Electrocardiology (ISHNE) published a consensus statement on the standards of measurement, mechanism and clinical applications (Bauer et al., 2008). The document provides a concise review of major HRT-related studies. For the purposes of this book, I would like to focus on what is most likely to be salient to its audience, that is, those who may consider applying HRT to non-cardiac medical disciplines in much the same way as they have applied HRV in their respective fields. The topics covered in this chapter are measurement technique, mechanism and advantages and disadvantages of HRT over HRV.

* Acceleration alone had been noted earlier (Döhleman et al., 1979).

5.2 Measurement Technique

We know from spectral analysis that human heart rate over the day is influenced by myriad intrinsic oscillations. In addition, human heart rate is influenced by non-periodic event-related changes, such as change in posture or activity or mental state (Roach et al., 1999). Many routine events such as eating, sleeping and physical exercise trigger many different autonomic reflexes. Therefore, a plot of RR interval (time from peak of one QRS complex to the next on electrocardiogram [ECG]) against time in a healthy subject has a jagged stochastic appearance. However, if a plot of RR interval against beat number (called a tachogram) is averaged over many cycles aligned to an abrupt event, the stochastic and multiple cyclic events cancel out and reveal a pattern that is solely related to the event. Computation of HRT uses the VPC as the fiduciary or anchor point, while the newer measure of phase-rectified signal analysis (Bauer et al., 2009), discussed in the next chapter, uses each instance of RR lengthening as the anchor (Figure 5.1). Averaging of the VPC-anchored tachograms is done over all valid VPC tachograms found in a 24 h Holter record.

The VPC tachogram sequence should include two sinus rhythm RR intervals before the VPC, the coupling interval and compensatory pause and 15 subsequent sinus RR intervals. If a tachogram is contaminated by any ectopic beats, it is excluded from the averaging process. Interpolated VPCs (VPCs that are not followed by a compensatory pause) are also excluded. HRT is quantified by two parameters termed turbulence onset (TO) and turbulence slope (TS) that correspond to the early acceleration and late deceleration of heart rate after the VPC. TO and TS are both calculated from the final averaged VPC tachogram. In other words, it is important not to calculate multiple TO and

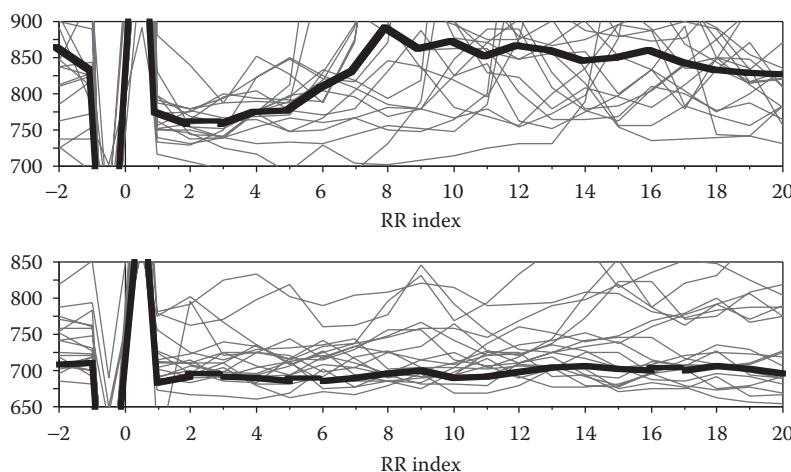


FIGURE 5.1

Seventeen VPC tachograms (gray lines) and their average (thick black line). The upper panel is from a patient with normal heart rate turbulence. The lower panel is from a patient who has normal turbulence onset but no turbulence slope. The numbers on the abscissa are the indices of the RR intervals. The points off the scale to either side of RR[0] correspond to the VPC and the compensatory pause. Note how averaging smooths the minute ups and downs.

TS values from individual tachograms and then average them. First, the tachograms are averaged to get one overall tachogram and then the TO and TS are calculated from that single tachogram.

TO is calculated using the following equation:

$$TO = \frac{(RR_1 + RR_2) - (RR_{-2} + RR_{-1})}{(RR_{-2} + RR_{-1})} \times 100,$$

where RR_{-2} and RR_{-1} are the two RR intervals immediately preceding the coupling interval of the VPC and RR_1 and RR_2 are the two RR intervals immediately following the compensatory pause (Figure 5.2). TO is a unitless ratio. A negative TO is considered normal. In other words, any acceleration of the heart rate in the two beats after the VPC and compensatory pause is a sign of good autonomic health. The second HRT parameter TS is defined as the maximum slope (>0) of a regression line assessed over all sequences of 5 consecutive RR intervals within the first 15 RR intervals after the VPC (Figure 5.2). $TS \geq 2.5$ ms/beat is considered normal. In other words, a rapid slowing of heart rate after the initial acceleration is a sign of good autonomic health.

In risk stratification studies, HRT values have been used to classify patients into three categories, category 0: both TO and TS normal; category 1: either TO or TS abnormal; and category 2: both TO and TS abnormal. If HRT could not be calculated because there is no suitable VPC tachogram found in the recording, patients are sometimes classified as belonging to HRT category 0 (Tuomainen et al., 2005).

Various filters are used to select valid VPC tachograms. A VPC with long coupling interval (time from last sinus beat to the VPC) is expected to cause less of a drop in blood pressure, so a VPC appearing more than 80% of the way through the next expected RR interval value (mean of the five last sinus rhythm intervals preceding the VPC) is excluded. Likewise, compensatory pause should be $>120\%$ of the expected value. This criterion excludes interpolated VPCs. VPC tachograms with short (<300 ms), long (>2000 ms) or

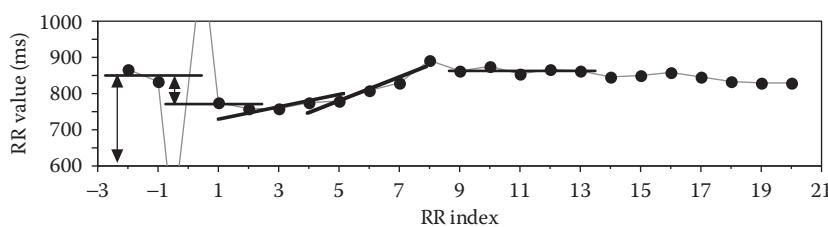


FIGURE 5.2

A visual representation of how the heart rate turbulence parameters turbulence onset (TO) and turbulence slope (TS) are calculated. TO is the ratio of the change in the RR intervals from the average of the two beats before the VPC (baseline RR) to the average of the two beats after the compensatory pause, to the baseline RR ($\Delta RR/baseline RR$). If heart rate accelerates after the VPC, the RR interval diminishes relative to the baseline and produces a negative TO. TS 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. Three out of the eleven regression lines considered are shown. The regression line slope was 2.4 for the 1st through 5th RR intervals after the compensatory pause RR interval, 28.5 for the 4th through 8th and -1.0 for the 9th through 13th. The steepest slope was for the middle one. Therefore, the TS value for this particular average of 17 tachograms (same as in upper panel of Figure 5.1) would be 28.5 ms/beat.

highly variable (>200 ms beat-to-beat RR interval difference, or difference >20% from the five preceding sinus RR intervals) RR intervals should also be excluded. TO and TS are not significantly affected by the sampling frequency of the ECG signal until the sampling rate falls below 50 Hz (Bauer et al., 2008).

The number of VPCs averaged greatly affects the HRT values, as might be expected from the fact that averaging is what brings out the HRT phenomenon in relief (Figure 5.3). Low VPC counts tend to produce high TS values, since any large beat-to-beat increase in the RR interval produces a high slope by linear regression. TS calculation is blind to the correlation coefficient of the regression fit. If a slope for one sequence of five beats is greater than that of the other five-beat sequences in the averaged tachogram, it automatically becomes the TS value, regardless of fit. Fortunately, high TS is indicative of a healthy baroreflex, as is a low number of VPCs. Therefore, the spuriously high value of TS that may be obtained due to low VPC count in a 24 h record does not change the categorization of a patient. Indeed, in some epidemiological studies, patients showing lack of any VPCs on their Holter records have been lumped with normal HRT (both TS and TO normal, i.e., HRT category 0) (Tuomainen et al., 2005). The one caveat to this relaxed assumption is the occasional presence of patients with a large number of ectopic beats, ventricular or atrial, in whom valid VPC tachogram counts are low because few sequences of 15 clean (sinus) RR intervals are available and not because they have few VPCs. The percentage of Holter records in which HRT could not be measured because of atrial fibrillation or lack of VPCs has ranged from about 15% to 30% in the post-myocardial infarction population (Watanabe, 2003). The percentages have increased with time because advances in cardiac care for myocardial infarction patients have reduced extent of myocardial scarring and morbidity, and with it, the number of VPCs. Five is commonly mentioned as the minimum number of VPC tachograms that should be averaged. However, as discussed earlier, it has also been recommended that HRT be calculated even if there is only one VPC (Schneider et al., 2004).

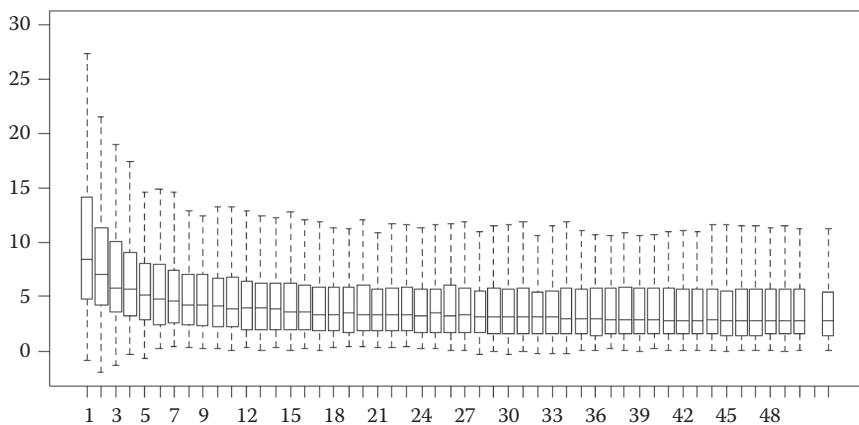


FIGURE 5.3

A plot showing the dependence of turbulence slope (TS) values (ordinate) on the number of VPCs (abscissa) averaged. This plot shows the distribution of TS values from 163 patients who had at least 50 VPCs each in the ISAR database. For $x = 1$, only the first VPC in the 24 h Holter record was used to calculate TS in each patient, for $x = 2$, the first two VPCs were used and so on. The last box plot shows the distribution of TS values in these 163 patients when all VPCs were used for TS calculation. (From dissertation of Melanie Gehring, 2007, Technische Universität München.)

5.3 Autonomic Basis of HRT

At its core, HRT is a baroreflex measure. A VPC causes an instantaneous drop in the volume of blood ejected from the heart and, therefore, a transient drop in blood pressure. The drop in volume is caused by several factors, including electrical restitution characteristics (shorter contraction time due to insufficient recovery of myocyte ion channels), shorter time for diastolic filling, loss of atrial kick, higher afterload and asynchronous ventricular contraction. The systolic blood pressure produced by the compensatory pause beat has also been found to be lower than baseline (Wichterle et al., 2006). The drop in blood pressure caused by these two beats activates the baroreflex arc, leading to heart rate acceleration and sympathetically mediated vasoconstriction. However, because the drop in blood pressure due to a VPC is transient, the compensatory mechanisms that increase the cardiac output and blood pressure kick in when the heart is back in sinus rhythm, producing a normal stroke volume and leading to a blood pressure overshoot. This, in turn, triggers slowing of heart rate. This interplay between blood pressure and heart rate can be seen by plotting the beat-to-beat blood pressure values and the VPC tachogram together (Davies et al., 2001; Roach et al., 2002, 2003; Wichterle et al., 2006). Blood pressure drops, then increases above baseline, peaking around the eighth post-VPC beat, before returning to baseline, with the RR intervals behaving similarly but with a delay. As might be expected, based on this mechanism, both TO and TS have been found to correlate highly with the baroreflex sensitivity assessed by the phenylephrine method (Iwasaki et al., 2005; La Rovere, 2011), as well as the α -index obtained from computing the cross-spectra between HRV and blood pressure variability (Davies et al., 2001). Davies et al. also found a high correlation between baroreflex sensitivity and the ratio of RR slope to systolic blood pressure slope.

Based on the time scale at which the HRT phenomenon unfolds and on the biochemistry of neurotransmitters and receptors, one presumes that the initial heart rate acceleration after the VPC is due to vagal withdrawal. The heart rate slowing in the later stage of HRT is likely due to the combined withdrawal of sympathetic activity and reinstatement of vagal activity. The surge of muscle sympathetic nerve activity recorded after the VPC has been found to begin not earlier than the first post-VPC beat (Lombardi et al., 1989; Welch et al., 1989). Consistent with such assumptions and observations, atropine, a muscarinic (vagal) receptor blocker, causes HRT to flatten, that is, both TS and TO tend toward 0 (Marine et al., 2002; Lin et al., 2002). β -Blockade (esmolol) has been found to have little effect on HRT (Lin et al., 2002), as might be expected from the fact that vasoconstriction is α -adrenergically, rather than β -adrenergically, mediated. Since the blood pressure profile is not affected, the vagus is still able to slow the heart rate after the blood pressure overshoots.

There is known to be a dependence of HRT on heart rate across individuals as well as within individuals (Watanabe, 2006; reviewed in Watanabe and Schmidt, 2004). The mechanisms responsible for this dependence are not completely understood but have led some to suggest correcting HRT for heart rate (Cygankiewicz et al., 2004).

5.4 Advantages of HRT

One of the most appealing aspects of HRT is its simplicity. There are not many adjustable parameters affecting its calculation, such as selection of window size and selection of

frequency limits. There is also little subjectivity involved, such as might arise during manual overreading of the Holter record to exclude segments of the record with artifact. These attributes mean that researchers from different institutions given the same RR interval record should come up with the same HRT values without the need for prior consultation with each other or use of the same software. HRT also has only two parameters, TS and TO, which, moreover, have clearly defined cutoff values between normal and abnormal, $TS = 2.5 \text{ ms/beat}$ and $TO = 0$. These cutoff values have been validated in large clinical studies. Lack of stationarity of the signal is not a cause for concern, since shifts in baseline cancel each other out during the averaging process. Finally, with respect to the large population of patients who have a history of myocardial infarction, HRT has been found to perform as well as, or somewhat better than, HRV in risk stratification. This advantage is usually apparent from multivariate analyses in which one or both HRT parameters are found to be independent, while conventional HRV parameters that are significant predictors in univariate analyses fail to show independence.

5.5 Limitations of HRT

As with HRV, HRT cannot be measured in patients with atrial fibrillation, which unfortunately is an increasingly common disorder in older people. A distinctive limitation of HRT is that its measurement requires the presence of multiple VPCs in the Holter record being analyzed. Since patients with cardiac disorders have frequent VPCs, HRT measurement is not a problem in this population, especially if patients with no VPCs are categorized as having normal HRT. However, studies whose aim is to achieve better understanding of the mechanism of HRT using healthy or young individuals or experimental animals are difficult to design and perform. It also makes it harder to use HRT to study the changes in the autonomic nervous system in patients who have non-cardiac disorders. This requirement also makes it difficult to measure HRT using short ($<24 \text{ h}$) ECG records, or when trying to study circadian variability of HRT, that would require VPCs to be evenly distributed over the day so that HRT parameters can be compared from one time window to the next (Watanabe, 2007). One of the ways around this problem is to study what is called induced HRT (Watanabe et al., 2002), that is, HRT demonstrated by pacing the heart directly, for example, during invasive programmed ventricular stimulation, or even via devices such as cardiac defibrillators (Marine et al., 2002; Watanabe et al., 2002; Roach et al., 2002).

However, in populations of patients who do have frequent VPCs, HRT measurements in short time periods can provide clinically interesting observations. HRT has been measured in short implantable cardiac defibrillator (ICD) records with only 1000 RR intervals (Watanabe, 2006). That particular study showed that the mean and the standard deviation of TS were reduced in imminent ventricular tachycardia and fibrillation, but only in patients who had normal HRT in the baseline ECG recorded at the time of ICD implantation. Patients with low HRT, to begin with, could not demonstrate such a reduction.

In another study of patients with frequent VPCs, the relationship between obstructive sleep apnea episodes and HRT parameters was studied (Watanabe et al., 2008). TS was found to correlate significantly with oxygen desaturation duration per apnea event in rapid eye movement (REM) stage sleep. Combined with the higher VPC frequency in REM sleep compared to the wake periods in patients with more severe apnea, it was concluded

that long apnea events could produce sympathetic dominance (reduced HRT) even during sleep and perhaps explain why patients with obstructive sleep apnea had a proclivity for sudden death during sleep (Gami et al., 2005) compared to patients without apnea who tend to die suddenly during the midmorning hours.

5.6 Conclusion

HRT is a non-invasive baroreflex sensitivity test. It is easy to calculate and visualize, and its mechanism is fairly straightforward to understand. It has only two parameters, with well-defined cutoff values indicating whether a patient has normal or abnormal HRT. The TO parameter is likely determined solely by vagal activity. The TS parameter depends on both sympathetic and vagal activities. Large-scale retrospective and prospective studies have firmly established HRT as a robust and independent risk predictor of mortality after an acute myocardial infarction. There is potential for its use outside the cardiac arena, so long as the patient population is one in which several VPCs can be found in the Holter record.

Abbreviations

ECG	Electrocardiogram
HRT	Heart rate turbulence
HRV	Heart rate variability
REM	Rapid eye movement
TO	Turbulence onset
TS	Turbulence slope
VPC	Ventricular premature beat

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6

Phase-Rectified Signal Averaging: Methods and Clinical Applications

Raphael Schneider, Alexander Müller and Georg Schmidt

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6.1 Introduction

The assessment of heart rate variability (HRV) offers a glimpse into the operation of the autonomic nervous system. One characteristic of a healthy autonomic nervous system is the ability of an organism to adjust its heart rate to changing demands. Because the events that trigger changes in the heart rate are not necessarily correlated with each other, the heart rate signals are quasiperiodic; they consist of periodic patches that are not in phase

with each other. Because of this quasiperiodic behavior, conventional methods such as spectral analysis often do not allow a comprehensive quantification of autonomic behavior. We have developed a new method called phase-rectified signal averaging (PRSA), which identifies the periodic patches, aligns these patches in phase and calculates their average. This process allows PRSA to detect and quantify quasiperiodic oscillations that are masked by the non-stationary elements of complex signals.

The next section describes the PRSA method in detail. Section 6.3 gives an overview of how PRSA is used in clinical applications. The last section describes an extension of the PRSA method, which allows quantification of the correlations between the oscillations present in two biosignals.

6.2 Methods

In the following subsections, detailed descriptions of the PRSA method and of the parameters that influence certain aspects of the PRSA method are given.

6.2.1 The Algorithm

Biosignals, such as series of heartbeat intervals (RR intervals) as shown in Figure 6.1, are complex. An RR interval time series contains oscillations of different frequencies, each of which reflects a physiological regulation process controlled by intrinsic closed-loop regulation. The magnitude of these oscillations is of clinical interest; it gives insight into the functional status of the cardiovascular system of the patients and provides prognostic information. In survivors of acute myocardial infarction (MI), diminution or loss of these oscillations indicates high mortality risk.

Typically, oscillations have a specific wavelength that varies within a limit and can temporarily get out of phase with each other. We refer to these oscillations as quasiperiodic. Both frequency variations and phase shifts destroy the autocoherecy of the signal and broaden its power spectrum.

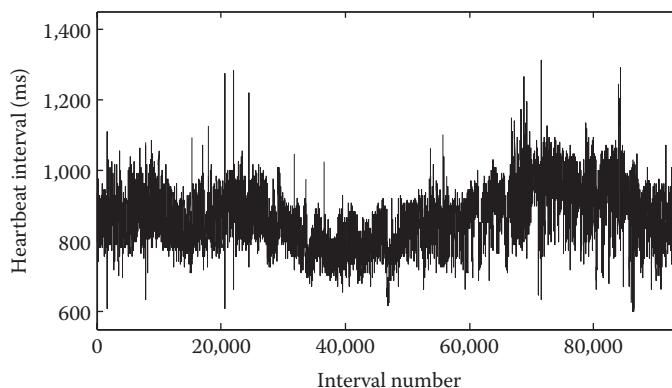


FIGURE 6.1

Example of a heartbeat interval time series over 24 h from a post-infarction patient. The example shows the complexity of physiological signals.

The RR interval time series of Figure 6.1 is taken from a 24 h electrocardiogram (ECG). Typically, such a long-term recording is composed of about 100,000 RR intervals. The main physiological sources of RR interval oscillations are respiratory activity, baroreflex function and circadian rhythms. Respiratory activity, for one, induces periodic prolongations and shortenings of RR intervals (termed respiratory sinus arrhythmia) that can be modified (e.g., by physical activity) or be interrupted (e.g., by coughing).

HRV analysis by means of the PRSA technique provides a better signal-to-noise ratio than standard HRV analysis methods. Furthermore, the PRSA technique allows separate analyses of HRV related to heart rate decelerations and heart rate accelerations. The PRSA transformation is short; free of non-stationarities, artifacts and noise; and contains all relevant quasiperiodicities.

The basic principle of the PRSA technique is to align the segments of a time series to a predefined feature, which we call an anchor. In the case of HR analysis, this is typically a beat-to-beat prolongation of RR intervals. The method consists of three steps:

In the first step, the RR intervals are separated into two categories: the so-called deceleration anchors (defined as intervals longer than the preceding intervals; Equation 6.1a) and acceleration anchors (defined as intervals shorter than the preceding intervals; Equation 6.1b).

$$\text{RRI}_i > \text{RRI}_{i-1}, \quad (6.1a)$$

$$\text{RRI}_i < \text{RRI}_{i-1}. \quad (6.1b)$$

Note that typically between one-third and one-half of all points of the time series will be anchor points, by any of these definitions. Figure 6.2 shows a short RR interval series with anchor points for decelerations (panel A) and accelerations (panel B) marked. It is also possible to define the anchor points not only by comparing single RR interval values but also by comparing the sums (or, equivalently, averages) of more than one interval before and after an anchor point candidate. These extended anchor point selection criteria are discussed in more detail in Section 6.2.2.

In the second step of the PRSA method, windows of length $2L$ around each anchor point are defined with the anchor point at the center of the window. The number of these windows is equivalent to the number of anchor points found. The chosen window length " L " should exceed the expected coherence time of the periodicities in the data; it must be larger than the period of the slowest oscillations that one wants to detect. Anchor points close to

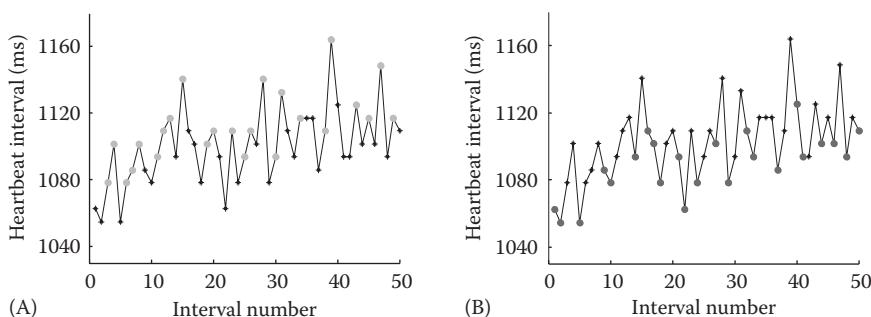


FIGURE 6.2

(A) Anchor points related to prolongations between consecutive RR intervals (light gray dots). (B) Anchor points related to shortenings between consecutive RR intervals (gray dots).

the beginning or the end of the signal, where no complete segments of length $2L$ are available, are ignored. If we denote the positions (indices i) of each anchor point considered by i_ν , $\nu = 1, \dots, M$, the points in window number ν , corresponding to anchor i_ν will be

$$\text{RRI}_{i_\nu-L}, \text{RRI}_{i_\nu-L+1}, \dots, \text{RRI}_{i_\nu+L-2}, \text{RRI}_{i_\nu+L-1}. \quad (6.2)$$

The definition of segments in the sample RR interval series is visualized in the top part of Figure 6.3. Here, only the windows for the deceleration-related anchor points are shown. For the sake of clarity, an example with window length of 10 heartbeat intervals ($L = 5$) is used. As can be seen in the figure, the selected segments overlap.

In the third step, the phase-rectified signal average $\bar{\text{RRI}}_k$ is calculated by first aligning all windows with their anchor points at the center (Figure 6.3, middle part); this is the phase rectification part of PRSA. Then the RR interval values are averaged over all M windows (Equation 6.3). Note that the aligned windows build a complex picture comprising all detected oscillations or patches around each anchor point. Visual inspection of these windows leads to no conclusion about the captured oscillations. Only after the averaging step do the oscillations become apparent.

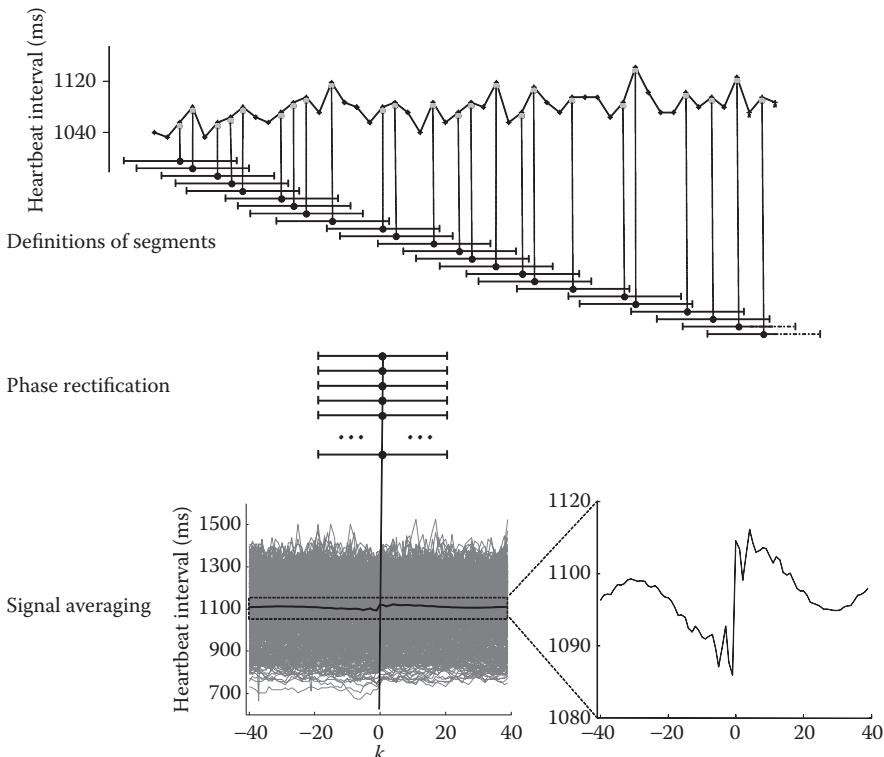


FIGURE 6.3

The upper part shows a part of the heartbeat interval time series from Figure 6.1; the light gray dots mark the deceleration-related anchor points. Around each anchor point, windows are defined with length $2L$. Here, L was chosen to be five heartbeat intervals before and five heartbeat intervals after the corresponding anchor point. For the phase rectification, all windows are aligned with the anchor points at the center (middle part). The averaging over all windows results in the PRSA signal (lower part).

$$\overline{\text{RRI}_k} = \frac{1}{M} \sum_{v=1}^M \text{RRI}_{i_v+k} \quad \text{for } k = -L, \dots, 0, \dots, L-1. \quad (6.3)$$

Here, $\overline{\text{RRI}_0}$ is the average of the anchor RR intervals and $\overline{\text{RRI}_1}$ and $\overline{\text{RRI}_{-1}}$ are the averages of RR intervals immediately following and preceding the anchors, respectively. In the resulting PRSA signal $\overline{\text{RRI}_k}$ (Figure 6.3, lower part), non-periodic components that are not phase-synchronized with the anchor points, that is, non-stationarities, artifacts and noise, are canceled out, and only events that have a fixed phase relationship with the anchor points, that is, all periodicities and quasiperiodicities, “survive” the averaging procedure. In our example, the PRSA signal contains two relevant quasiperiodicities, which can be clearly seen. Note that the PRSA method allows an assessment of the periodic content of long-term recordings by looking at a rather short signal; all important periodic or quasiperiodic components of the original RR interval time series are centered on the defined anchor points.

The midpoint of periodic signals are aligned, and the signal decays the farther one is away from the anchor (larger absolute value of k) if the coherence time is finite. This fact has two important consequences: (a) the central peak of the PRSA signal contains contributions of all (quasi) periodicities in the original signal and (b) the decay of the oscillations toward large $|k|$ conveys information about their coherence time. In addition, any asymmetry of the PRSA curve indicates a break of time reversal symmetry, which cannot be seen in classical power spectral analysis. Hence, in some applications, it can be useful to characterize RRI_k by certain values or slopes at specific distances from the center.

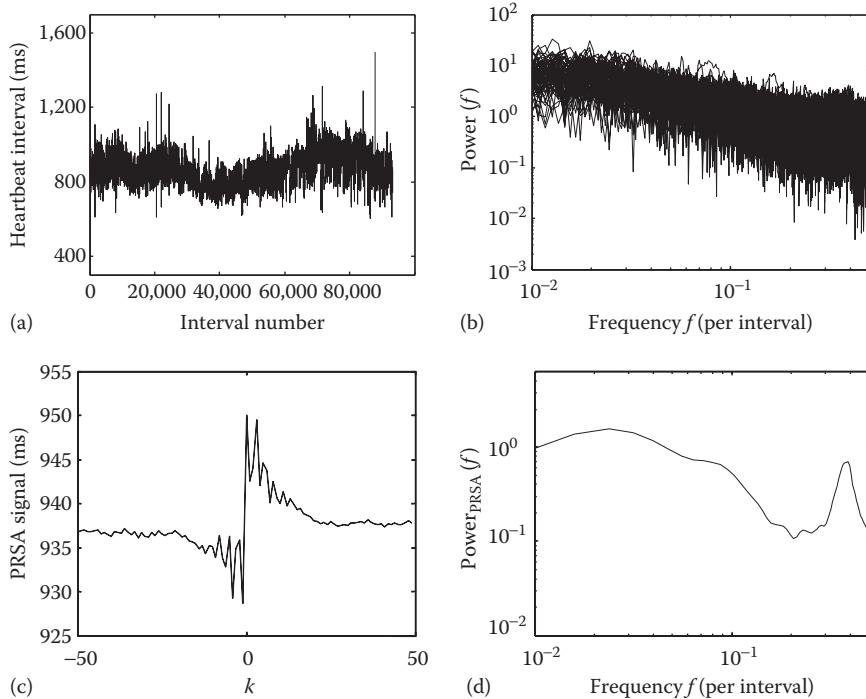
6.2.1.1 Frequency Content of PRSA Signal

The selection of deceleration anchor points is phase-synchronized with the signal, even if the phase is unstable or if non-stationarities occur. Since all patches are aligned with respect to their phase of oscillation (i.e., phase-rectified), the synchronization of the signal patches is ensured, and all patches can contribute to the PRSA signal and its power spectrum. In Figure 6.4, we compare for a 24 h RR interval series, the classical power spectrum in the time domain (Figure 6.4a and 6.4b) and the corresponding PRSA signal and its power spectrum (Figure 6.4c and 6.4d). Both power spectra show peaks for the characteristic periodic components of the signal, but the peaks are much clearer in the phase-rectified spectrum (Figure 6.4d) than in the conventional power spectrum (Figure 6.4b); the signal-to-noise ratio of the phase-rectified spectrum is considerably higher.

6.2.2 Filter Criteria

The previous section described the PRSA method in its simplest setting. There are several parameters of the PRSA algorithm that can be adapted to help answer specific questions. These filter criteria and additional options are discussed first in overview and then in detail.

It is possible to compare more than one interval before and after an anchor candidate. One may, for example, select anchor points by comparing the average of T values before and after the anchor candidate. When using a higher number of T , the anchor selection

**FIGURE 6.4**

Comparison of the original heartbeat interval series recorded over 24 h (a) and the corresponding power spectrum of the original data (b) with the PRSA-transformed signal calculated for prolongations in heartbeat intervals with $T = 1$ and $L = 50$ (c) and the power spectrum of the PRSA signal, the phase-rectified spectrum (d).

becomes an additional low-pass filter. Low-frequency oscillations become dominant in the PRSA signal. Hence, the parameter T can be thought of as a *filter length*.

As already mentioned, it is possible to distinguish between deceleration- and acceleration-related modulations in the heart rate signal. For this purpose, a simple filter, which defines the direction of change (positive or negative), has to be applied. In addition to this simple filter, one can also use the amount of change as a selection criterion. The change can be assessed either relatively (using the ratio of values before and after an anchor candidate) or absolutely (using the difference of values before and after an anchor candidate).

A large number of non-sinus rhythm RR intervals (e.g., ventricular/supraventricular premature complexes) do affect the outcome of PRSA calculations. We will discuss briefly the influence of non-sinus rhythm RR intervals.

6.2.2.1 Filter Length

Anchor point selection is the first step in the PRSA method. When comparing prolongations or shortenings between two succeeding beats, all oscillations are “caught,” independently of the frequency of the oscillations. We can also use more than one RR interval on both sides of an anchor candidate to detect prolongations/shortenings; here, the mean values of T RR intervals before and after an anchor candidate are compared (Equations 6.5a and 6.5b). When doing this, high-frequency components of the data are partially suppressed in the PRSA signal.

$$\frac{1}{T} \sum_{j=0}^{T-1} \text{RRI}_{i+j} > \frac{1}{T} \sum_{j=1}^T \text{RRI}_{i-j}, \quad (6.5a)$$

$$\frac{1}{T} \sum_{j=0}^{T-1} \text{RRI}_{i+j} < \frac{1}{T} \sum_{j=1}^T \text{RRI}_{i-j}. \quad (6.5b)$$

Figure 6.5 illustrates the anchor point selection with filter lengths of $T = 1$ (panel A), $T = 3$ (panel B) and $T = 5$ (panel C). Small filter lengths detect oscillations within a broad frequency band, and more or less all changes in the heart rate pass this filter. The higher filter lengths disregard the changes with high frequencies and therefore low frequencies become dominant.

The influence of different filter lengths applied to Holter ECG recordings is depicted in Figure 6.6; the filter length values used are $T = 1$ (left), $T = 5$ (middle) and $T = 20$ (right). One can see that with larger filter length values, the oscillations with lower frequencies are extracted from the RR interval time series and the oscillations with higher frequencies are attenuated (middle part) or completely removed (right part).

6.2.2.2 Window Length

The window length is not directly related to anchor point selection. The window length is $2L$, where L is the distance from the anchor point. The chosen window length should

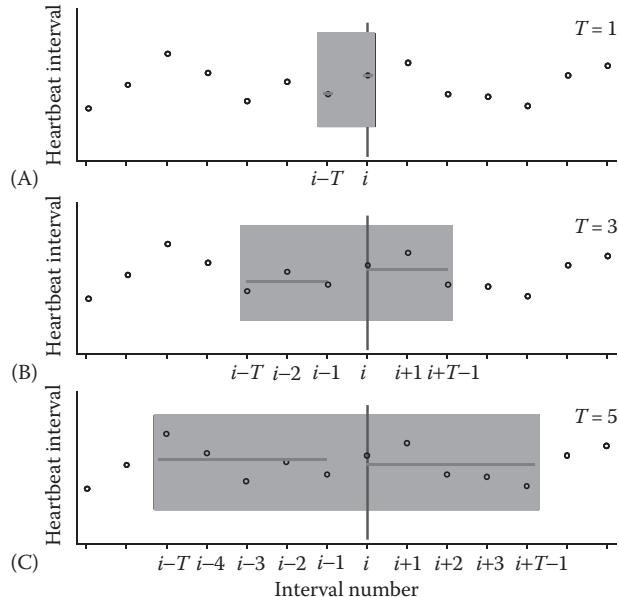
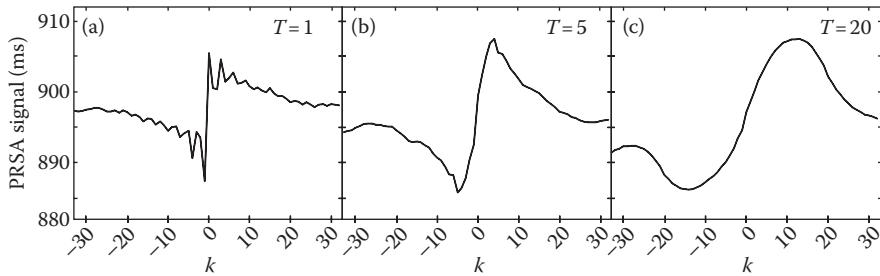


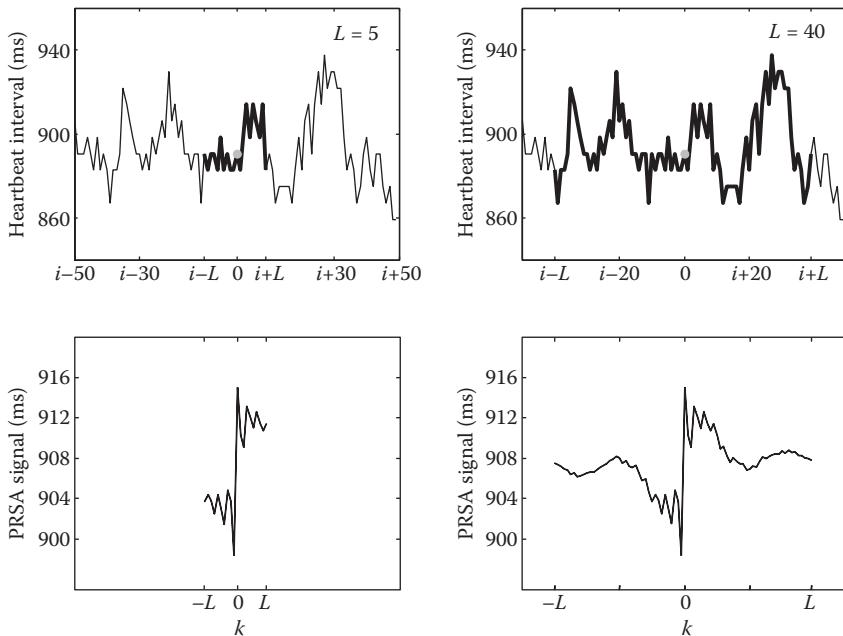
FIGURE 6.5

Anchor point selection using different filter lengths T . The perpendicular line marks the current anchor candidate at interval i . (A) With $T = 1$, only two single intervals are compared with each other. With this filter length, fast oscillations as well as patches out of slower oscillations are detected. (B, C) When using higher values of the filter length ($T = 3$ and $T = 5$), the anchor point selection behaves like a low-pass filter; fast oscillations are “averaged out” and are not taken into account when comparing the values before and after an anchor candidate. Note that in case of $T = 1$ and $T = 3$, a deceleration anchor would be found; when using $T = 5$, an acceleration anchor would be found.

**FIGURE 6.6**

(a–c) Deceleration-related PRSA signals of heartbeat interval series for different values of filter length T . With an increasing filter length, higher-frequency components are filtered out of the PRSA signal and only lower-frequency components are present.

be larger than the period of the slowest oscillations that one wants to detect. The information found in the signal at points away from the anchor gives us two ways to analyze the PRSA-transformed signal RRI_k , by visual inspection and by spectral analysis in the frequency domain. Figure 6.7 shows an example using two different window lengths $L = 5$ (left panel) and $L = 40$ (right panel). The segment around a single anchor point gives just the “noisy” image of the oscillations, whereas the PRSA signal gives a clear image of the

**FIGURE 6.7**

The upper two graphs show the same part of heartbeat intervals with the anchor point in the middle. On the left side, a window length of 5 is used, and on the right side, a window length of 40 is used (bold part of the signal). The lower part shows the PRSA signal from the same heartbeat interval time series but with different window lengths. Using a small window length of $L = 5$ (lower part, left) results in a PRSA signal in which one can only identify one faster oscillation (and an offset between the part before and after the anchor point location). The PRSA signal with a window length of $L = 40$ (lower part, right) shows not only the fast oscillation seen in the PRSA signal for $L = 5$ but also a second oscillation with a lower frequency.

(quasi)periodic oscillations in the signal. Using only a small window length ($L = 5$) results in an average signal, which shows the oscillations with short wavelengths and parts of oscillations with longer wavelengths. The longer window length ($L = 40$) gives us more detailed information about the oscillations with longer wavelengths, while still providing information about the faster oscillating periodicities.

6.2.2.3 Amount of Change as Additional Filter Criterion

As we have discussed so far, the simplest way to analyze oscillations in a time series by PRSA is using all decelerations or accelerations as anchor points. Here, we introduce an additional filter that also takes into account the rate of change of the deceleration or acceleration. With this additional filter, it is possible to exclude triggers that have either too small (e.g., noise added by preprocessing the signal) or too large amplitudes (e.g., premature atrial complexes). There are two ways to distinguish between intervals or patches of intervals to classify a deceleration (or an acceleration), comparing with either a relative change or an absolute change. The relative filter widens or shortens the range of acceptance for anchor points with respect to the current heart rate. On the other side, the absolute filter accepts prolongations (or shortening) of a predefined length in milliseconds independent of the current heart rate.

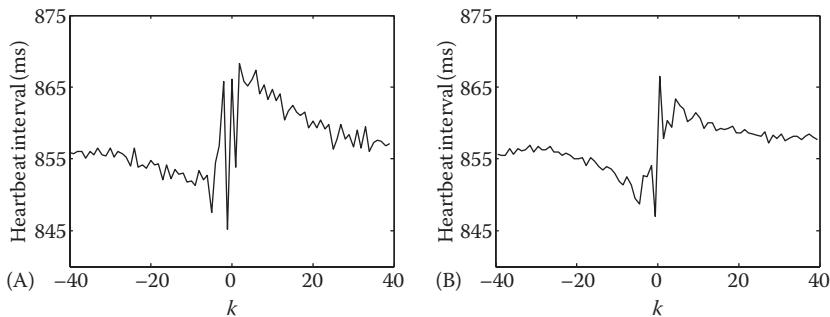
With both filters, it is also possible to look at changes in RR intervals, which have a minimum change and a maximum change. For example, the relative filter can accept prolonged RR intervals, which are at least 102% but not more than 110% of the preceding interval. If a longer filter length T is used, the additional criterion, now described, has to be applied to the average of T intervals before and after the anchor candidate.

6.2.2.4 Influence of Non-Sinus Rhythm RR Intervals

The influence of artifacts or non-sinus rhythm beats (e.g., premature ventricular complexes) on the PRSA method depends on their amount. One would imagine that there are two options for reducing the impact of artifacts on PRSA. The first option is to exclude artifacts from being anchor candidates. Although this is the simpler method, unfortunately, non-sinus beats occurring in the extracted segments around acceptable anchor points still influence the PRSA signal, even if non-sinus intervals are excluded and only normal-to-normal RR intervals are used in a segment. The second correction method avoids this problem by excluding all segments with artifacts or non-sinus rhythm beats anywhere in the segment from the final averaging process. Then, we can be sure that there are no gaps in the segments and that the non-normal RR intervals do not influence the PRSA signal. Figure 6.8 shows an example of two PRSA signals from a Holter ECG recording that contains more than 7800 PVCs. Panel A shows the PRSA signal obtained when segments containing PVC-related RR intervals are used to calculate PRSA. Before the anchor points, the compensatory pause of the PVCs leads to bigger interval values; after the anchor points, the coupling interval of the PVCs leads to smaller values. Thus, the PRSA signal no longer represents only HRV. Panel B of Figure 6.8 shows the PRSA signal when only segments with normal sinus rhythm RR intervals are used; this is the correct PRSA signal.

6.2.3 Sampling Rate

Natural analog signals have to be digitized before further analyses can be performed in computer systems. Therefore, the continuous signal is scanned with a defined sampling frequency to get a discrete signal. The sampling frequency, f_s , defines the number

**FIGURE 6.8**

(A) The PRSA signal when segments with premature ventricular beats were used for calculating the PRSA signal (of the around 30,000 segments used, around 7,800 segments contained at least one PVC-related heartbeat interval). One can see that the central part of the PRSA signal is distorted by the coupling interval and the compensatory pause preceding and following the PVC, respectively. (B) The PRSA signal when segments with PVCs were not used.

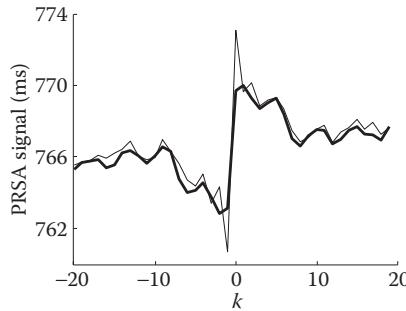
of samples per second and is given in Hertz. The inverse of the sampling frequency is the sampling period or sampling interval, which is the time between two adjacent samples.

To demonstrate how f_s influences the PRSA method, we look at two hypothetical time series, one sampled at 1000 Hz (SigA) and the other at 100 Hz (SigB). The corresponding sample periods are 1 and 10 ms, respectively. First, we start with anchor point selection and define all prolongations between two consecutive intervals in a time series as an anchor. When applying PRSA to SigA, prolongations of 1 ms or longer are selected as anchor points. In SigB, the prolongations need to be at least 10 ms before becoming anchor points. Thus, in SigB, prolongations at time positions with little change are not considered. After anchor point selection, the averaging step in the PRSA method is also affected by the sample frequency. From the signal with the higher sample rate (SigA), additional segments, compared to signal SigB, with smaller changes, are used to calculate the PRSA signal. This results in a PRSA signal where the central amplitude is smaller. On the other hand, a higher sampling rate allows extraction of oscillations with small amplitudes that might be overlooked when using a lower sampling rate.

To study the influence of the sample frequency in ECG recordings, we analyzed 300 short-term recordings of 30 min each. These ECGs were digitized with a sampling frequency of 1600 Hz, meaning that the continuous signal was scanned with a sampling period of 0.625 ms (1/1600 s). We used the detected QRS positions to create new time series of QRS position with lower sample frequencies. For these time series, we determined the RR intervals for each sample frequency and calculated the PRSA signal. Figure 6.9 shows two example PRSA signals, one using the 1600 Hz RR intervals (bold black curve) and the other using the 100 Hz RR intervals (light black curve). As mentioned earlier, the central part of the PRSA signal calculated from the 1600 Hz signal has a lower amplitude than that from the 100 Hz signal.

In Figure 6.10a, we depicted the mean deceleration capacity (DC)* value (y -axis) for all 300 short-time recordings against the sample rate. It can be clearly seen that the DC values decrease with increasing sample rate. Figure 6.10b shows the mean number of anchor points found in the 300 short-term recordings against the sample rate. As expected, the

* DC assesses the amplitude of the central part of the PRSA signal. The definition of deceleration capacity is given in Section 6.2.4.

**FIGURE 6.9**

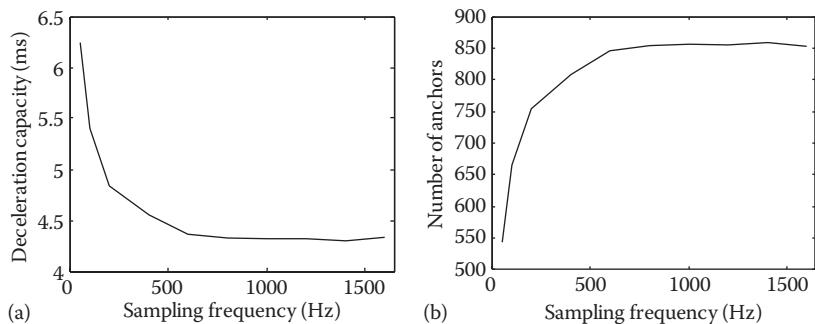
The PRSA signal depicted by the bold black curve was calculated from the heartbeat interval values assessed from an ECG recording with a sample rate of 1600 Hz. The PRSA signal depicted by the light black curve was calculated from the interval values from the same ECG recording but now with a sample rate of 100 Hz.

number of anchor points increases at higher sample rates. Thus, when comparing PRSA signals (or derived parameter) from different recordings, it is important to make sure that the same sample rate has been used.

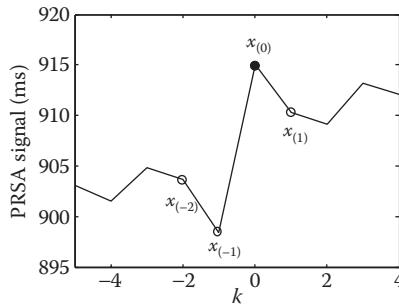
6.2.4 Quantification of the PRSA Signal

To obtain frequency-specific as well as time-specific information from the PRSA signal, we suggest the usage of wavelet analysis, since it allows one to select both the time scale s (inverse of the frequency) and the time position p relative to the center. This way, the frequencies and the coherence times in both time directions can be studied for all quasiperiodicities. To study the wavelet transform of a PRSA signal, Equation 6.6 can be used, which uses a Haar wavelet with mother wavelet w . A more detailed discussion can be found in Bauer et al. (2006a) and Kantelhardt et al. (2007).

$$\overline{\text{RRI}_w}(s, p) = \sum_{k=-L}^L \overline{\text{RRI}_k} \times w\left[\frac{k-p}{s}\right]. \quad (6.6)$$

**FIGURE 6.10**

Dependency of PRSA signals on the temporal resolution of the heartbeat interval series. (a) Mean DC (parameter assessing the amplitude of the central part of the PRSA signal) against sample rate. (b) Mean number of found anchor points against sample rate. The higher the sample rate, the more segments are found in a signal as smaller changes between two subsequent intervals are measurable. This results in lower DC values.

**FIGURE 6.11**

Intervals of the deceleration-related PRSA signal used for the calculation of DC as shown in Equation 6.4.

In the following, we describe one set of specific PRSA settings for analyzing RR interval time series. The parameters using these settings are called deceleration capacity (DC) and acceleration capacity (AC). Both parameters were developed in a large post-infarction cohort (Bauer et al., 2006b) as risk stratifiers. The settings described next are optimized for the purpose of risk stratification of post-MI patients, and it is possible that these settings have to be adjusted for other clinical questions. A more detailed discussion of the clinical application of PRSA is given in Section 6.3.

DC is based on decelerations in the heart rate and uses prolongations between two consecutive RR intervals as anchor candidates. AC is based on accelerations and therefore uses shortenings in RR intervals as anchor candidates. For both parameters, a filter length of $T = 1$ is used. In order to avoid anchor points that are artifacts, we use a relative filter of <5%, which excludes large prolongations or shortenings from being selected as anchor points. After the anchor point selection, we extract the segments with a window length of $L = 2$. For the calculation of DC/AC, we end up with a PRSA signal of length 4. When further frequency analysis or visual analysis of the PRSA signal has to be performed, a higher value of L has to be chosen. Equation 6.7 shows how to calculate DC/AC by using wavelet analysis. In laymen terms, DC and AC assess the difference between the intervals before and after the PRSA signal. By that, it is a measure of the averaged amplitude of all (quasi)periodic oscillations in the signal. Figure 6.11 shows the intervals used for the calculation of DC for the deceleration-related PRSA signal.

$$\text{DC}(\text{AC}) = \frac{1}{4} (\overline{\text{RRI}_0} + \overline{\text{RRI}_1} - \overline{\text{RRI}_{-1}} - \overline{\text{RRI}_{-2}}). \quad (6.7)$$

6.3 Clinical Applications

The ACC/AHA/ESC Guidelines for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death (Zipes et al., 2006) state that “HRV, which is a beat-to-beat variation in cardiac cycle length resulting from autonomic influence on the sinus node of patients in sinus rhythm, has been shown to independently predict the risk of sudden cardiac death and total mortality in patients post-MI both with and without impaired LV function.” The main motivation for the development of PRSA was to measure this autonomic influence to assess the mortality risk of patients who survived an MI. We will therefore begin with

a detailed description of the clinical application of PRSA and, in particular, DC to post-MI patients. Then in the next two sections, we present how PRSA is used in patients with atrial fibrillation and unborn fetuses with growth retardation. Lastly, we describe PRSA in healthy subjects and the effects of depression and air pollution by ultrafine particles on PRSA.

6.3.1 Post-Myocardial Infarction

Since the first publication in 2006, PRSA and, in particular, one of the parameters derived from it called DC have been used to identify patients with high mortality risk after surviving an MI. The association between decreased DC and higher mortality has been shown recently by our group (Bauer et al., 2006b). To determine the optimal cutoff values of DC, the ISAR-HRT study population (Barthel et al., 2003) consisting of 1455 post-MI patients was used (using the optimal PRSA method settings as described in Section 6.2.4). The optimal cutoff values for differentiating between low-, intermediate- and high-risk patients are >4.5 , $4.5\text{--}2.6$ and ≤ 2.5 ms, respectively. Figure 6.12 shows examples of PRSA signals

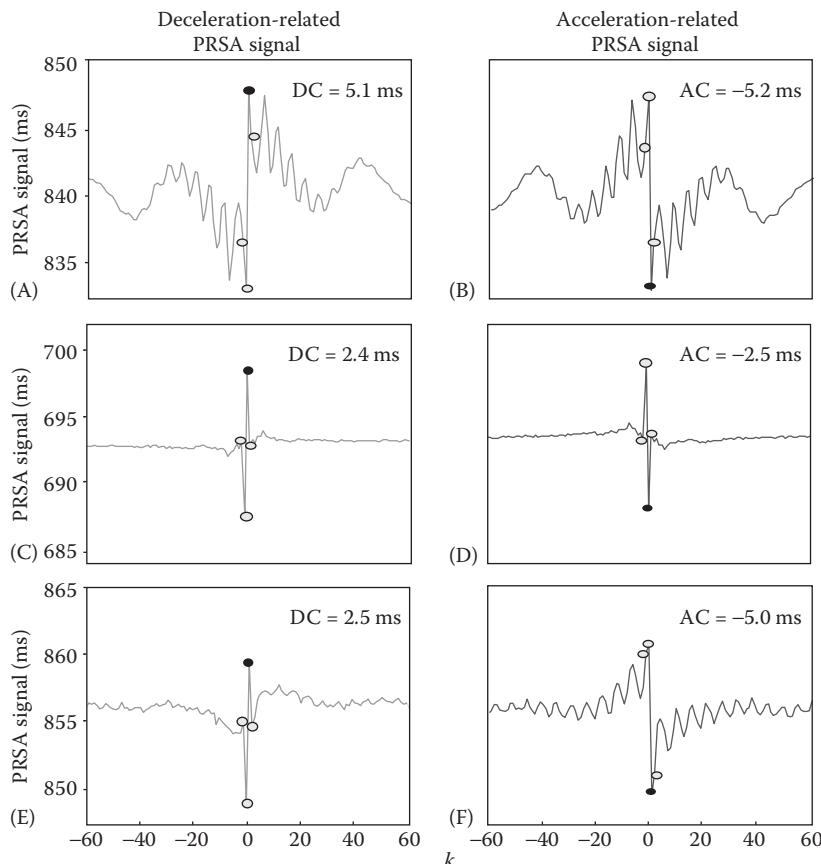


FIGURE 6.12

Examples of PRSA signals of 24 h recordings of heartbeat intervals from patients after an MI. The left part shows the PRSA signals related to decelerations, and the right part shows the acceleration-related PRSA signals. (A, B) The PRSA signals from a patient who survived the follow-up period. (C–F) The PRSA signals from patients who died 3 and 5 months after their index infarction, respectively. DC: Deceleration capacity; AC: Acceleration capacity. (From Bauer, A., Kantelhardt, J.W., Barthel, P., et al. *Lancet*, 367, 1674–1681, 2006b. With permission.)

from post-MI patients; deceleration- and acceleration-related signals are shown on the left- and right-hand sides, respectively. The signals in the first row (panels A and B) are from a patient who survived the follow-up period. DC is in the normal range and both deceleration- and acceleration-related signals show similar behavior. The signals in the middle row (panels C and D) are from a patient who died during the follow-up period. DC is in the abnormal range and again, the deceleration- and acceleration-related signals are similar. The signals in the last row (panels E and F) are from a patient who also died in the follow-up period. Here, DC is again in the abnormal range, but now deceleration- and acceleration-related signals are no longer similar and AC is in the normal range. When constructing receiver operating characteristic curves using the ISAR-HRT population, the area under the curve (AUC) is 77% for DC and 61% for AC. Furthermore, the AUC for left ventricular ejection fraction (LVEF) and the HRV parameter SDNN are 70% and 68%, respectively. The reason DC has a higher association with mortality than AC is unclear as of yet. For now, we hypothesize that decelerations are associated more with vagal modulations and accelerations with sympathetic modulations. As a fully functional vagal system plays a more important role in the well-being of a post-MI patient than a sympathetic system, this could explain why DC is the most suitable parameter for this question.

Based on these findings, we tested the performance of DC in two independent post-MI populations: the St. George's Hospital (London, UK) population and the Multiple Risk Factor Analysis Trial (MRFAT, Oulu, Finland) population. DC showed a strong association with mortality in these validation populations as well, an association that was greater than that for the current gold standard of risk prediction, LVEF. Table 6.1 shows the AUC values for all three study populations. Figure 6.13 shows the Kaplan–Meier mortality curves for the three study populations combined, stratified by the three DC risk groups. The mortality of the patients with normal DC (>4.5 ms) was approximately 2.5% after 2 years and 22% for patients with abnormal DC (≤ 2.5 ms).

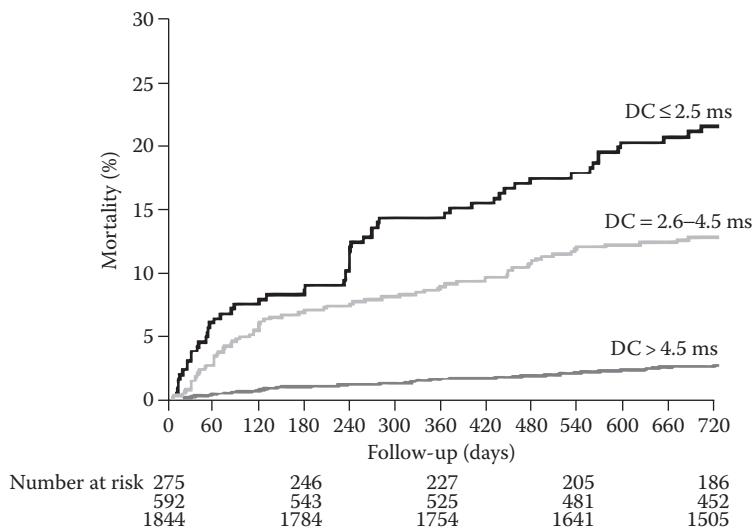
In a follow-up study (Bauer et al., 2009a,b), we introduced the concept of severe autonomic failure (SAF) by combining DC with HRT (Schmidt et al., 1999). SAF was tested in 2343 consecutive survivors of acute MI with a follow-up period of 5 years. SAF was positive if the patients showed both abnormal HRT (defined as having abnormal values for both the turbulence slope and turbulence onset parameters using standard cutoff values) and non-normal DC ($DC \leq 4.5$ ms) in their Holter recordings. Table 6.2 shows the statistical performance indicators (positive and negative predictive accuracy, sensitivity and specificity) for the prediction of all-cause mortality, cardiac mortality and sudden cardiac death in the three high-risk groups of this patient population: (1) LVEF $\leq 30\%$, (2) SAF positive and (3) SAF positive plus LVEF $> 30\%$. It can be seen that these performance indicators

TABLE 6.1

Association of DC, LVEF, and SDNN with All-Cause Mortality Assessed with the Area under the Receiver Operating Characteristic Curve in Post-MI Cohorts from Munich (ISAR-HRT), London (St. George's Hospital Cohort) and Oulu (MRFAT)

	Munich	London	Oulu
DC (%)	77 ± 3	80 ± 3	74 ± 3
LVEF (%)	70 ± 3	67 ± 4	60 ± 4
SDNN (%)	68 ± 3	69 ± 4	64 ± 3

In all three cohorts, the association of DC with mortality is the strongest in the tested parameters.

**FIGURE 6.13**

Kaplan-Meier curves of mortality of patients from Munich (ISAR-HRT), London (St. George's Hospital cohort) and Oulu (MRFAT) stratified by the three DC categories: high-risk (≤ 2.5 ms), intermediate-risk (2.6–4.5 ms) and low-risk (> 4.5 ms). (From Bauer, A., Kantelhardt, J.W., Barthel, P., et al. *Lancet*, 367, 1674–1681, 2006b. With permission.)

TABLE 6.2

Description of Risk-Stratification Performance of LVEF and SAF Parameter in 2343 Post-MI Patients for All-Cause Mortality, Cardiac Mortality, and Sudden Cardiac Death by Positive and Negative Predictive Accuracies (PPA and NPA), Sensitivities and Specificities

	LVEF $\leq 30\%$	SAF	SAF and LVEF $> 30\%$	LVEF $\leq 30\%$ or LVEF $> 30\%$ and SAF
Number of patients (n)	120	152	117	237
All-cause deaths (n)	39	52	37	76
PPA (%)	37.9	39.9	38.6	38.2
NPA (%)	92.2	92.8	93.9	93.9
Sensitivity (%)	21.1	28.2	26.0	42.1
Specificity (%)	96.5	95.7	96.5	93.1
Cardiac deaths (n)	29	40	27	56
PPA (%)	27.6	29.9	27.1	27.3
NPA (%)	95.9	96.4	97.2	97.2
Sensitivity (%)	27.1	37.2	34.8	52.9
Specificity (%)	96.1	95.2	96.0	92.2
Sudden cardiac deaths (n)	12	16	14	26
PPA (%)	12.0	11.6	13.4	12.8
NPA (%)	97.7	97.8	98.3	98.3
Sensitivity (%)	22.1	27.1	30.7	46.6
Specificity (%)	95.4	94.1	95.3	90.9

When combining the risk parameters (LVEF $\leq 30\%$ and LVEF $> 30\%$ and SAF positive), it is possible to double the sensitivity by nearly identical PPAs compared to using LVEF $\leq 30\%$ alone.

are similar when either using the current gold standard LVEF $\leq 30\%$ or SAF in patients with preserved ejection fraction (LVEV $> 30\%$). It is noteworthy that when combining the risk indicators LVEF $\leq/ > 30\%$ and SAF (preserved LVEF) positive/negative, the sensitivity nearly doubles without decreasing the positive predictive accuracy.

In another study, Bauer et al. (2009c) investigated in patients with MI if and how the extent of salvaged myocardium due to reperfusion therapy influences the autonomic function measured by DC. According to the salvage index (proportion of initial perfusion defect that recovered after reperfusion therapy), patients were put into three groups: patients with salvage index $<30\%$, 30%–60% and $>60\%$. The patient group with the least amount of salvaged myocardium had lower DC values (median 5.2 ms, interquartile range 3.5–7.1 ms), compared to the group of patients with the highest amount of salvaged myocardium (median DC value 6.4 ms, interquartile range 5.0–8.0 ms). When testing if the association of DC with mortality was influenced by the salvage index, they found that there was no influence; lower DC values were associated with higher mortality, independent of the salvage index. On the other hand, patients with a lower salvage index had a higher mortality risk, independent of the DC value in these patients. This signifies that “... *salvage index is an independent predictor of autonomic dysfunction but does not affect its prognostic value*” (Bauer et al. 2009c).

6.3.2 Atrial Fibrillation

Bauer et al. (2006c) showed that DC and, therefore, autonomic function were influenced by the atrial fibrillation ablation procedures. The authors studied how DC evolves in patients who underwent circumferential and segmental pulmonary vein ablation. All changes were measured relative to the DC values before ablation. The authors found, for both procedures, a significant decrease in DC directly after ablation, which improved over time. The group that underwent segmental pulmonary vein ablation took 1 month to regain the DC value before ablation. In this group, DC improved further when measured at the 6- and 12-month visits. The circumferential pulmonary vein ablation group also showed an immediate decrease in DC directly after ablation, followed by an improvement over time. But in contrast to the other group, DC stayed significantly below the pre-ablation value in the circumferential pulmonary vein ablation group. The authors speculate that the circumferential pulmonary vein ablation procedure has a more destructive effect on the parasympathetic nerves located in the ganglionated plexus and thus permanently reduces the vagal efferent function in the atrium but also results in an imbalance of afferent sympathetic and parasympathetic inputs to the autonomic nervous system.

Another topic of research in atrial fibrillation is the assessment of the dominant frequency of the atrial fibrillation waves. The dominant frequency is used to characterize the current atrial fibrillation episode and guide atrial fibrillation management. In surface ECG recordings, it is difficult to extract the signal of the fibrillation waves as they are small compared to the ventricular signal seen in an ECG; especially, as in atrial fibrillation, the loss of synchronized atrial activation results in lower signal amplitudes of the fibrillation waves. Preprocessing steps are frequently needed to cancel out the ventricular activation signals from the ECG recording, to be able to extract the frequency of the atrial waves. Estimation of the dominant frequency of atrial fibrillation is normally done by calculating the Fourier spectrum of the signal and then using the frequency component with the highest energy. Lemay et al. (2008) investigated whether applying PRSA to the ECG before calculating the Fourier spectrum could improve the accuracy of dominant frequency assessment in atrial fibrillation. They made the assumption that the atrial

fibrillation waves were quasiperiodic, while the ventricular activation occurrences were irregular (neither periodic nor quasiperiodic). They hypothesized that the atrial fibrillation wave component should be more pronounced, whereas the influence of the ventricular activation on the signal should decrease. The authors were able to show in simulated data that by applying PRSA first, the accuracy of the assessed dominant frequency increased. They used signals with and without removed ventricular activations, and in both types of signals, PRSA reduced the percentage of false detections by a factor of approximately 2. However, Lemay et al. (2008) discovered that this improvement came at the expense of a loss of all information about the power of the dominant frequency component.

6.3.3 Fetal Heart Rate

One problem in pregnancy is intrauterine growth retardation of the fetus. It is known that intrauterine growth retardation negatively influences the cardiovascular system, which results in lower fetal HRV. The current standard method for assessing fetal HRV is the calculation of the short-term variation developed by Dawes et al. (1992) using the fetal heart rate signal from cardiotocograms.* The short-term variation is used for monitoring growth retardations, and a decreasing short-term variation is associated with a deterioration of the fetal blood supply. Huhn et al. (2011) used PRSA to analyze the fetal heart rate signal from cardiotocograms and compared the clinical performance of the PRSA-based parameter that they developed with the clinical performance of short-term variation. For the extraction of the relevant information from the fetal heart rate signal, the authors found that for the parameter T , a value of 40 heart rate samples (i.e., 10 s) and for window length L , a value of 400 heart rate samples (i.e., 100 s) were optimal. The first finding was that for fetal HRV, AC (acceleration-related PRSA signal) showed a higher association with growth retardation than DC and thereby probably assessed the sympathetic influence more. The second finding was that AC of fetal heart rate showed a higher association with growth retardation than short-term variation. Namely, for the areas under the receiver operating characteristic curves for AC and short-term variation, the current standard measures were 81.4% and 70.5%, respectively. A limitation of the study is that the calculation of the PRSA parameters was optimized in the same dataset. Therefore, a follow-up study using an independent dataset is necessary to validate the findings of that study.

6.3.4 Other Applications

6.3.4.1 Schizophrenia

Cardiovascular mortality is the most common natural cause of death in schizophrenic patients. One hypothesized reason is therapy with antipsychotic medications, which can lead to problems in atrioventricular conduction and an increase in ventricular arrhythmias. Birkhofer et al. (2007) compared DC measured in schizophrenic patients taking antipsychotic medications with DC measured in a healthy control group, both assessed in 24 h Holter recordings. The authors found that DC was significantly reduced in the schizophrenic group with a mean DC value of 5.36 ms as compared to 8.25 ms in the control group ($p < .05$). The effect was even more pronounced, when comparing a period of 4 h during the day (5.14 vs. 8.21 ms, $p < .001$). It remains to be seen whether DC differs

* Cardiotocograms record the uterine contractions of the mother and the heart rate of the fetus. The fetal heart rate is measured by assessing the motion of the fetal heart with an ultrasound transducer; every 250 ms, a new heart rate value is recorded.

between schizophrenic patients on and off antipsychotic medications, that is, whether the difference was due to the medications or to the disease itself.

6.3.4.2 Influence of Air Pollution

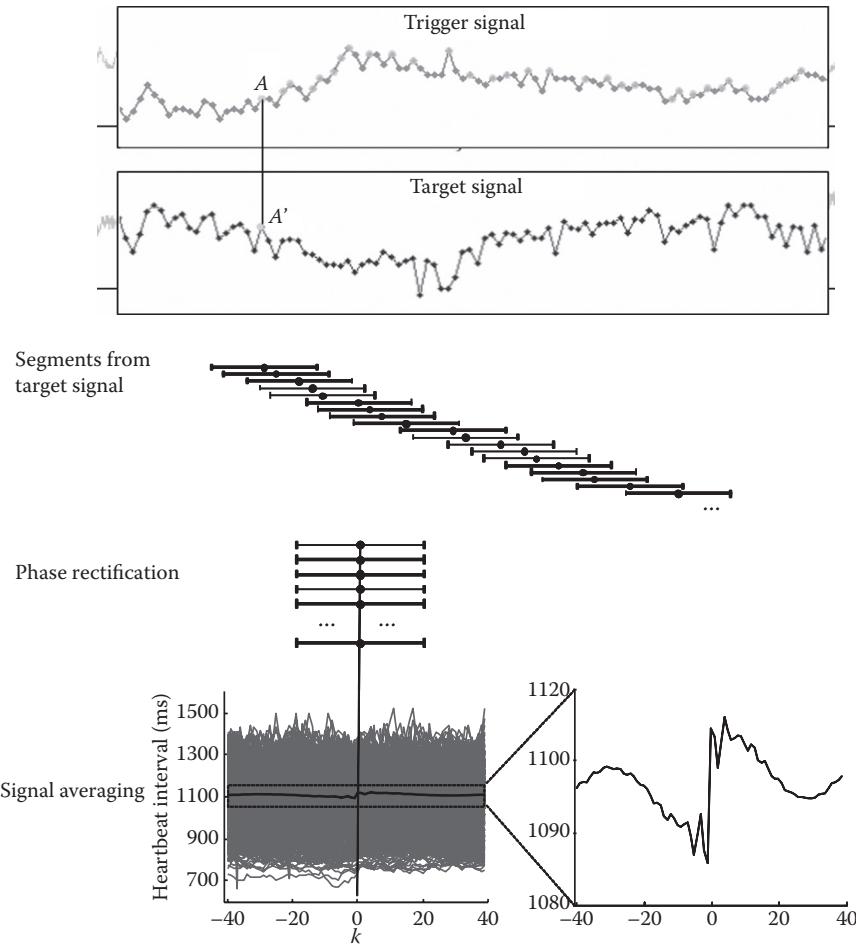
Schneider et al. (2010) investigated, in an epidemiological study of 56 people with chronic ischemic heart disease, the influence of ambient air pollution on various HRV parameters (5 min recordings: normalized high-frequency power, RMSSD; 24 h Holter recording: RMSSD, pNN50, DC). The observation period for each participant was 24 weeks, and a 24 h Holter recording was recorded every 4 weeks. The authors found that an increase in air pollution results in a significant decrease in DC, showing the most pronounced effect of all assessed HRV parameters.

6.3.4.3 Influence of Age

It is known that cardiovascular mortality risk increases with age. One effect of aging is that the autonomic nervous system responds less to afferent inputs. Campana et al. (2010) investigated the influence of age on DC and AC in healthy individuals aged between 21 and 60 years. For the calculation of the PRSA parameters, 5 min recordings were used. The authors found a significantly lower DC and a significantly higher AC in older participants, compared to younger participants. The decrease in DC was 0.29 ms/year, and for AC the increase was 0.27 ms/year. This influence of age in healthy persons was also studied by Schumann et al. (2010) but in a wider age range of 20–89 years. Schumann et al. (2010) studied whether DC in different sleep stages and when the participants are awake differed with age. They found that the influence of age was similar in the different sleep stages and when awake; the decrease in DC per age-year was between 0.12 ms (deep sleep) and 0.16 ms (awake). One interesting aspect of the data presented by Schumann et al. (2010) and by Campana et al. (2010) is that nearly all DC values, even for the oldest age group investigated, are in the normal range ($DC > 4.5$ ms). Thus, the cutoff values, described by Bauer et al. (2006b), appear to be applicable to older patients above 75–80 years, for determining abnormal/diminished autonomic nervous control.

6.4 Bivariate PRSA

So far, the standard PRSA method selects anchor points in the same signal, which is then analyzed. Another possibility is to select anchor points in one signal called the trigger signal (e.g., respiration) and calculate PRSA at the time of these anchor points in a second signal called the target signal (e.g., heart rate). As two signals are involved, it is called bivariate PRSA. Figure 6.14 depicts the steps needed to perform bivariate PRSA analysis. First, the anchor points A are selected in the trigger signal; this step is exactly the same as in univariate PRSA. In the second step, the points in time of the anchor points A' are located in the second time series, the target signal. Steps three to five (select segments, phase rectify segments and average segments) are then again the same as in univariate PRSA, except now using the segments from the target signal. The next section will illustrate some of the characteristics of the bivariate PRSA method using simulated

**FIGURE 6.14**

The upper part shows two signals, the trigger signal (gray curve) and the target signal (black curve). In the trigger signal, trigger-anchor points A are identified. The temporal locations of the trigger-anchor points A are used to select the windows in the target signal (around target-anchor points A'). The windows from the target signal are then phase-rectified by aligning all the windows with the target-anchor point in the center (middle part). The averaging over all windows results in the PRSA signal (lower part).

signals. Section 6.4.2 will show how bivariate PRSA can be used to analyze the relationship between heart rate and blood pressure.

6.4.1 Characteristics of Bivariate PRSA

Bauer et al. (2009d) illustrate the characteristics of bivariate PRSA using artificial time series in their paper “Bivariate phase-rectified signal averaging – a novel technique for cross-correlation analysis in noisy non-stationary signals.” They created three time series composed of $1/f$ noise and one or two quasiperiodic oscillations. Table 6.3 describes the three signals and how they are related to each other.

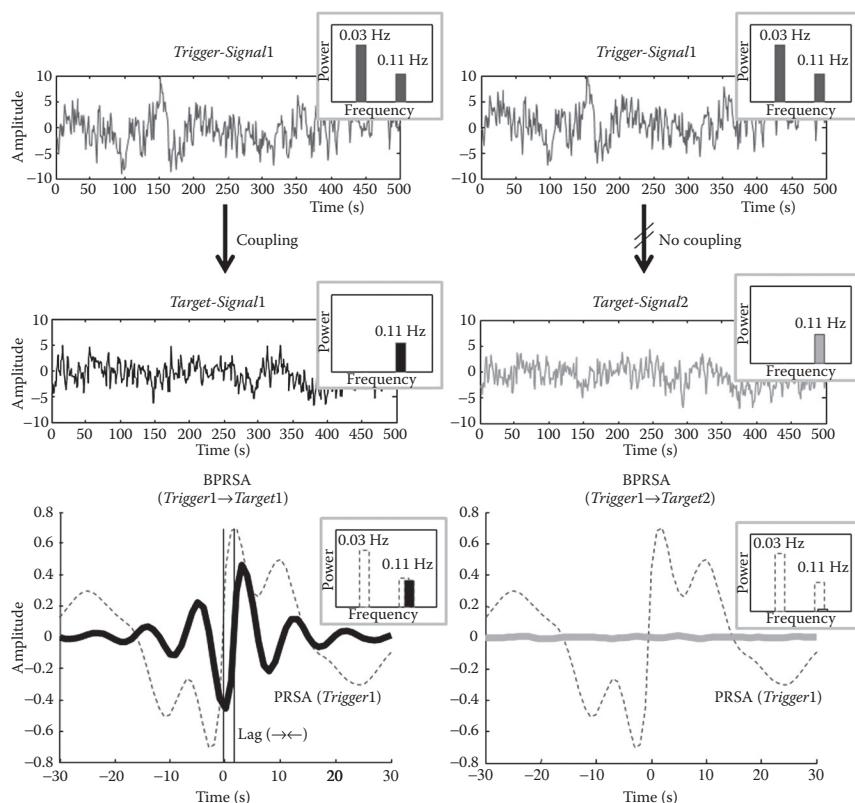
Figure 6.15 shows the results of performing bivariate PRSA using the combination *Trigger-Signal + Target-Signal1* (left side) and *Trigger-Signal + Target-Signal2* (right side).

TABLE 6.3

Artificial Signals Created to Investigate Characteristics of Bivariate PRSA

Signal	Description
Trigger-Signal	1/f noise plus two quasiperiodic oscillations of 0.03 and 0.11 Hz
Target-Signal1	1/f noise plus one quasiperiodic oscillation of 0.11 Hz coupled to 0.11 Hz oscillation in trigger signal with time lag of 2 s
Target-Signal2	1/f noise plus one quasiperiodic oscillation of 0.11 Hz not coupled to 0.11 Hz oscillation in trigger signal

The top row shows the trigger signal for both combinations and the middle row shows *Target-Signal1* on the left side and *Target-Signal2* on the right side. In the lower row, the univariate PRSA-transformed signal of the trigger signal is depicted by the dotted line and the bivariate PRSA-transformed signals are depicted by the solid thick lines. The univariate PRSA of the trigger signal results in the typical PRSA pattern, which contains oscillations of 0.03 and 0.11 Hz; these frequencies were used to create the trigger signal.

**FIGURE 6.15**

Application of bivariate PRSA to simulated data with and without coupling. The upper two rows show trigger and target signals with (left) and without coupling (right). Only the first 500 of 10,000 s are shown. The power spectra in the small boxes were calculated from the signals using Fourier transformation; only the peaks of the spectra are visualized by bars. The lower graphs show the resulting monovariate and bivariate PRSA signals. (From Bauer, A., Barthel, P., Müller, A., Kantelhardt, J. and Schmidt, G., *J. Electrocardiol.*, 42, 602–606, 2009d. With permission.)

The bivariate PRSA of the combination *Trigger-Signal + Target-Signal1* also results in a typical PRSA pattern. However, it contains only the oscillation of 0.11 Hz, which is present in both signals, trigger signal and target signal. Furthermore, the bivariate PRSA signal is shifted to the right by 2 s with respect to the univariate PRSA signal of the trigger signal, which is the time lag used for 0.11 Hz oscillation when creating *Target-Signal1*. On the other hand, bivariate PRSA of the combination *Trigger-Signal + Target-Signal2* shows no oscillation in the PRSA signal, although *Target-Signal2* also contains an oscillation of 0.11 Hz. The difference between *Target-Signal1* and *Target-Signal2* is that the 0.11 Hz oscillation of *Target-Signal1* is coupled to the 0.11 Hz oscillation in the trigger signal. Thus, bivariate PRSA extracts from the two signals only those oscillations that are related to each other. The source of the relationship can be either a process resulting in changes in the two signals simultaneously or changes in one signal triggering responses in the other signal. If the oscillations in the two signals are not related to each other, bivariate PRSA will result in a nearly flat line.

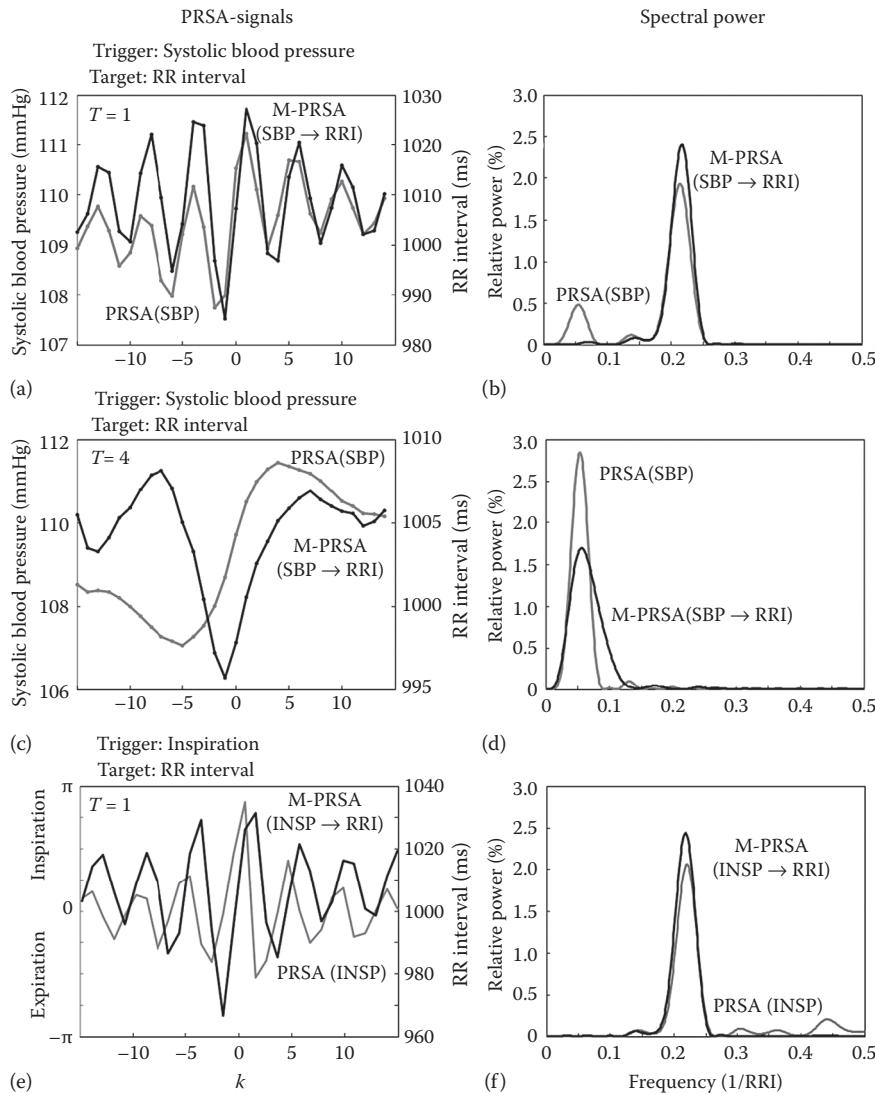
6.4.2 Relationship between Systolic Blood Pressure and Heart Rate

One of the first relationships analyzed by bivariate PRSA was that between arterial pressure, heart rate time and breathing (Schumann et al., 2008; Bauer et al., 2010). Having three signals, the combinations of arterial pressure + heart rate and breathing + heart rate were used, in which heart rate is the target signal and either arterial pressure or breathing is the trigger signal. From the arterial pressure, breathing and heart rate signals, the systolic pressure, respiration phase (inspiration/expiration) and RR interval values were used, respectively.

Figure 6.16 shows the results of bivariate PRSA for a representative example; on the left side, the univariate and bivariate PRSA signals are shown, and on the right side, the frequency spectra of the PRSA signals are shown. The black PRSA signals and spectra are from bivariate PRSA, and the gray lines are from the univariate PRSA analysis (systolic pressure and respiration phase signal). The top and middle rows are the results for the combination systolic pressure + RR interval, and the bottom row depicts the results for the combination respiration phase + RR interval. For the analysis of the relationship between the systolic pressure and the RR intervals, two different anchor point selection criteria were used, allowing extraction of the high-frequency oscillations ($T = 1$, top row) and the low-frequency oscillations ($T = 4$, mid row).

As one can see, all bivariate PRSA signals show oscillations, meaning that the oscillations in the signals are related to each other. Univariate PRSA analysis of the systolic pressure signal with $T = 1$ shows two oscillations, which are at around 0.06 and 0.23 Hz. After performing bivariate PRSA analysis for the combination systolic pressure + RR intervals and $T = 1$, only the oscillation with 0.23 Hz stays in the signal; the oscillation with 0.06 Hz is nearly gone. Also of interest is that there is no time lag between the univariate PRSA signal of the systolic pressure signal and the bivariate PRSA signal of the combination systolic pressure + RR interval. This could mean that the oscillation with 0.23 Hz is triggered by a higher-order control process. When using $T = 4$, the analysis focuses on the oscillation at 0.06 Hz, both in univariate and bivariate PRSA analyses. Of interest here is that the time lag between univariate and bivariate PRSA signals is around 1 RR interval, meaning that most probably the slow-changing systolic pressure values trigger a response in the heart rate.

The univariate PRSA analysis for the respiration phase shows only one oscillation at around 0.23 Hz. When performing bivariate PRSA analysis for respiration phase + RR

**FIGURE 6.16**

(a–f) Application of bivariate PRSA to synchronously recorded series of heartbeat intervals, systolic blood pressure and respiration. Black lines represent bivariate PRSA signals and spectra, gray lines represent univariate PRSA signals and spectra. (From Bauer, A., Barthel, P., Müller, A., Kantelhardt, J. and Schmidt, G., *J. Electrocardiol.*, 42, 602–606, 2009d. With permission.)

interval, this oscillation is still present. However, there is now a time lag between the univariate PRSA signal of respiration and the bivariate PRSA signal of combination respiration phase + RR interval. This again could mean that the changes in respiration phase trigger changes in heart rate. When doing bivariate PRSA analysis for combination respiration phase + systolic pressure (not shown), one can also see a time lag between univariate and bivariate PRSA signals. This finding corroborates our earlier assumption that the oscillation with a frequency of 0.23 Hz in the systolic pressure and RR interval signal is triggered by a higher-order process; in this case, respiration.

6.4 Conclusion

PRSA is a novel tool for HRV analysis that has been validated as a risk stratifier in post-MI patients and appears to be useful in non-cardiac fields as well. Bivariate PRSA offers insights into the complex interplay between blood pressure, heart rate and respiration.

Abbreviations

AC	Acceleration capacity
DC	Deceleration capacity
ECG	Electrocardiogram
HRT	Heart rate turbulence
HRV	Heart rate variability
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
PRSA	Phase-rectified signal averaging
SAF	Severe autonomic function

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Section II

Clinical Applications of Heart Rate Variability—Monitoring

7

Heart Rate Variability Analysis for the Monitoring of Fetal Distress and Neonatal Critical Care

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Maria Gabriella Signorini and Sergio Cerutti**

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7.1 Introduction

There is a debate about the management of compromised fetuses. The issue is whether the intrauterine time gained by delaying the delivery is largely advantageous for the fetus or comes at the greater expense of increased perinatal complications. In this context, fetal evaluation is crucial and needs to accurately reflect fetal well-being, anticipate the most likely course of progression and accurately predict perinatal outcomes of critical importance. The principal purpose of fetal monitoring is, thus, to provide quantitative and reliable clinical tools for early detection of an emergence of life-threatening conditions.

In this chapter, we will review several techniques for analyzing fetal heart rate (FHR) signals obtained during pre-natal monitoring. Moreover, we will consider tools for monitoring fetuses after they are born, namely, heart rate variability (HRV) parameters for monitoring neonates in the neonatal intensive care unit (NICU) to predict or recognize sepsis. Both traditional and advanced techniques will be discussed, with an emphasis on recent findings and non-linear methods in HRV.

7.2 Fetal and Neonatal Cardiovascular Physiology and Monitoring Systems

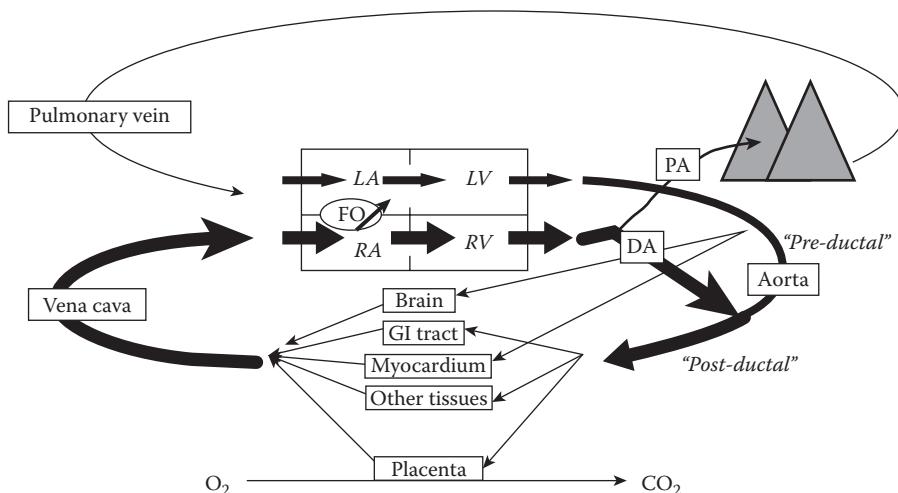
The main role of the cardiovascular system in fetuses is the same as in adults: the uptake of oxygen and substrates from the environment and their delivery to the body to maintain homeostasis. The heart is the first organ to become fully functional; it drives the circulation necessary for embryogenesis and subsequent fetal growth. The heartbeat in the human fetus originates in the ventricular myocytes and is reported to begin between 21 and 23 days after fertilization. The heart rate (HR) at this stage is approximately 100 bpm. Caudal fusion of the atrial and ventricular components of the primitive heart tube is associated with an increase in the frequency of pulsation, so that a peristaltic wave begins in the atrium and is transmitted to the ventricle. The increase in the HR between the 5th and 8th gestational weeks is probably related to a combination of factors, including the sinus venosus becoming the definitive pacemaker, the heart responding to the rapidly increasing demands of the developing embryo and the increase in the systemic arterial pressure with growth. The variability in HR from 15th gestational week to full term reflects further progression of autonomic innervation of the heart, causing it to be more responsive to both intrinsic and extrinsic stimuli (Polin and Fox, 1992).

The ability of the fetus to survive, grow and successfully complete the transition from fetal to neonatal life is critically dependent on the appropriate regulation of the fetal blood pressure, blood volume and fluid dynamics. Disturbances in the development and regulation of the fetal cardiovascular function can produce a variety of problems that increase both mortality and morbidity of the late-gestation fetus and in the newborn. Here, physiological mechanisms controlling the fetal cardiovascular system are presented by focusing mainly on the neural and endocrine elements in the schema of cardiovascular function and control.

The general principles governing the control of blood pressure and blood volume form a basis of comparison of the fetal and adult control mechanisms. In adults, we have:

1. The general principle of negative feedback. Blood pressure elevation stimulates an increase in the firing rate of arterial baroreceptors, which activate a reflex response that ultimately reduces the HR, cardiac contractility, sympathetic vasoconstriction tone and rate of secretion of the pressor hormones (Guyton, 1990).
2. The hormonal system, which influences the blood pressure and volume. It is influenced by neural receptors on both the high- and low-pressure segments of the cardiovascular system (Share, 1967).
3. The mechanisms controlling ventilation. They are integrated with the mechanisms controlling the blood pressure.

In some respects, the fetal cardiovascular control systems are similar to those in adults. In other respects, the control of the fetal cardiovascular system is different. In fact, it is optimized to maintain the perfusion of the placenta, which is the organ of gas exchange. The fetal cardiovascular system is anatomically arranged in such a way as to allow blood to bypass lungs and to provide perfusion of the placenta. This is accomplished by the presence of several shunts within the fetal cardiovascular system that establish both lungs

**FIGURE 7.1**

Schematic representation of the course of fetal circulation. LA, left atrium; RA, right atrium; LV, left ventricle; RV, right ventricle; PA, pulmonary artery; DA, ductus arteriosus; FO, foramen ovale. (Reproduced from Wood, C. and Tong, H., *Am. J. Physiol. Regul. Integr. Comp. Physiol.*, 277, R1541–R1552, 1999. With permission.)

and the placenta as parallel circuits within a circulation, in which both ventricles pump in parallel (Figure 7.1).

Much of the blood pumped into pulmonary artery from the right ventricle passes through ductus arteriosus rather than through lungs. Indeed, only 8% of the combined ventricular output perfuses the lungs of the fetus in late gestation. Conversely, a portion of the blood entering right atrium passes through foramen ovale into the left atrium. The placenta is perfused in parallel to the other systemic vascular beds and does not exhibit much inherent autoregulation of blood flow; therefore, its flow is affected by the prevailing arterial blood pressure (but sensitively modified by vasoconstrictors). For this reason, regulation of the fetal arterial blood pressure is important for maintaining efficient gas exchange within the umbilical-placental circulation. Not accidentally, fetal blood volume (expressed as a proportion of fetal body weight) is higher, fetal blood pressure is lower and the FHR is higher, compared to those of adults. The need for perfusion of the low-resistance circuit of umbilical-placental circulation, combined with the need for fetal fluid sequestration, which is essential for fetal growth, dictates a prevailing blood pressure that is 50%–60% that of adults. The low blood pressure impairs the ability of the fetus to preserve blood flow in critical organs during periods of transient hypotension.

Because of the relatively low blood pressure, neural control of fetal circulation is far more dependent on chemoreceptor control compared to that of adult circulation. This adaptation is of particular advantage for the fetus, because major function of the fetal cardiovascular system is the transport of oxygen and carbon dioxide to and from the placenta and because changes in gas exchange can only be effected via changes in placental perfusion. In other words, the rate of gas exchange in the fetus is modified by altering fetal arterial blood pressure and circulating concentrations of constrictor hormones, based on chemoreceptor inputs.

7.2.1 Fetal Distress and Fetal Growth Retardation

The most common cause of fetal distress is decreased oxygen delivery to the fetus. Any factor that decreases oxygen content of the maternal blood, such as altitude, lung disease and anemia, will also decrease oxygen delivery to the fetus. Other factors can be vascular disease of the uterus, abruption of the placenta and knots in the umbilical cord. If the decrease in oxygen delivery is severe enough, the fetus will eventually become acidotic due to an increase in the production of metabolic acids. In some situations, decreased carbon dioxide elimination complicates the problem and leads to acidosis. Acidosis is increased acidity induced by an increase in hydrogen ion concentration in the blood plasma (arterial pH falls below 7.35). The fetus can adapt to a decreased oxygen content of the arterial blood in several ways, which are summarized as follows:

1. The first potential mechanism is to increase *oxygen extraction*, thus decreasing the oxygen content of the venous blood and recovering some of the oxygen consumed that would otherwise be lost. Decreasing *oxygen consumption* is another possible adaptation. The fetus and the newborn can decrease oxygen consumption by one-third without developing acidosis. It has been hypothesized that the ability of the fetus and the newborn to decrease oxygen consumption is due to turning off of a portion of oxygen being consumed that is normally devoted to growth (Sidi et al., 1983).
2. The fetus has another potential mechanism to adapt itself to a decreased oxygen content of the blood: the *redistribution of placental venous return*. Because of the parallel arrangement of fetal circulation, highly oxygenated blood from ascending aorta is more efficiently and selectively distributed to organs that are essential for short-term survival. During stress, fetal venous blood flow patterns change. In general, the proportion of umbilical venous return crossing ductus venosus increases. Prolonged hypoxia or hypotension increases the proportion of umbilical venous blood flowing across ductus venosus from 53% to 90% (Behrman et al., 1970). During fetal stress, the proportion of the highly oxygenated umbilical venous return crossing ductus venosus may increase, and this increase may provide a faster transit time for a more rapid filling of the atria. However, there is no increase in the distribution of this blood across the foramen ovale to essential organs, the heart and the brain, supplied by the ascending aorta.
3. Another adaptation mechanism of the fetus to hypoxia is the *redistribution of arterial blood flow*. In the fetus, blood flow to the heart, adrenal glands and brain increases consistently when the oxygen content of the blood decreases, in order to maintain a stable oxygen delivery to these organs and prevent ischemia (this phenomenon is also called "brain sparing effect"). During hypoxia, the blood flow diverges from the lungs: even a modest decrease in the blood oxygen content can cause a 50% decrease in the pulmonary blood flow. The most adaptive response for the fetus, during a decrease in the oxygen content of the blood returning from the placenta, is to correspondingly increase placental blood flow. There is, in fact, evidence from several studies that the placental vascular resistance increases during hypoxia.
4. The *circulatory responses*. Hypoxia increases blood pressure and decreases HR and combined ventricular output in the fetus. The decrease in HR may be initially due to neural reflexes, but chemoreceptors in the aortic and carotid vessels may

contribute to bradycardia as well. Severe hypoxia, particularly with acidosis, may depress the HR by direct effects on the myocardium: the vagal output associated with baroreflex and chemoreflex depresses contractility and stroke volume (Polin and Fox, 1992).

Fetal growth retardation (FGR) or intrauterine growth restriction (IUGR) describes a condition of the fetus associated with an increased risk of perinatal mortality and morbidity. The incidence of IUGR is estimated to be approximately 5%–7% (Brodsy and Christou, 2004). Despite advances in obstetric care, IUGR remains prevalent in industrialized countries. However, causes of IUGR in these areas are different from those in developing nations. In most Western societies, placental insufficiency is the major cause of IUGR, while inadequate maternal nutrition and malaria infections play a greater role in developing countries. However, a large number of etiologies are not identified and known associations involve fetal, placental and/or maternal factors (Table 7.1).

Identification of IUGR is essential because proper evaluation and management can result in a favorable outcome. Some pregnancies are at high risk for growth restriction, although a substantial percentage of cases occur in the general obstetric population. Dating fetal growth accurately in early pregnancy is essential for a diagnosis of IUGR. Fetal biometry, which is based on non-invasive ultrasound techniques, is the gold standard for an assessment of fetal size and the amount of amniotic fluid. Therefore, it is an useful tool for identifying small for gestational age (SGA) fetuses, which are characterized by dimensions below the 10th percentile of the population standards. Despite numerous approaches to managing IUGR, there are no effective therapies to improve the growth pattern of a fetus, so pre-natal management is primarily aimed at determining the ideal timing and mode of delivery (Baschat, 2004). This assessment must be individualized, depending on several variables: gestational age of the fetus, maternal health, severity of the IUGR and fetal well-being. Perhaps, optimizing the delivery time and removing the fetus from a suboptimal environment can prevent the risk of hypoxia and significant morbidities.

The gestational age of the fetus is a critical factor of the decision-making component. If a growth-restricted fetus is near term with either deficient growth or associated severe maternal preeclampsia, delivery is recommended. Similarly, an IUGR fetus between the 34th and 37th gestational weeks should be delivered if there are similar concerns in the

TABLE 7.1

Maternal, Placental and Fetal Etiologies of IUGR

Maternal	Placental	Fetal
Vascular disorders (25%–30%)	Abnormal trophoblast invasion	Genetic (20%)
Hypertension	Placenta infarcts	Chromosomal abnormalities
Diabetes mellitus	Placenta previa	Syndrome/congenital malformations
Renal disease	Circumvallate placenta	Multiple gestation (5%)
Collagen vascular disease	Chorioangioma	Intrauterine infection
Hypercoagulable states	Velamentous umbilical cord insertion	Cytomegalovirus
Thrombophilia	Umbilical-placental vascular anomalies	Malaria
Antiphospholipid antibody syndrome		Parvovirus
Persistent hypoxia (e.g., pulmonary disease)		Rubella
Undernutrition, toxins (e.g., alcohol, tobacco)		Toxoplasmosis
Uterine malformation or masses		Herpes virus
		HIV

Source: Brodsy, D. and Christou, H., *J. Intens. Care Med.*, 19, 307–319, 2004.

setting of mature fetal lung indices. The management of a premature infant of <34th gestational week is more challenging. Indeed, the risk of intrauterine compromise has to be weighed against potential risks arising from elective premature delivery, which are typically higher for deliveries before 32nd to 34th gestational weeks (Brodsky and Christou, 2004).

In the group of IUGR fetuses with unclear indications for immediate delivery, the obstetrician must rely on other assessment tools to monitor fetal well-being and to determine the safest time for delivery. Currently, there are two crucial problems that need to be solved: differentiation of fetuses with pathological SGA from fetuses that are small but healthy and the lack of evidence-based guidelines for clinical management of SGA fetuses.

7.2.2 Neonatal Sepsis

According to the Sepsis Conference definition, sepsis consists of systemic inflammatory response syndrome (SIRS, diagnosed by the presence of two or more values of extreme body temperature, rapid HR, rapid respiratory rate and abnormal white blood cell counts) and the presence of a culture-documented infection. If, in addition to sepsis, there is low blood pressure (hypotension) or insufficient blood flow (hypoperfusion) to one or more organs (causing, e.g., lactic acidosis), it is called septic shock.

In neonates, sepsis is difficult to diagnose clinically. They may be relatively asymptomatic until hemodynamic and respiratory collapse are imminent. Therefore, if there is even a remote suspicion of sepsis, they are frequently empirically treated with antibiotics until cultures are sufficiently proven to be negative.

IUGR infants have compromised humoral and cellular immunocompetence, including decrease in concentrations of IgG antibodies, phagocytic index and lysozymes. Studies have shown that culture-proven sepsis is more common in those born at term with less than the third percentile birth weight. Neutropenia (an abnormally low number of neutrophils) in extremely preterm IUGR infants, which occurs frequently in those born to preeclamptic mothers, substantially adds to the risk of sepsis (Yu and Upadhyay, 2004).

Therefore, an early diagnosis of subacute, potentially catastrophic sepsis in neonates is important. Several early physiological markers of neonatal sepsis have been proposed, such as reduced variability and transient decelerations of the HR.

7.2.3 Fetal Monitoring Systems

The identification of risky conditions that are not associated with a clearly identified pathology but that may lead the fetus to a pathological state in the remaining time of the pregnancy still remains the most challenging problem in fetal monitoring. In this context, the generic term *fetal distress* is used to label the most common life-threatening state and is defined as a decreased oxygen delivery to the fetus, which can lead to brain damage. Unfortunately, subtle signs of fetal compromise can be missed, and moreover, during the past few decades, many studies have shown that antenatal surveillance in unselected population is of little value (Malcus, 2004).

The first step in finding a solution for this problem is represented by the possibility of quantifying physiological variables from available measures, such as the FHR signal, and thus finding new parameters that provide evidence of anomalies.

Discussion about the management of fetal distress frequently revolves around the issue of whether the intrauterine time gained by delayed delivery is advantageous for

the fetus or whether it comes at the expense of increased perinatal complications that are a result of allowing a worsening of fetal health. In the last few decades, clinical research has been engaged in the study of the progression and prediction of the course of pathological conditions (Bilardo et al., 2004; Ferrazzi et al., 2002). Furthermore, new methods for fetal surveillance have been proposed in order to identify pathophysiology in pregnancies at risk.

7.2.3.1 Cardiotocography

In the early 1970s, continuous-wave (CW) Doppler ultrasound was introduced as a new method for FHR monitoring. A few years later, the ultrasound pulsed-Doppler method was introduced, bringing with it an improved signal-to-noise ratio and the ability to detect signals from a defined depth.

Using this method, a pulse typically consisting of about 100 cycles of 1 MHz is transmitted toward the fetal heart. Then, the ultrasound crystal is electrically switched to the receiving mode. The reflected pulse, slightly shifted in frequency (Doppler shift) by the contractions of the fetal heart, will be compared with the transmitted pulse (demodulation). In earlier fetal monitors, beat-to-beat FHR was calculated using peak detection (the procedure measures time T from the highest peak in the first heartbeat to the highest peak in second heartbeat). Since these two heartbeats can have similar double peaks, up to four different time intervals, T_1 to T_4 , can be estimated and consequently, four different FHR values are possible. However, peak-to-peak detection lacked accuracy due to "jitter" (artificial variability) affecting the beat-to-beat FHR. With the introduction of the autocorrelation method, successive heart signals are compared and tested for their similarity. Thus, a complete waveform related to a heart cycle is compared to the following one. The autocorrelation method has led the ultrasound technology to closely approach the "gold standard" of direct ECG in detecting the FHR signal (Lawson et al., 1983).

Even slight movements of the fetus or the mother and other sources can change the detected Doppler signal. To overcome these problems, an average buffer with several weighted heartbeat durations is built up and the most probable HR is generated. The actual FHR signal produced by cardiotocography (CTG) device (it can be printed or recorded) is obtained by sampling the buffer at a constant rate (usually 2 Hz), independently from the value of the buffer itself. This means that an FHR value can be sampled twice and the resulting series displays high persistence. Thus, the advantage of easily picking up the fetal heart activity must be balanced with the disadvantage of a limited beat-to-beat accuracy. In Western countries, CTG has become the leading fetal monitoring system during labor.

7.2.3.2 Abdominal ECG and Scalp ECG

The analysis of FHR over long periods of time or during continuous monitoring is a powerful tool in detecting the problems occurring during pregnancy. Doppler ultrasound, which is extensively used, is not suitable for long periods of monitoring. Therefore, medical researchers have focused lately on abdominal ECG signal processing to obtain information on FHR and uterine contractions.

Fetal ECG (FECG) monitoring is completely non-invasive and can be used over extended periods. It consists of recording electrical activity from the mother's abdomen, which is then analyzed, starting with the detection of the fetal R-wave peaks (Solum et al., 1980).

The main drawback of this technique is that the FECG has low signal-to-noise ratio because of the interference caused by many sources of noise. The maternal electrocardiogram (MECG), by itself, is the major contribution of noise. The maximum amplitude of the maternal QRS complex usually oscillates from 100 to 150 μ V, while it is less than 60 μ V for the fetal QRS complex. Other sources of interference are electromyogram (EMG) activity and motion artifacts.

Several methods of FECG extraction have been developed over the last few decades. These methods are based on adaptive filtering (Widrow et al., 1975), subtraction (Meijer, 1981), digital filtering and averaging (Cerutti et al., 1981), principal component analysis (PCA) and independent component analysis (ICA) (Callaerts et al., 1986; Lathauwer et al., 2000; Martens et al., 2007).

ECG recorded from the fetal scalp electrodes is still the gold standard for the measurement of cardiac electrical activity of the fetus. The advantage of this technique is that it provides a direct and non-invasive measurement of the electrical activity of the fetal heart, including visualization of the ECG waveform. However, it can only be measured during labor, after rupture of the membranes.

The ST segment and *T*-wave reflect the repolarization of myocardial cells in preparation for the next contraction. This repolarization process is energy consuming. An increase in *T*-wave height occurs when the energy balance within the myocardial cells is threatened. During hypoxia, this balance becomes negative and myocardial cells produce energy by β -adrenoceptor-mediated anaerobic breakdown of glycogen reserves. This process not only produces lactic acid but also potassium ions (K^+), which affect the myocardial cell membrane potential and cause a rise in the ST segment of the ECG (Amer-Wählin et al., 2005).

Rosen and Kjellmer (1975) observed progressive changes in the ST interval prior to bradycardia in FECG tracings in experimental hypoxia induced in animals. The ST waveform can be assessed qualitatively by its shape and quantitatively by the height of the *T*-wave in relation to the height of the QRS wave (*T/QRS* ratio). Greene et al. (1982) found a correlation between high *T/QRS* with persistently elevated ST waveforms and anaerobic metabolism in chronically instrumented lambs. Westgate et al. (2001) reported on the ST waveform changes during repeated umbilical cord occlusions in near-term fetal sheep. They described a progressively increasing *T/QRS* ratio with an increasing degree of hypoxia by reducing the interval between cord occlusions from 5 to 2.5 min. The authors concluded that an increase in *T/QRS* ratio indicates hypoxic stress and that the appearance of negative and biphasic ST waveforms, i.e., an ST segment that slopes downward to become negative relative to the baseline (isoelectric line), followed by an initially lowered *T*-wave, which becomes positive, may be a useful marker of increasing fetal hypoxia.

ST changes may also occur in response to the general surge of stress hormones (adrenaline) occurring during labor (Høegard et al., 1979). However, the physiology behind biphasic ST events can be related to the mechanical performance of the myocardium and the relationship between inner (endocardium) and outer (epicardium) layers of the walls of ventricles in particular. In this case, biphasic ST illustrates an imbalance between these two layers. The biphasic ST may be caused not only by hypoxia, *per se*, but also, basically, by all factors substantially altering the balance and performance characteristics within the myocardial wall (prematurity, infections, etc.). This can explain why automatic ST analysis (STAN) of the fetal electrocardiography does not seem to have reduced the rate of neonatal acidemia and the rate of operative intervention during labor (Ojala et al., 2006).

7.3 FHR Variability Analysis and Identification of Fetal Distress

At the beginning, FHR monitoring was adopted as a valuable clinical tool only for intrapartum management. Since the evaluation of FHR traces was made by obstetricians through visual inspection, empirical findings outlined earlier determined the definition of quantitative measures. In fact, clinical practice had highlighted that certain fetal heart rate patterns (FHRPs), particularly certain transient decelerations associated with uterine contractions, were frequently associated with fetal hypoxia. Moreover, these observations led to an assumption that, in addition to a constant vagal tone, there was an oscillatory vagal tone, which acted on the intrinsic rate, giving a slightly variable time between adjacent cardiac contractions. This interpretation of signal oscillations led to the definition of two parameters: the short-term irregularity or variability (STV) parameter to describe very rapid oscillations and the so-called long-term irregularity or variability (LTI) parameter to characterize slow fluctuations (Laros et al., 1977).

In the construction of an automated system for the evaluation of FHR recordings, a reproducible determination of the baseline is a fundamental starting point. In fact, interpretation of the HR pattern is performed by the physician, who analyzes deviations of the signal from the baseline, usually a hypothetical running average of the HR. Accelerations and decelerations are defined as deviations from the baseline, and several attempts to quantitatively define them have been made, starting from the work of Dawes et al. (1982). The most common approach in clinical application is that suggested by Mantel et al. (1990a).

The Mantel method consists first in the estimation of a histogram of RR values. A reference RR baseline value is computed at the beginning of baseline computation procedure, scanning the RR histogram from high to low values. The RR basal value is located after at least 0.167 of the whole area of the histogram is scanned. This still ensures a baseline value that fits near the lower level of the basal HR, but it avoids problems with subjects suffering from fetal tachycardia (or showing episodes of tachycardia, with a basal HR higher than the average HR).

Accelerations and decelerations are deviations of the FHR from the baseline, lasting for a sufficient amount of time (accelerations are positive deviations, while decelerations are negative). They are correlated with normal activities of the fetus and the most common fetal behavioral states.

In the second half of pregnancy, these episodes of activity or rest become increasingly linked to specific parameters of the FHRP and eye movements (EM), which finally result in fetal behavioral states that are widely viewed as reflective of the developing central nervous system. Four fetal behavioral states have been identified in concert with the state scoring methods developed for neonates (Table 7.2). Although not identical with newborn states, these approximate quiet sleep (1F), REM sleep (2F), quiet waking (3F) and active waking (4F) states, respectively. FHRPs have been visually classified by obstetricians as A, B, C and D (Nijhuis et al., 1982). FHRP A is a stable HR with a narrow oscillation bandwidth. Isolated

TABLE 7.2

Criteria for the Classification of Fetal Behavioral States (S)

	S1F	S2F	S3F	S4F
FHRP	A	B	C	D
Body movements	Incidental	Periodic	Absent	Present
Eye movements	Absent	Absent	Present	Present

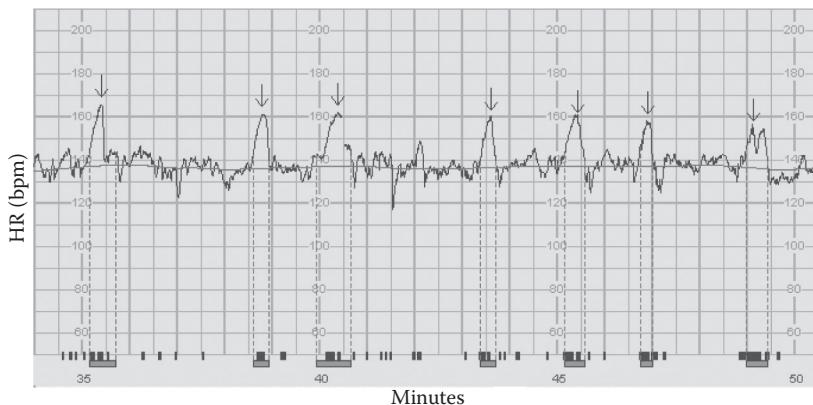


FIGURE 7.2

An example of cardiotocographic tracing is illustrated (41 min); the signals have been recorded at the 38th gestational week of a healthy fetus. The figure shows FHR in bpm; the smooth continuous line is the baseline. The arrows mark the accelerations, and the chunks represent the acceleration duration. Analysis performed by SEA 2CTG2 system.

accelerations that are strictly related to body movements do occur. FHRP B has a wider oscillation bandwidth with frequent accelerations during movements. FHRP C is a stable HR pattern with an oscillation bandwidth wider than that of FHRP A, but without accelerations. FHRP D is unstable, with large and long-lasting accelerations, which are frequently fused into a sustained tachycardia. The study of fetal behavioral organization has provided important information concerning the emergence and maturation of basic biological processes.

Decelerations are infrequent and are usually correlated with uterine contractions. Since arteries supplying the placenta follow a winding course through the complex uterine musculature, each contraction restricts the supply of blood, thus reducing the oxygen support, leading to a decrease in the heart rate.

As suggested by Arduini et al. (1993), and also by Mantel et al. (1990b), accelerations can be divided into two groups according to their maximum deviation (LMAX) above the baseline. It is thought that these two groups might have varying diagnostic importance. Large accelerations have $LMAX > 15$ bpm, while smaller ones have $10 < LMAX \leq 15$ bpm. In Figure 7.2, an FHR signal recorded by means of a cardiotocographic device is illustrated. The same figure displays the baseline and a few accelerations computed with techniques described earlier.

Inter-observer and intra-observer variability are major weaknesses of intrapartum CTG monitoring, and computerized analysis of CTGs has been proposed as an alternative to overcome this limitation (Ayres-de-Campos et al., 1999).

7.3.1 Traditional Analysis

Classical FHR statistics are primarily expressed as time domain measures. In the following, interbeat interval sequences (most often called RR interval series) will be used in place of HR sequences. The principal indices are presented in the following:

Long-term irregularity (LTI). Several comparative studies have demonstrated that a majority of indices proposed for measuring long-term variability have two major limitations: they increase linearly with the increase in the STV and they do not increase linearly with the increase in high-frequency (HF) oscillation in the HR signal (Parer et al., 1985; Laros

et al., 1977). However, these comparative analyses have demonstrated that the index LTI proposed by Haan et al. (1971) is unique because it shows less correlation with the STV index compared to other proposed indices. The LTI is usually computed from a short segment of the RR interval signal.

Given 3 min of RR interval signal, the index LTI is defined as the interquartile range [1/4; 3/4] of the distribution of the modulus $m(j)$, where

$$m(j) = \sqrt{T(j+1)^2 + T(j)^2} \quad (7.1)$$

and $T(i)$ is a downsampled version of $RR(i)$, for instance, by averaging the RR intervals over 2.5 s periods.

In the FHR analysis, such indices can be assessed both by considering the entire recording and by excluding the intervals with acceleration and deceleration episodes, as suggested by Arduini et al. (1993), in order to avoid spurious measures of variability.

Delta. Delta is a coarse measure of variability, which is defined as the range of the RR interval signal in a given time interval. "Normality" of an FHR tracing, in clinical routine, is often assessed by means of the values of Delta. For a 1 min segment of RR interval signal, the Delta is defined as

$$\text{Delta} = \max_i(T(i)) - \min_i(T(i)), \quad (7.2)$$

where i refers to the number of beats in the 1 min segment of the signal being considered.

Short-term variability (STV). STV quantifies FHR variability over a very short time scale, usually on a beat-to-beat basis. In some automated systems, this index is implemented by adopting the definition provided by Arduini et al. (1993): for a 1 min segment of the RR interval signal, STV is defined as

$$\text{STV} = \text{mean}(|T(i+1) - T(i)|) = \frac{\sum_{i=1}^N |T(i+1) - T(i)|}{N}, \quad (7.3)$$

where N are the number of points in 1 min.

Interval index: The interval index (II) proposed by Yeh et al. (1973) is a dimensionless parameter that measures the variability over a short period:

$$\text{II}_Y = \frac{\text{std}(T(i))}{\text{mean}(T(i))}. \quad (7.4)$$

It is the ratio between the standard deviation and the average values of $T(i)$, a downsampled version of $RR(i)$.

The parameter II_Y is assessed over 30 s segments of the RR interval signal. Arduini et al. (1993) proposed a modification of the earlier definition, in order to quantify differences between successive heartbeats:

$$\text{II} = \frac{\text{std}(|T(i+1) - T(i)|)}{\text{mean}(|T(i+1) - T(i)|)} = \frac{\text{std}(|T(i+1) - T(i)|)}{\text{STV}}. \quad (7.5)$$

The aforementioned parameter is assessed over 1 min segments of the RR interval signal.

Power spectral analysis. Power spectral analysis is used to represent how the power of a given signal (its variance) is distributed over a frequency range. The power spectrum is a classical tool in signal processing (Oppenheim and Schafer, 1989; Kay and Marple, 1981) and has been found to be very useful in biomedical signal analysis. The more commonly used parameter, that is, the power spectral density (PSD) of a signal, is proportional to the modulus of its Fourier transform. Power spectral analysis has been found to be invaluable in the analysis of beat-to-beat interval series to understand the physiological mechanisms involved. If a physiological mechanism (e.g., a control loop) is responsible for modulating heart periods at a certain frequency, the corresponding frequency component of HRV may be used as a measure of these modulations, provided the heartbeat time series is a stationary process. The interbeat series is most often considered to be a realization of a stochastic process that is (i) stationary and (ii) ergodic for first- and second-order statistics. Several techniques for estimating the variance of the signal under consideration have been proposed. They are generally classified into non-parametric and parametric methods of estimating the power spectrum. The former method does not require the formulation of a specific model to describe the signal, but one needs a longer signal to obtain a more robust and accurate estimate of the power spectrum. The parametric method is feasible when one assumes an underlying stationary model that can generate the observed signal, and it provides better frequency resolution even for short data lengths.

The analysis of FHRV signal also includes the PSD estimation, which is carried out on the RR interval sequences. The computation is performed on short sequences of signals lasting 3 or more minutes, and the absolute power and percentage of power in different frequency bands are estimated. In contrast to the PSD of the HR of an adult subject, which has three primary bands of power (Task Force, 1996), the FHR spectrum has four bands. These are identified as follows:

1. The very-low-frequency (VLF: 0–0.03 Hz) band is related to long periods of oscillations and includes non-linear contributions.
2. The low-frequency (LF: 0.03–0.15 Hz) band is mainly correlated with the neural control system, sympathetic activity in particular.
3. High frequency (HF: 0.5 to Nyquist frequency) marks the presence of fetal breathing.
4. Movement frequency (MF: 0.15–0.5 Hz) typically falls within the FHR spectrum.

The MF component has been correlated with fetal movements (basically of the trunk) by Sibony et al. (1994) and Breborowicz et al. (1998). It also depends on maternal breathing. In fact, an analysis comparing the maternal and FHR signals showed a high correlation between the fetal MF component and the maternal respiratory frequency when the fetus was quiet (no respiration and no body movement). This would confirm the complex interaction between the mechanical influence of the maternal respiratory activity and the fetal neural reflexes generated mainly by the baroreceptors (Cerutti et al., 1989). Parameters derived from the PSD of FHR include the LF/(HF + MF) ratio, which quantifies the autonomic balance between the neural control mechanisms from different origins. Analogous to the LF/HF ratio normally calculated in adults (Signorini et al., 2003), the LF/HF ratio derived from FHR is also believed to reflect the sympathovagal balance (Malliani et al., 1991).

7.3.2 Advanced Techniques

The detection and classification of accelerations and decelerations represent the primary objective of CTG analysis, because significant changes in the computed basal FHR value represent fetal distress. In particular, during labor, an FHRP that includes accelerations and high beat-to-beat variability is considered “reassuring” by obstetricians, while an FHR tracing is considered “non-reassuring” if there are repeated decelerations after uterine contraction or lack of accelerations and if there is low beat-to-beat variability (Tharmaratnam, 2000). Nevertheless, CTG could not identify the early onset of important life-threatening conditions for fetuses, such as uteroplacental insufficiency (Baschat, 2005).

In the recent past, there has been a significant effort to study and demonstrate the non-linear nature of HRV in adults (Goldberger et al., 1985). The development of chaos theory has supplied a conceptual framework to study non-linear dynamical systems through an analysis of the recorded HRV signal.

A few years ago, the concept of mean rate of creation of information, also known as entropy (or Kolmogorov–Sinai invariant) (Eckmann and Ruelle, 1985), was introduced to describe the important properties of the time series generated by dynamical systems.

However, the Kolmogorov–Smirnov (K-S) entropy ran into practical problems when applied to real systems. In fact, it assumes infinite values for all processes with superimposed noise and, thus, is unable to distinguish between classes of processes that are generated from different dynamical systems. Pincus (1995a) proposed a measure for analyzing noisy time series. He introduced a modification to the K-S entropy algorithm, limiting its purpose to measure signal regularity instead of assessing the presence of chaotic dynamics. The statistic defined by Pincus (1991), the approximate entropy (ApEn), is not an approximation of the K-S entropy previously outlined, although it was inspired by it. ApEn measures the regularity in patterns with a tolerance r , by comparing them with a given pattern of length m , where m and r are fixed values; m is the detail level at which the signal is analyzed and r is the threshold that filters out irregularities.

ApEn can supply only one index about the general behavior of a time series and cannot be used to infer anything about the underlying dynamics. Thus, if signal X has a lower value of entropy than signal Y, we can only say that X is more regular than Y, but we cannot infer with certainty that it is also less complex. If the original purpose of entropy was to identify chaotic dynamics, the statistic ApEn has not fulfilled this goal, since it only quantifies the regularity of a given signal.

Recently, Richman and Moorman (2000) developed a modification of this algorithm in order to remove what they considered as the defects of ApEn and called it sample entropy (SampEn). SampEn has the advantage of reducing the bias of ApEn and of displaying relative consistency when ApEn fails to do so.

In order to capture signal fluctuations on different time scales, another new method has been introduced with the goal of computing entropy at different degrees of resolution, that is, in a multiscale manner (Costa et al., 2002). This statistic is called multiscale entropy (MSE). The idea is that a signal may contain information at different time scales and, therefore, methods working only on a single time scale are unsuitable. The procedure to compute MSE consists of setting up consecutive coarse-grained time series $y^{(\tau)}$ as a function of factor τ :

$$y^{(\tau)} = \sum_{i=(j-1)\tau+1}^{j\tau} x_i, \quad \text{for } 1 < j \leq N/\tau,$$

where x_i is the time series.

For each sequence $y^{(t)}$, an entropy measure is calculated and is plotted as a function of the scale factor. The rationale for this procedure is an enhancement of the time series repetitive patterns as a function of different scales. The distribution of the MSE values at various time scales could help one understand the time series in terms of regularity and structure (i.e., short range vs. long range).

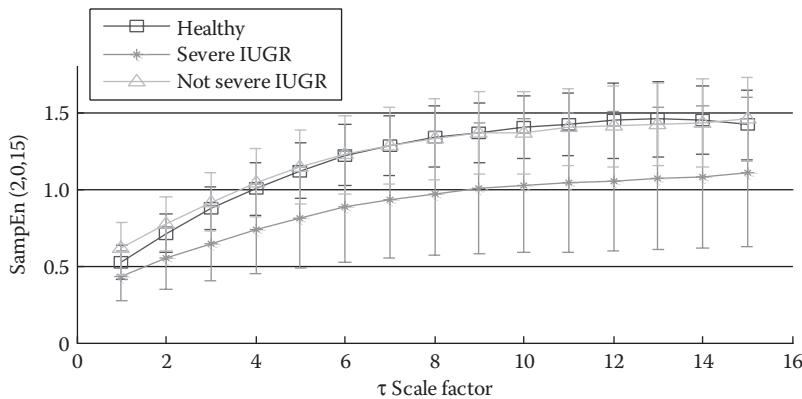
Using a different approach, Lempel and Ziv introduced a measure to quantify the so-called algorithmic complexity, which is defined according to information theory as the minimum quantity of information needed to define a binary string (Lempel and Ziv, 1976). The Lempel-Ziv complexity (LZC) measure reflects the gradual increase in new patterns arising with the development of a sequence. The time series is encoded into a binary string. The addition of a new sample to the time series generates new strings of characters. The LZC measures the numbers of characters, which contribute to form new substrings in the sequence. A description of the method can be found in Ferrario et al. (2009). LZC has also found extensive application in event detection in biological signals, such as for epileptic seizure (Radhakrishnan and Gangadhar, 1998). In the following section, we summarize research that has demonstrated how the new indices or analyses can be useful and integrate information from the traditional parameters commonly adopted in fetal monitoring.

Ferrario et al. (2007) analyzed the HR signals of fetuses whose gestational ages were between 27th and 34th gestational weeks, using several indices. The fetuses were classified as normal, severe IUGR and not severe IUGR. The normal group included fetuses without pathologies, delivered by spontaneous labor and had a good Apgar score at delivery. The severe IUGR group comprised small fetuses prematurely delivered by caesarean section (before 34th gestational week and weight <10 percentile) because of the appearance of life-threatening conditions. The moderate IUGR group included small fetuses delivered after 34th gestational week and were classified as IUGR at delivery. For all recordings, a standard analysis procedure was carried out through the identification of the baseline and the detection of accelerations and decelerations.

The reliability and reproducibility of FHR indices were evaluated with respect to dependence (i) on the length of signal subsets on which the parameters are computed, (ii) on the choice of overlapping subsets and (iii) on the quality criterion for accepting subsets to be analyzed. The parameters compared in the study were (i) the time domain parameters, computed both from the original signal and from signals that excluded the accelerations and decelerations; (ii) frequency domain parameters, computed by adopting a power spectral estimation based on the parametric method; and (iii) the complexity parameters ApEn, SampEn and the LZC with different coding procedures.

The analyses demonstrated that only some parameters (the LZC indices, the mean value and the LF power component) were relatively independent of the parameter extraction procedure, that is, they present a percentage variation within 5% of their value. The most interesting results were obtained with the LZC index, which demonstrated significant differences between the three groups of fetuses. Delta index and STV were also able to discriminate IUGRs from healthy fetuses, but the analysis showed that these parameters were correlated with each other and strongly dependent on parameter extraction procedure, making them unsuitable for clinical use. The introduction of regularity parameters (ApEn and SampEn) did not provide any improvement in the FHR classification.

MSE and the slope estimated from MSE plots were evaluated in a separate study (Ferrario et al., 2009). The MSE analysis provided important results. In particular, the entropy values on their own were able to significantly separate fetuses with severe IUGRs from both not

**FIGURE 7.3**

Multiscale sample entropy results (mean \pm SD). The open squares mark healthy fetuses; the asterisks, severe IUGRs and the triangles, not severe IUGRs. SampEn values ($N = 5000, m = 2, r = 0.15$) became statistically significant when the scale factor $\tau > 3$. (From Ferrario, M., Signorini, M.G. and Magenes, G., *Med. Biol. Eng. Comput.*, 47, 911–919, 2009.)

severe IUGRs and normal fetuses. In particular, the entropy values of fetuses with severe IUGRs were lower than those of other two groups, whereas entropy values of fetuses with not severe IUGRs and healthy subjects were very similar (Figure 7.3).

Furthermore, it was noted that the increase in the entropy values at the lower scale factors was reduced for the severe IUGR group compared to other two groups. As previous studies have demonstrated, pathological conditions can be identified not only by the entropy values but also by the distribution of values in function of the scale factors. In fact, the trend can provide important hints about the signal structure and the dynamical system involved. For this reason, interpolation was performed on the MSE ranging over multiple scales and the respective slopes were considered as new indices.

A k-mean cluster analysis was applied to the indices selected in this study. The most interesting results were obtained by taking into account the LZC and the slope α_{1-2} assessed from the intercept of scale factors 1 and 2 on MSE. The cluster analysis was able to group fetuses with severe IUGRs together and separate them from fetuses with moderate IUGRs and from normal fetuses. Cluster analysis provided a sensitivity of 77.8% and an accuracy of 82.4%. Notice that same indices, when used individually, did not yield as good a performance for accuracy.

Multiscale analysis showed promising results when employed for the identification of fetal distress during labor. Cao et al. (2006) analyzed FHR signals using MSE analyses and found that for scale factors higher than 1, a significant difference existed between the CTG traces classified as “assuring” from those classified as “non-reassuring”. Moreover, they have demonstrated that a combination of frequency components, depth and lateness of the decelerations with respect to uterine contractions and low HRV measured by MSE analysis can match the interpretation of the situation provided by qualified obstetricians.

The effectiveness of MSE in the identification of high-risk fetuses was evaluated in antepartum recordings as well. Ferrario et al. (2006) reported that traditional techniques were not able to distinguish between the normal fetuses and the distressed ones. The LTI was significantly different only for fetuses whose gestational age was more than 39 weeks, but most fetuses presenting severe distress problems do not reach this stage of gestation,

since obstetricians induce a premature delivery. On the contrary, regularity analyses for both short (single scale) and long (multiscale) time windows are able to significantly discriminate distressed and pathological fetuses from those that are healthy and not suffering. The MSE approach for the whole recording time (about 40 min) showed that there were no significant differences between normal fetuses and distressed fetuses without pathology at birth (i.e., the fetuses that were judged as suffering in the antepartum period but were healthy at birth). On the other hand, significant differences were found between normal fetuses, distressed fetuses and those ill at birth. In this case, pathological fetuses presented lower entropy values than healthy ones at all scale factors, supporting the hypothesis that, as in adults, pathological conditions induce an increase in signal regularity in the long term, due to a possible loss of complexity (information reduction) in regulatory mechanisms.

The entropy estimates provide interesting insights from a physiological point of view. An analysis of fetal behaviors by Gonçalves et al. (2007) showed that FHRPs during active sleep or active wakefulness demonstrate significantly more signs related to the autonomic nervous system activity, such as sympathovagal imbalance and significantly less signs related to the complexity or irregularity of the control systems compared to FHRPs during quiet sleep or quiet wakefulness. The decrease in nearly all FHR entropy indices during periods of enhanced fetal activity may reflect a genuinely decreased activity of some of the central nervous system centers or a more focused coordination of sympathetic activation (slow oscillations). Similar results were obtained by Magenes et al. (2004), where normal fetuses were submitted to vibroacoustic stimulation. They reported that when fetuses were in a quiet period before the stimulus was given, ApEn values were higher than during the activity period after the vibroacoustic stimulation. Analysis of both the linear and non-linear properties of fetal HRV may improve the sensitivity and specificity of FHR monitoring, as experimental protocols on animals suggest (Frasch et al., 2009).

7.4 Neonatal HRV Analysis: Monitoring in the NICU

Mathematical analysis of HRV has found important applications in the NICU. These patients are at high risk for sepsis, a highly unstable and precarious condition, and frequently have premature cardiorespiratory and neurological development. Laboratory tests to detect early stages of sepsis in NICU patients are severely limited, thereby making HRV analysis an important tool. In particular, infants who end up in the NICU are often distressed fetuses before birth, so the HRV is useful both for monitoring their pre-natal distress as well as for screening their post-natal tendency to develop sepsis-like symptoms. We note here that there are significant differences between fetal HRV and neonatal HRV. During early post-natal development, both HR and HRV values decrease when compared to their corresponding values when these neonates were fetuses in the womb. Respiratory sinus arrhythmia (RSA) appears along with episodes of bradycardia, and rhythms related to sleep-waking stages and feeding also appear.

Continuous monitoring of the HR in NICU infants with sepsis and SIRS shows that such infants have markedly decreased variability and the presence of transient decelerations. These features are abnormal in fetal HR. It is critical to accurately identify sepsis and SIRS in order to avoid misdiagnosing them as less than life-threatening disorders.

Over the last decade, researchers from the University of Virginia have proposed new approaches to the analysis of the regularity and complexity of time series of HR dynamics. They specifically designed algorithms to analyze and interpret alterations in HRV observed in NICU newborn babies who are at risk of suffering from sepsis. The proposed techniques are aimed at extracting the information from the HRV that is useful for screening premature, very low birth weight (VLBW, <1500 g) NICU patients, by deriving indices for an early diagnosis of sepsis and for potential therapeutic interventions.

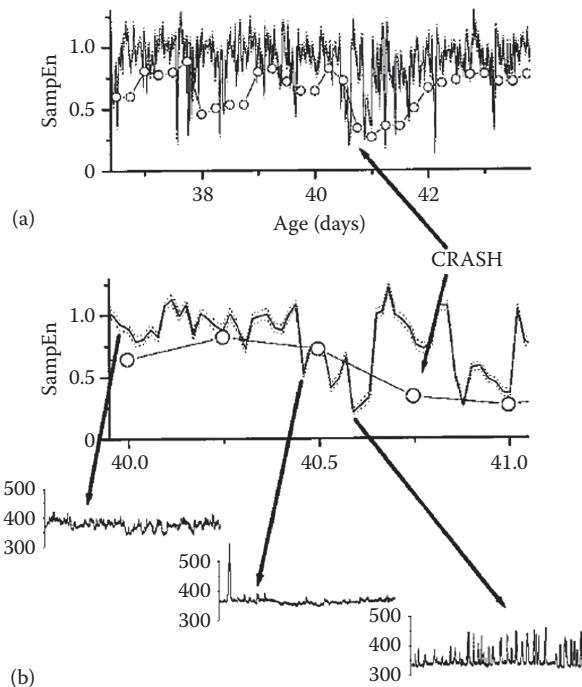
The approximate entropy (ApEn) proposed by Pincus (1991, 1995a,b) was shown to be reduced in distressed and/or sick fetuses (Pincus et al., 1991; Pincus and Viscarello, 1992), suggesting an increased regularity of cardiac rhythms in such patients.

The application of entropy estimators to neonatal HRV (Richman and Moorman, 2000; Moorman et al., 2006) led to several significant results:

1. The 10th percentile value of SampEn determined over 6 h epochs was found to fall early in the course of neonatal sepsis and sepsis-like illness: reduced variability and transient decelerations in the HR were observed before neonatal sepsis, and it was hypothesized that SampEn would fall before the clinical diagnosis. Multivariable logistic regression modeling showed that SampEn added independent information to birth weight, gestational age and days of age in predicting sepsis by up to 24 h (Lake et al., 2002; Figure 7.4).
2. Some HR records in patients from NICU had steep and sudden rises, which were termed as "spikes." Lake et al. (2002) analytically and experimentally demonstrated that SampEn falls in the presence of spikes and concluded that reduced SampEn in the neonatal HR data may depend on the spikes, rather than simply increased regularity, which reveals a sensitivity of this parameter to artifacts and irregular episodes, and potentially limits the association between its decrease and an actual change in regularity.
3. SampEn of neonatal HR records is not very sensitive to missing points: this overcomes the main limitations of spectral analysis of HRV, although frequency domain analysis enables one to identify the sympathetic and parasympathetic neural regulatory rhythms.

Such findings were consistent with the earlier work of Pincus, who found reduced ApEn in acidotic fetuses (Pincus and Viscarello, 1992) and sick newborns (Pincus et al., 1991). Given the limitations related to discrimination between accelerations and decelerations, which can be overcome by the use of skewness of the HRV distribution, and those related to the issue of spikes and regularity assessment, these results obtained from the application of SampEn have been found to be clinically useful for monitoring infants at risk of sepsis.

The importance of skewness of the HRV distribution and the issue of the main pathophysiological implications of the HRV characteristics in sepsis-prone infants were further discussed by more recent research by the same group. Moorman et al. (2006) proposed the use of mathematical measures to distinguish abnormal heart rate characteristics (HRC) from normal patterns in neonatal HR. They examined histograms of the FHR recorded from normal fetuses and from neonates with pathology. While the HR of normal group of neonates results in a symmetric histogram, due to a comparable number of large accelerations and decelerations, abnormal NICU infants display a strongly asymmetric RR

**FIGURE 7.4**

SampEn is decreased before episodes of neonatal sepsis. (a) SampEn as a function of time is shown as a solid line for one infant, with standard errors shown as dotted lines. The time at which the clinical diagnosis of sepsis was suspected is labeled "CRASH" (Cultures, Resuscitation and Antibiotics Started Here). The open circles are the 10th percentile lowest values of the preceding 12 h and are given every 6 h. (b) Data from close to the time of diagnosis on an expanded time scale. Insets: time series of 4096 RR intervals from the designated times show the development of the characteristic abnormalities of reduced variability and transient decelerations. (From Lake, D.E., Richman, J.S., Griffin, M.P. and Moorman, J.R., *Am. J. Physiol. Regul. Integr. Comp. Physiol.*, 283, R789–R797, 2002.)

histogram, characterized by several large decelerations and a small number or lack of accelerations. The asymmetry and skewness of the histogram of NICU patients prompted Moorman and colleagues to conclude that the HRV of ICU neonates is characterized by low regularity and high complexity, thereby suggesting the use of non-linear methods to fully extract the information content of HRV and to overcome the limitations of power spectral analysis of HRV.

The observation of histogram asymmetry was instrumental in the introduction of novel mathematical approaches to the analysis of HR: in addition to the entropy estimators, Moorman et al. (2006) proposed a sample asymmetry index. On the basis of a measure previously introduced by Kovatchev et al. (1998), the sample asymmetry index was introduced to quantify the ratio between decelerations and accelerations and, thus, characterize the skewness of the histogram (Moorman et al., 2006).

As low SampEn does not distinguish between HR decelerations (which are of interest for the prediction of sepsis) and accelerations, incorporating the skewness in the model enables the physician to discriminate between data records where low SampEn is associated with decelerations and records characterized by low SampEn but different HR patterns.

Further, their results suggest that non-stationarity of the HRV series increased in NICU patients with sepsis. They hypothesized the following mechanisms to explain reduced variability and increased transient decelerations:

1. *Reduced parasympathetic activity.* The post-natal development of the vagus nerve control of HR has been documented through power spectral analysis of HRV, which showed a reduction in the ratio between LF ($0.04 < f < 0.15$ Hz) and HF ($0.15 < f < 0.4$ Hz) power of the HRV spectrum after birth (the number of decelerations and accelerations is about the same at birth, and then decelerations increase). However, it is to be noted that the mean HR does not change appreciably in all cases of neonatal sepsis; sepsis and endotoxemia are associated with decreased total, LF and HF power of HRV and unaltered LF/HF ratio; and decelerations should be intuitively explained by augmented vagal activity, not a reduction of it.
2. *Hypoxia is the cause of decelerations.* This explanation assumes that apnea leads to hypoxia, which in turns leads to bradycardia. This mechanism might contribute, but not all deceleration episodes have been shown to be linked, to episodes of apnea.
3. Circulating cytokines are increased following an insult such as bacterial infection, and they may interfere with the physiological control of HR by sympathetic and parasympathetic systems.

The introduction of SampEn and the incorporation of non-linear methods overcome many practical limitations in the computation of the HRV spectral analysis, which make the LF/HF ratio often unreliable in providing a comprehensive representation of the sympathovagal balance and of the sympathetic activation.

More recently, Flower et al. (2010) focused on the periodic cycles of HR in infants, moving from the observation that while the complexity in HR, albeit easy to visually identify, is hard to define, the regularity is easier to both identify and define precisely. Both adults and infants show (a) RSA-related cycles of the duration of few seconds in adults and of approximately 1 s in infants admitted to NICU, with an amplitude of approximately $\pm 2\text{--}4$ ms; and (b) Mayer waves-related cycles, whose period is about 10 s in adults and 12–14 s in NICU patients, with an amplitude of approximately ± 10 ms. In addition to these two rhythms, NICU infants show large deceleration episodes, lasting for approximately 15 s, with an RR interval amplitude of about 200 ms (from 350 to 550 ms, corresponding to 170 to 110 bpm).

To better analyze these cycles, Flower et al. (2010) developed a wavelet-based detector and derived a mathematical interpretation of the clusters of periodic decelerations. They interpreted the patterns as arising from a Hopf bifurcation, when it loses stability giving rise to oscillatory modes. From the point of pathophysiology, these results suggest that the HR in neonates born with underdeveloped autonomic HR control could go into previously uncharacterized oscillatory modes and also that HR control might be amenable to mathematical description.

From the point of clinical utility, application of these results to HR records did result in improved predictive accuracy of identifying both the onset of sepsis and increased risk of mortality in NICU settings. For example, the HRC and SampEn analysis was applied to infants at risk of urinary tract infection (Griffin et al., 2005) and to assess the neurodevelopmental outcome in VLBW infants (Addison et al., 2009), which showed that HRC

(including transient decelerations, decreased variability and lack of accelerations) can indicate an increased risk of sepsis and SIRS, as well as an increased incidence of cerebral palsy and developmental delay compared to full-term infants.

7.5 Conclusion

We have reviewed different methods and parameters of fetal HRV and argued that the traditional indices from time domain and frequency domain analyses should be complemented with the non-linear parameters.

The commercially available CTG monitors provide only a few indices that describe the pathophysiological condition of distressed fetuses. It is no wonder that CTG traces can be used only to give a rough idea of whether fetal conditions appear to be "reassuring" or not. Various research studies by others agree with our finding that only advanced methods of HRV analysis provide enhanced FHR information content and help identify life-threatening conditions (Goncalves et al., 2006).

A decisive improvement in fetal monitoring could be achieved by the integration of all available information from different measurements (Doppler fluximetry, FHRV indices, etc.) and by the development of new techniques to measure the oxygenation of placental and fetal tissues, which are the only prognostic indicators of actual fetal well-being. Currently, only the transabdominal puncture of the umbilical cord and the sampling from the clamped umbilical cord at the time of delivery are considered reliable measures of fetal oxygenation and acid-base balance, although these techniques are invasive. The clinical utility of the antepartum evaluation of the biochemical parameters in IUGR fetuses has already been demonstrated, especially when it is associated with abnormal Doppler velocimetry of the umbilical artery (alteration of the pulsatility index) (Pardi et al., 1993).

Finally, because many compromised fetuses such as those with IUGRs have a high probability of being admitted to an NICU after delivery, it appears that an integration of the information contained within the HRV before and after delivery could provide a more comprehensive picture of the response of neonates to extrauterine life.

Abbreviations

ApEn	Approximate entropy
CTG	Cardiotocography
EM	Eye movements
FGR	Fetal growth retardation
FHR	Fetal heart rate
FHRP	Fetal heart rate pattern
HRC	Heart rate characteristics
II	Interval index
IUGR	Intrauterine growth restriction

LTI	Long-term irregularity
LZC	Lempel-Ziv complexity
MSE	Multiscale entropy
SampEn	Sample entropy
SGA	Small for gestational age
STV	Short-term variability
VLBW	Very low birth weight

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9

Effects of Exercise Training on Heart Rate Variability in Patients with Hypertension

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9.1 Introduction

The Joint National Committee (National Institutes of Health, USA) defines hypertension, or the chronic elevation of resting arterial blood pressure (BP), as a resting systolic blood pressure (SBP) of ≥ 140 mmHg and/or a diastolic blood pressure (DBP) of ≥ 90 mmHg (Chobanian et al., 2003). Hypertension is estimated to afflict nearly 1 billion adults worldwide, and the lifetime risk of developing the disease may be as high as 90% in some populations (Chobanian et al., 2003). The overall severity of these statistics is compounded by a relatively low disease awareness and a poor rate of targeted BP control (Chobanian et al., 2003; Fields et al., 2004; Hajjar and Kotchen, 2003). Hypertension increases the risk of developing cardiovascular disease (CVD), with specific long-term complications including increased incidence of coronary artery disease, peripheral vascular disease, stroke, renal failure and both systolic and diastolic heart failure (Bonow et al., 2012; Leite-Moreira, 2006; Pescatello et al., 2004). Hypertension is a significant health concern for both sexes (Mathers et al., 2009), although women, particularly those in their sixth decade of life, display an elevated risk of hypertension and hypertension-related CVD (American Heart Association, 2011). The weight of evidence currently suggests that the risk of death from ischemic heart disease and stroke increases in a linear fashion with an increasing resting arterial BP of greater than 140 mmHg SBP and 90 mmHg DBP (Arguedas et al., 2009), although high-normal and prehypertensive values may also increase the risk (Chobanian et al., 2003; Vasan et al., 2001). However, while the deleterious clinical implications of hypertension

are well known, the underlying etiology that is responsible for the increases in resting BP still remains unclear. Of the hypothesized pathways involved in the disease initiation and progression, changes in the neural control of BP are well studied and considered to be responsible for at least 50% of all hypertension cases (Esler, 2009). These alterations primarily manifest as excessive sympathoexcitation and parasympathetic inhibition and have been confirmed in studies measuring muscle sympathetic nerve activity (MSNA), norepinephrine spillover, baroreceptor reflex sensitivity and heart rate variability (HRV).

The management of hypertension often includes a combination of pharmacological and lifestyle modifications (diet, smoking cessation and exercise) that are designed to reduce resting BP, improve the hypertension-associated risk factors and lower the overall rates of CVD mortality. The effectiveness of pharmacological therapy is often inconsistent, with as many as 50% of the medicated or treated hypertensives, in particular older women, still possessing an elevated BP (Hajjar and Kotchen, 2003; Lloyd-Jones et al., 2005). These statistics reiterate the need for adjunct non-pharmacological treatments, such as habitual physical activity, to manage BP targets. The focus of this chapter will be to delineate the effects of exercise training (aerobic, resistance and isometric) on HRV in patients with hypertension. The experimental and physiological evidence that we present will demonstrate the ability of exercise training to reduce resting BP and improve indices of autonomic nervous system (ANS) function, which are thought to be critical to the development and progression of human hypertension.

9.2 Autonomic Dysfunction in Hypertension

Although the mechanisms that are responsible for the chronic elevation of BP are still a subject of debate, the classification of hypertension into primary (essential) and secondary is widely accepted. Primary or essential hypertension afflicts the majority of the hypertensive population (more than 95%), and numerous neural, hormonal, vascular, genetic and environmental factors are thought to play a role in its development. By contrast, secondary hypertension is better understood and results from a known cause or disorder, such as renovascular disease, Cushing's syndrome, primary aldosteronism or hyperparathyroidism (Chobanian et al., 2003). This chapter will focus on research related to human essential hypertension, while Chiong et al. (2008) and Mansoor (2004) provide general reviews on secondary hypertension.

There is compelling evidence to suggest that augmented neural function contributes to the altered cardiovascular control of the central and peripheral regulators of arterial BP. The individual roles of the parasympathetic and sympathetic nervous systems in hypertension development and progression are likely influenced by temporal factors related to the disease stage. Prehypertension is characterized by reduced parasympathetic activity and increased sympathetic activity, particularly to the heart and kidneys. Julius et al. (1971) demonstrated that pharmacological parasympathetic blockade elicited smaller increases in heart rate and cardiac output in young, borderline hypertensive participants than in matched normotensives. Conversely, markers related to enhanced sympathetic activity, such as increased norepinephrine spillover (Esler et al., 1989; Ferrier et al., 1993), MSNA (Anderson et al., 1989; Floras and Hara, 1993; Greenwood et al., 1999; Matsukawa et al., 1991; Smith et al., 2004) and β -adrenergic receptor density or hyperresponsiveness (de Champlain, 1990) have been observed in prehypertensive or mild hypertensive participants. Such evidence of neural adaptations in both the parasympathetic and sympathetic

nervous systems provides a mechanism to explain the increases in resting cardiac output and heart rate (i.e., hyperkinetic circulation) often found in prehypertension.

In the later stages of hypertension, the magnitude of parasympathetic withdrawal appears to plateau while sympathetic activity increases concomitantly with disease severity (e.g., the BP increases). The latter was elegantly demonstrated by Grassi et al. (1998), who observed stepwise increases in the measures of MSNA and mean BP between normotensive, mild hypertensive and severe hypertensive participants, with significant correlations reported between the MSNA burst incidence and BP. No differences in the resting heart rate existed between the groups, suggesting non-cardiac sympathetic effects on BP. However, more recent studies have also reported a reduced MSNA in participants with severe hypertension compared to mild and borderline hypertensives (Smith et al., 2004). This may reflect methodological differences or relate to the large variability in muscle sympathetic outflow among hypertensives (Grassi et al., 1998). Nevertheless, in addition to the direct effects of the sympathetic nervous system on the heart (i.e., cardiac output) and the vasculature (i.e., vasomotor tone), the chronic increases in sympathetic outflow to the kidneys (RSNA) also produce hemodynamic effects by decreasing renal excretory function (i.e., increasing renal sodium retention, increasing the renal vascular resistance and/or increasing the release of renin) (DiBona, 2004). In particular, renin is important as it facilitates the production of the potent vasoconstrictor angiotensin II (ANG II), while RSNA-driven sodium retention and water retention raise the total blood volume and cardiac output, collectively increasing the resting arterial BP. Hypertension has also been associated with the impairment of nitric oxide-mediated, endothelium-dependent relaxation (Raij, 2001) and the over-expression of endothelin-I (ET-I), a potent endothelium-derived vasoconstrictor (Schiffrin, 1999), thus impacting intrinsic factors regulating vascular tone. The synthesis of ET-I is upregulated by ANG II, and although nitric oxide deficiencies may contribute to the development of hypertension, once the disease is in the chronic stage ANG II and ET-I appear to be important factors in its maintenance (Raij, 2001). Additionally, excessive sympathetic activation is also associated with cardiac and vascular hypertrophies, coronary spasm, platelet activation, cardiac arrhythmias and sudden cardiac death (Esler, 2000; Gilmour, 2001; Julius, 1998).

The mechanisms responsible for the reduced parasympathetic activity and heightened sympathetic activity in primary (essential) hypertension are still poorly understood. However, disturbances in the central control of sympathetic outflow, such as increased angiotensin type I receptors and increased oxidative stress in the rostral ventrolateral medulla, appear to play a critical role (Esler, 2000; Hirooka, 2011). In addition to the increased rates of sympathetic nerve firing and the reduced neuronal norepinephrine reuptake, genetic factors (e.g., salt sensitivity and renin-angiotensin system [RAS] abnormalities) and lifestyle choices, such as poor dietary habits and cigarette smoking, alone or via their interaction, have been implicated in the development of hypertension (Caulfield et al., 1994; Luft, 2001; Schmieder and Rockstroh, 1994; Sleight, 1993) and as mechanisms of sympathetic hyperactivity (Esler, 2000; Kougias et al., 2010; Schlaich et al., 2004). It has been suggested that a dysfunction in the central control of sympathetic outflow may act as a mediator of the peripheral sympathetic activation that is observed with various lifestyle and/or behavioral factors (Esler, 2000). Finally, other humoral abnormalities, such as augmented catecholamine secretion (Goldstein, 1983), RAS activation (Zimmerman et al., 1984) and insulin metabolism anomalies (Ferrannini et al., 1987), may also affect the parameters of arterial BP regulation and contribute to the pathophysiology of hypertension.

Autonomic dysfunction may also be the result of adaptations in peripheral input from afferent reflexes. The arterial baroreceptors have long been recognized as important

short-term controllers of BP (Kougas et al., 2010), while more recent evidence supports their role as a mechanism for longer-term arterial BP control as well (Thrasher, 2004). Experimental data suggest that hypertension induces a chronic resetting of the baroreceptor reflex to a higher set point (thus, a higher threshold arterial BP is required to activate the receptors and trigger the regulatory cascade) (Head, 1995; Krieger, 1989; Sleight et al., 1977). Although chronic resetting in hypertension is not well understood, it is believed to occur as a result of damaged receptors, genetics, inept receptor–vascular wall interactions and/or reduced vascular distensibility, where the latter may also be responsible for an overall reduction in baroreceptor sensitivity (Andresen, 1984; Brown et al., 1976; Rowe, 1987). Thus, hypertension not only resets the baroreflex to a higher operating range, but also reduces the sensitivity of the receptors to detect changes, limiting their ability to reduce the sympathetic activity and increase the vagal activity in an effort to reduce BP (Head, 1995; Krieger, 1989; Parmer et al., 1992). In human hypertension, the baroreflex modulation of heart rate, relating to reflex parasympathetic activity, is consistently demonstrated to be impaired (Laterza et al., 2007; Matsukawa et al., 1991; Sevre et al., 2001), while the baroreflex modulation of MSNA remains unclear and may be reduced (Laterza et al., 2007; Matsukawa et al., 1991; Miyajima et al., 1988) or unchanged (Grassi et al., 1998; Rea and Hamdan, 1990; Schlaich et al., 2004). The discrepancy in MSNA findings may be related to differences in study methodologies or cohorts (i.e., age, medication status, hypertension severity) (Laterza et al., 2007). Alternatively, other conditions characterized by sympatho-excitation, such as heart failure, have demonstrated intact arterial baroreflex control of MSNA (Floras, 2009), providing further evidence for a centrally mediated increase in sympathetic outflow. Changes in arterial baroreflex modulation may therefore occur secondary to the disease state. The removal of the hypertensive stimuli can reverse the degree of baroreflex resetting back to the normal range. However, this effect appears highly related to the length and severity of the BP load and the associated cardiac and vascular adaptations (Salgado and Krieger, 1973; Sumitani and Krieger, 1981). Gender differences in baroreflex function may also provide a potential explanation for the higher prevalence of hypertension in older women, as hypertensive women display lower baroreflex sensitivity of heart rate and greater sympathetic vascular responses to stress, compared with age-matched hypertensive men (Lipsitz et al., 2006; Sevre et al., 2001). Finally, while impaired arterial baroreflex function may be a mechanism or consequence of hypertension-related autonomic changes, the contributions of the cardiopulmonary and chemoreflex may also serve important roles (Grassi et al., 2010).

A confounder in cross-sectional studies and mechanistic investigations of hypertension is the parallel adaptations in neurovascular control that occur with aging. In general, aging is associated with a decline in arterial compliance and a reduction in baroreflex modulation of heart rate as well as an increase in sympathetic outflow (Ferroni et al., 2006; Parker Jones et al., 2003). The resulting increase in the total peripheral resistance contributes to a chronic increase in the resting arterial BP, particularly the SBP (Rowe, 1987). As a result, the prevalence of hypertension also increases with age (Lloyd-Jones et al., 2005).

9.3 Effects of Hypertension on HRV

The current evidence suggests that autonomic dysfunction is integral to the development, progression and maintenance of hypertension. In general, hypertension is associated with

increased sympathetic activation (Anderson et al., 1989; Yamada et al., 1989) and inhibition of the vagal heart rate modulation (Singh et al., 1998). Overwhelmingly, the HRV data suggest that vagal modulation of the heart rate is reduced in hypertensive patients. This is of particular importance, as the efferent sympathetic activity is progressively attenuated as the level of the vagal activity increases (Levy, 1984). As stated in previous chapters, HRV may be effective in indirectly assessing modulations in ANS function, thereby providing important prognostic information on hypertensive populations.

A number of large-scale studies have examined the prognostic value of HRV in identifying the future risk of developing hypertension. The Atherosclerosis Risk in Communities (ARIC) study, a population-based cohort study of almost 12,000 participants, has produced two prospective reports on the effects of HRV on incident hypertension (Liao et al., 1996; Schroeder et al., 2003). In the first study of a subset of the larger cohort, the high-frequency (HF) power and the standard deviations of all normal RR intervals (SDNN) were negatively associated, while the low frequency-to-high frequency (LF/HF) ratio was positively associated with the cumulative hypertension incidence, over a 3-year follow-up period (Liao et al., 1996). As seen in Figure 9.1, the highest incidence of hypertension was found in the lowest quartiles of the HF power and SDNN and in the highest quartile of the LF/HF ratio. In a larger second trial, the assessments of HRV were only completed using time domain methods and demonstrated an inverse relationship between the SDNN as well as the square root of the mean squared standard differences of successive normal RR intervals (rMSSD) and the incident hypertension risk in the participants followed for 9 years (Schroeder et al., 2003). Similarly, data from the Framingham Heart Study demonstrated a significant negative association between the logarithmically transformed LF power and the hypertension incidence in men at a 4-year follow-up (Singh et al., 1998). Overall, these results suggest that individuals with an altered autonomic function are at an increased risk of developing hypertension. This is consistent with the neural changes that are thought to characterize the early stages of hypertension (Julius et al., 1971). Alterations in cardiac autonomic function have also been reported in normotensive participants with a positive family history of hypertension, such as a reduced HF power or an increased LF/HF ratio (Maver et al., 2004a,b; Piccirillo et al., 2000; Wu et al., 2008), corroborating previous norepinephrine spillover results (Ferrier et al., 1993). A familial history is a significant risk factor for future hypertension development (Goldstein et al., 2008) and, taken together,

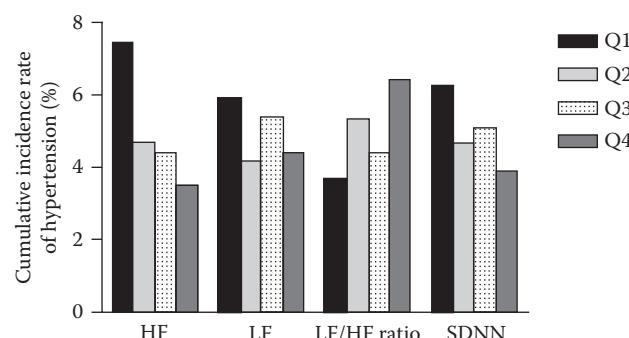


FIGURE 9.1

The cumulative incidence of hypertension (%) by quartiles of the heart rate variability (HRV) indices, 3 years of follow-up—The ARIC study. (Adapted from Liao, D., Cai, J., Barnes, R.W., Tyroler, H.A., Rautaharju, P., Holme, I. and Heiss, G., *Am. J. Hypertens.*, 9, 1147–1156, 1996. With permission.)

these findings underscore the role of both genetic factors and autonomic dysfunction in hypertension development.

Cross-sectional comparisons between normotensive and hypertensive participants have routinely reported reduced HRV in the time and frequency domains with hypertension (Chakko et al., 1993; Fagard et al., 2001; Guzzetti et al., 1988; Huikuri et al., 1996; 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). The evidence from the ARIC trial suggests that the observed differences in the time domain HRV measures (SDNN and rMSSD) between the normotensive and hypertensive individuals demonstrate similar reductions with aging, with the between-group baseline differences becoming smaller over a 9-year period (Schroeder et al., 2003). More controversial are the effects of hypertension on the frequency domain HRV, specifically the LF power, because of conflicting results. Previous studies have reported both LF power increases (Guzzetti et al., 1994; Prakash et al., 2005; Wu et al., 2008) and reductions (Liao et al., 1996; Sevre et al., 2001; Singh et al., 1998; Wu et al., 2008) in patients with prehypertension and/or hypertension (Figure 9.2). This discrepancy in findings may be attributed to differing experimental methodologies or may be related to different neural dysfunctions throughout the various stages of hypertension development. As the LF power is influenced by both the parasympathetic and the sympathetic nervous systems (Task Force, 1996), the reductions may be the product of vagally mediated attenuations in the LF power, potentially masking the classic sympathetically driven increases in the LF power. Additionally, the increased LF power observed in the prehypertensives may reflect the increase in the sympathetic activity that characterizes early or mild

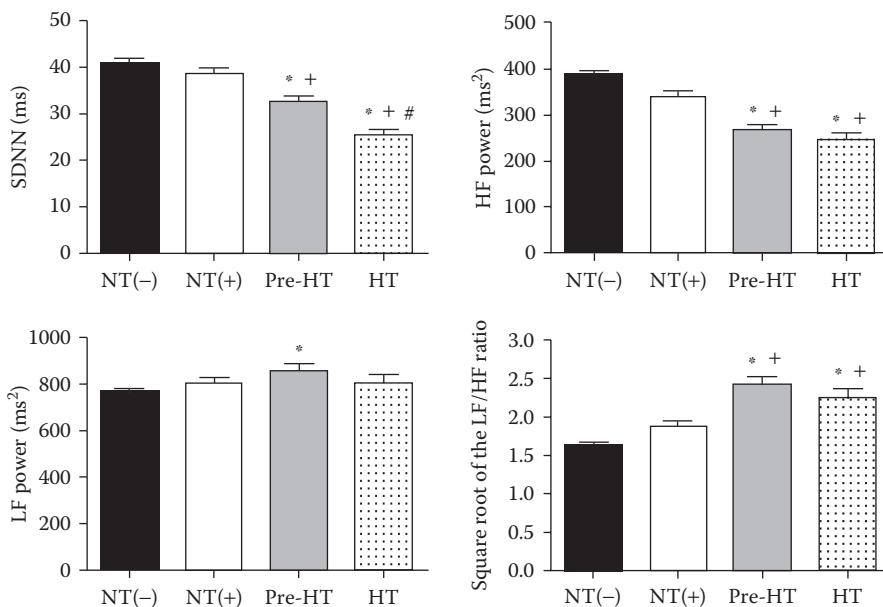


FIGURE 9.2

A comparison of the heart rate variability among persons with different blood pressures, including normotension (NT) with (+) and without (-) a family history of hypertension, prehypertension (Pre-HT) and hypertension (HT). Values are presented as means \pm SEM. *, difference compared with NT(-), $p < .05$; +, difference compared with NT(+), $p < .05$; #, difference compared with Pre-HT, $p < .05$. (Adapted from Wu, J.S., Lu, F.H., Yang, Y.C., Lin, T.S., Chen, J.J., Wu, C.H., Huang, Y.H. and Chang, C.J., *J. Am. Coll. Cardiol.*, 51, 1896–1901, 2008.)

hypertension (Anderson et al., 1989; Esler et al., 1989; Floras and Hara, 1993; Greenwood et al., 1999; Smith et al., 2004).

The assessment of HRV in patients with hypertension may be confounded by the medications that the patients are prescribed. This is supported by Liao et al. (1996), who observed a lower LF power in the medicated hypertensive patients compared to the untreated hypertensives, although a more recent large-scale comparison of the time domain HRV measures in medicated and untreated hypertensives did not support the medication-dependent differences in HRV (Schroeder et al., 2003). Alternative studies have also reported both an increased (Chilidakis et al., 2004; Schroeder et al., 2003) and a decreased (Gerritsen et al., 2000; Tsuji et al., 1996) HRV among individuals on β -adrenergic blockers, while the use of angiotensin-converting enzyme inhibitors and diuretics has been reported to reduce HRV (Gerritsen et al., 2000; Schroeder et al., 2003). The loss of the ability to modulate heart rate (reduced HRV) has been shown to increase the risk of cardiac events (Tsuji et al., 1996), of which the attenuating effects of specific antihypertensive medications on HRV may provide an explanation for the high rates of morbidity and mortality that are persistent in the controlled and uncontrolled medicated hypertensives (Fu et al., 2005; Ivanovic et al., 2004). Drug-specific comparisons, however, would be necessary to test this hypothesis. Overall, the effects of individual or specific combinations of pharmacological agents on HRV in hypertension remain largely unresolved. A second issue concerning the chronic pharmacological management of hypertension is their potential central adrenergic actions. Previously, β -adrenergic blockers and centrally acting antihypertensive drugs have been shown to reduce MSNA (Greenwood et al., 2000; Sundlöf et al., 1983; Wallin et al., 1984), while ANG II blocker plus diuretic use has increased MSNA (Fu et al., 2005). The insufficiency of some antihypertensive medications in modulating central sympathetic outflow may help explain the low percentage of medicated hypertensives with controlled BP. Del Colle et al. (2007) have reviewed the effects of antihypertensive medications on the sympathetic nervous system.

To date, the weight of the evidence demonstrates that (1) a reduction in HRV is associated with an increased risk of hypertension; (2) patients with hypertension demonstrate a low HRV in comparison with normotensives, although changes specifically in LF power may be related to methodological discrepancies between the investigative studies and/or the stage of the disease progression; and (3) antihypertensive medications, although not yet fully defined, may affect HRV, suggesting that HRV results in the medicated hypertensive patients must be interpreted with caution.

9.4 Effects of Aerobic and Resistance Training on Blood Pressure and HRV in Hypertension Patients

Currently, the available guidelines on the management of primary arterial hypertension recommend moderate-intensity dynamic aerobic exercise, for at least 30 min/day (Chobanian et al., 2003; Hackam et al., 2010; Pescatello et al., 2004). There is overwhelming evidence that aerobic exercise training reduces resting BP (Dickinson et al., 2006; Fagard and Cornelissen, 2007; Halbert et al., 1997; Kelley, 1999; Kelley and Kelley, 2001; Kelley et al., 2001; Whelton et al., 2002), with larger reductions commonly observed in hypertensive patients (Fagard, 2001; Kelley et al., 2001). The effectiveness of resistance training is less supported, although recent meta-analyses have noted small reductions in resting

BP (Cornelissen and Fagard, 2005b; Kelley, 1997; Kelley and Kelley, 2000). The magnitude of resistance training-induced BP reductions may be independent of the initial BP levels (Kelley and Kelley, 2000), in contrast to aerobic training. Based on such current evidence, the exercise guidelines recommend resistance training as an adjunct intervention to aerobic exercise-based lifestyle modifications for the management of hypertension (American College of Sports Medicine, 2010; Pescatello et al., 2004).

The mechanisms by which exercise reduces BP have not been established and may differ according to the type of exercise, along with the individual genetic and pathological profiles. In general, mean arterial pressure (MAP) is determined by the arithmetic product of central (i.e., the cardiac output) and peripheral (i.e., the total peripheral resistance) factors. Because neither chronic aerobic nor resistance training is normally associated with reductions in resting cardiac output (although resting heart rate decreases and stroke volume increases with aerobic training) (Anton et al., 2006; Cornelissen and Fagard, 2005a; Saltin, 1969), the BP adaptations are primarily attributed to the reductions in total peripheral resistance (Cornelissen and Fagard, 2005a). Total peripheral resistance is neurally regulated by sympathetically mediated changes in vasomotor tone or the constrictor state of the vasculature. Thus, alterations in autonomic function, in part, may be responsible for the observed reductions in BP following exercise training. Indeed, 4 months of aerobic exercise training was sufficient to restore the baroreflex control of the MSNA and heart rate, while reducing BP and MSNA in patients with untreated hypertension (Laterza et al., 2007). The use of HRV techniques may provide a relatively easy, non-invasive method to determine the effects of exercise training on autonomic modulation in hypertensive patients.

Pagani et al. (1988) documented the first study of aerobic exercise training on HRV in 11 hypertensive patients. Following the 6-month training program (five times per week), heart rate, SBP and DBP were reduced, in concert with reductions in the LF power and increases in the HF power and baroreflex gain of heart rate at rest. These results suggest improved sympathovagal interactions, most likely as a result of the enhanced cardiac vagal modulation caused by the increased cardiac baroreflex gain. Bryniarski et al. (1997) examined the effects of 4 weeks of exercise rehabilitation on HRV in post-myocardial infarction, normotensive and hypertensive patients. They noted similar increases in the SDNN, rMSSD and pNN50% (interpreted as reflecting an increased cardiac parasympathetic modulation) in the two patient groups that underwent 4 weeks of aerobic exercise-based training (five times per week) compared to the sedentary controls (Bryniarski et al., 1997). This study did not observe differences in pre-rehabilitation HRV measures, suggesting similar cardiac autonomic states in the normotensive and hypertensive patients prior to training. However, this study may be confounded by differential reductions in HRV measures following myocardial infarction (Björkander et al., 2009; Craelius et al., 1992; Lombardi et al., 1996), thus masking the potential differences. More recently, Knoepfli-Lenzin et al. (2010) compared the effects of 12 weeks of running versus football training (three times per week), perhaps more appropriately described as continuous versus intermittent or interval exercise training in a group of mildly hypertensive males. Their results demonstrated that both of the exercise interventions reduced resting SBP and DBP and increased supine measures of the rMSSD, pNN50% and SD1, compared to the sedentary control group (Knoepfli-Lenzin et al., 2010). These results suggest improved sympathovagal interactions in the form of sympathoinhibition and/or enhanced cardiac vagal modulation. The role of autonomic modulation in hypertensive patients following dynamic aerobic training may also be confirmed by reductions in the LF power of SBP (LF_{SBP}), which is thought to be representative of decreased sympathetic vasomotor tone (Iwane et al., 2000; Izdebska et al., 2004). Additionally, the reductions in LF_{SBP} that

were observed in hypertensive males following aerobic training were correlated with the reductions in BP and total peripheral resistance (Izdebska et al., 2004).

By contrast, Davy et al. (1997) studied eight prehypertensive and hypertensive postmenopausal women and found that SBP and DBP were significantly reduced after 12 weeks of aerobic exercise training (three to four times per week) without any change in the time domain or frequency domain measures of HRV and cardiac baroreflex sensitivity. However, this study was limited by both the absence of a control group and a small sample size. The latter is especially important considering that HRV measures can demonstrate high inter-individual variability (Nunan et al., 2010; Rickards et al., 2010), which reduces the statistical power. In two larger, more recent trials of prehypertensive postmenopausal women, both 8 and 24 weeks of aerobic exercise training (three to four times per week) were sufficient to increase the time and spectral measures of HRV compared to baseline or sedentary controls (Earnest et al., 2008; Jurca et al., 2004). The results of Jurca et al. (2004) are provided in Table 9.1. The observed increases in the LF power following aerobic training may reflect the increases in the total power and HF power and may be related to an increased cardiac vagal modulation. Additionally, both studies noted reductions in resting heart rate, but not in SBP and DBP, with training (Church et al., 2007; Earnest et al., 2008; Jurca et al., 2004). The study by Earnest et al. (2008) included over 350 participants and involved three different exercise groups to investigate the effect of exercise training intensity on HRV. They demonstrated that the parasympathetic indices of HRV were unchanged following aerobic exercise training at an energy expenditure of 4 kcal/(kg week) but increased equally with 8 and 12 kcal/(kg week). This underscores the importance of imposing an exercise training with sufficient intensity (i.e., above a specific threshold) to induce autonomic adaptations. Collectively, these three studies with postmenopausal women suggest that exercise-induced improvements in autonomic function,

TABLE 9.1

Effects of 8 Weeks of Moderate-Intensity Aerobic Exercise Training on Heart Rate Variability in Sedentary Post-Menopausal Women

Change Exercise	Control (<i>n</i> = 39)		Exercises (<i>n</i> = 49)		Versus Control	
	Pre	Post	Pre	Post	<i>p</i> ^a	<i>p</i> ^b
Heart rate (beats/min)	66.0 ± 6.4	65.8 ± 6.3	68.1 ± 8.5	65.0 ± 7.4*	.08	
<i>Time Domain Measures</i>						
rMSSD (ms)	20.5 ± 8.0	19.5 ± 7.5	18.1 ± 8.0	22.6 ± 9.6*	.001	.006
SDNN (ms)	29.0 ± 8.1	30.1 ± 8.8	26.4 ± 7.6	31.2 ± 8.7*	.01	.05
<i>Frequency Domain Measures</i>						
InP _{HF} (ms ²)	5.19 ± 0.86	5.05 ± 0.79	4.73 ± 1.03	5.23 ± 1.07*	.002	.008
InP _{LF} (ms ²)	4.96 ± 0.65	5.04 ± 0.62	4.72 ± 0.78	5.13 ± 0.86*	.03	.05
InP _T (ms ²)	6.65 ± 0.62	6.67 ± 0.58	6.40 ± 0.72	6.79 ± 0.79*	.001	.008
HF (nu)	54.2 ± 14.9	49.5 ± 15.1	49.4 ± 19.6	51.7 ± 19.3	.30	.58
LF (nu)	44.2 ± 14.6	48.8 ± 14.9	48.2 ± 18.8	46.8 ± 19.0	.36	.64

Source: From Jurca, R., Church, T.S., Morss, G.M., Jordan, A.N. and Earnest, C.P., *Am. Heart J.*, 147, e8–e15, 2004.

Values are mean ± SD.

^a Adjusted for baseline value.

^b Adjusted for baseline value and heart rate change.

**p* < .001 versus baseline.

as measured by HRV and reductions in the BP, do not necessarily parallel each other. It is important to remember that the HRV mainly reflects cardiac autonomic modulation and may not provide information on the potential neurovascular changes, a probable pathway for the exercise training-induced changes in the BP. Further work is required to ascertain the relationship between the HRV and the hemodynamic changes with exercise training.

Limited research exists on the effect of resistance exercise training on HRV in hypertensive patients. In the only reported study, Collier et al. (2009) directly compared the effects of aerobic and resistance exercise training on HRV in prehypertensive participants following 4 weeks of training (three times per week). Both aerobic training and resistance training caused small, significant reductions in SBP (aerobic: -3 mmHg vs. resistance: -4 mmHg) and DBP (aerobic: -3 mmHg vs. resistance: -4 mmHg), although heart rate was only significantly reduced following the aerobic training. An examination of the frequency domain measures of HRV demonstrated increases in the HF power, reflecting an enhanced cardiac vagal modulation, in the aerobic training group alone. The LF/HF ratio was also decreased post-training in the aerobic training group and increased following resistance training, suggesting improved sympathovagal interactions with chronic aerobic exercise. The increases in the LF/HF ratio following resistance training may reflect an enhanced sympathetic modulation, a finding previously reported following 12 weeks of eccentric resistance training in healthy older men (Melo et al., 2008).

It is possible that the time domain and frequency domain measures of the HRV are insensitive to the subtle modulations in HRV following resistance training. The application of non-linear methods of HRV analysis may be required to detect the changes in heart rate behavior. In normotensive populations, modulations in non-linear measures of HRV that have been considered beneficial have been observed following resistance exercise training (Heffernan et al., 2007, 2008, 2009) and concurrent aerobic and resistance training (Karavirta et al., 2009). However, these effects remain to be investigated in the hypertensive population. In general, results of resistance training studies demonstrate limited effects on HRV, a finding that may also be confirmed by the absence of a change in resting heart rate (Fagard and Cornelissen, 2007), although a lack of modulation in HRV does not necessarily rule out changes in the neural modulation or non-neural intrinsic sinoatrial function. Thus, the observed reductions in BP are not strictly the consequence of improved autonomic profiles (i.e., sympathoinhibition), although the generalizability of HRV to systemic sympathetic outflow is contentious.

To summarize, the current evidence suggests that beneficial modulations in HRV may be observed in male and female patients with hypertension following aerobic exercise training, but not with resistance training. These results are in accordance with the available normotensive data (Heffernan et al., 2007; Madden et al., 2006; Sanderson et al., 2005). Future research with non-linear HRV measures may detect subtle changes in heart rate dynamics following resistance training in hypertensive patients. The magnitude of these changes in HRV measures may be related to the specific exercise training principles, such as the intensity and the duration, or the methods of HRV analysis. The advantages of specific HRV methods (e.g., fast Fourier transform, autoregressive, coarse-graining spectral analysis and non-linear dynamics) in the hypertensive patient population remain unknown.

Overall, a paucity of data exists on the effects of exercise training on HRV in humans with essential hypertension. Most notably, the literature does not provide any direct comparisons of the exercise training effects in healthy normotensive and hypertensive participants to quantify the magnitude of the potential ANS modulatory effects.

9.5 Effects of Isometric (Static) Training on Blood Pressure and HRV in Hypertension Patients

The role of isometric (static) exercise training in reducing BP and as a potential hypertensive therapy remains underinvestigated (Pescatello et al., 2004), and no current guidelines are available for the hypertensive patients with respect to this training mode. Recent meta-analyses of small-scale isometric handgrip and leg training studies document mean reductions in resting SBP and DBP of 10–14 and 6–8 mmHg, respectively (Kelley and Kelley, 2010; Owen et al., 2010). Similar to aerobic training, research has demonstrated larger reductions for those with an elevated baseline BP (Millar et al., 2007). However, while the clinical potential of isometric training appears high, the mechanisms responsible for the observed reductions in resting BP are unknown. Analogous to the hypothesized mechanisms for the aerobic training adaptations, alterations in autonomic function have been thought to be involved in the hemodynamic adaptations of isometric exercise training (Millar et al., 2008; Taylor et al., 2003). To date, only two studies have examined the changes in HRV following isometric exercise training (Taylor et al., 2003; Wiles et al., 2010).

In the first study (Taylor et al., 2003), nine medicated hypertensive participants completed 10 weeks of thrice-weekly isometric handgrip training. Each isometric handgrip exercise session consisted of four 2 min contractions, each separated by 1 min of rest, and completed at 30% of maximal voluntary contraction. The training participants demonstrated large reductions (>10 mmHg) in resting SBP and mean BP, accompanied by increases in the HF power and a trend for a reduced LF/HF ratio, in comparison to the controls (Taylor et al., 2003). In addition to the alterations in the HRV, the isometric training group demonstrated significant changes in SBP variability, notably decreased LF power and LF/HF ratio and increased HF power. Collectively, these results may imply an altered neural control of both the heart rate and vascular tone, relating to increased vagal modulation and decreased sympathetic modulation, respectively. By contrast, 8 weeks of thrice-weekly isometric leg training was insufficient to change the spectral HRV of young, healthy, normotensive male participants, although small reductions (<6 mmHg) in resting SBP, DBP and mean BP were reported (Wiles et al., 2010). Thus, two small-scale interventional studies suggest that the antihypertensive effects of isometric training, similar to aerobic and resistance training, may not be solely dependent on ANS modulation.

9.6 HRV-Based Exercise Training

It is becoming increasingly evident that effective disease management may require, and benefit from, patient-specific treatments. This concept is largely the result of the advances in genomic analysis. In exercise training, the observed inter-individual differences in the training responses, the consequence of genetic and non-genetic factors, are thought to be responsible for the high variability in the training adaptations, such as maximal oxygen uptake ($\text{VO}_{2\text{peak}}$) and HRV (Hautala et al., 2009). This hypothesis is supported by research demonstrating specific genetic components or profiles that may predispose individuals to greater adaptations following exercise training (Bouchard and Rankinen, 2001; Hautala et al., 2007; Rankinen et al., 2010; Zago et al., 2010). One factor that may be related to the

degree of exercise training responses is the baseline status of the ANS. Hautala et al. (2003) demonstrated that the baseline HF power, assessed over 24 h, day or night, was correlated with the aerobic training adaptations in $\text{VO}_{2\text{peak}}$, such that the participants with the highest vagal dominance (HF power) at baseline demonstrated the largest training increases in $\text{VO}_{2\text{peak}}$. These results further support the notion that a greater system complexity or variability, commonly associated with vagal modulation, leads to improved responses to stress and reflects a healthier state.

The large inter-subject differences in the training adaptations using general exercise prescription recommendations may also suggest a role for individualized training programs that are tailored to maximize adaptations. Recent research has examined the use of HRV as a way to personalize aerobic training programs and optimize the training responses (Kiviniemi et al., 2007, 2010). The HRV-based training programs alter the aerobic exercise intensity based on daily HRV measures, in contrast to a set relative exercise intensity found in traditional training programs. Generally, the governing principle is to increase the exercise intensity when the HRV is increased or unchanged and to decrease the intensity when the HRV is reduced (Kiviniemi et al., 2007, 2010). In recreational male runners, a 4-week aerobic training study comparing the HRV-based and traditional training programs demonstrated greater improvements in $\text{VO}_{2\text{peak}}$ and maximal running performance with the HRV-based training (Kiviniemi et al., 2007). More recently, HRV-based aerobic training elicited comparable training responses in $\text{VO}_{2\text{peak}}$ to traditional set intensity training (50%–60% $\text{VO}_{2\text{peak}}$), with women demonstrating equivalent improvements in $\text{VO}_{2\text{peak}}$ with a reduced training intensity (Kiviniemi et al., 2010). Thus, limited evidence suggests that the aerobic exercise training programs may be individualized by HRV assessments, with similar, if not greater, success than the classic training programs. Overall, the prescription of exercise training programs based on feedback measures may be important for maximizing adaptations (e.g., BP reductions) in hypertensive patients, although further work is required.

9.7 Conclusions

The experimental and clinical evidence presented in this chapter highlight the presence of autonomic dysfunction in patients with hypertension. The data from HRV studies demonstrate that hypertension is associated with a low HRV and that in normotensive individuals, a low HRV is predictive of a future hypertension incidence. Aerobic exercise training is ideal in the management of hypertension, as it reduces resting BP and increases HRV. Currently, the potential roles for resistance and isometric training are not established and require further research. Finally, it is likely that an assessment of HRV may provide a barometer for individualizing exercise training programs, in order to maximize training adaptations.

Abbreviations

ANS	Autonomic nervous system
CVD	Cardiovascular disease

HF	High frequency
LF/HF	Low frequency-to-high frequency ratio
MSNA	Muscle sympathetic nerve activity
rMSSD	Square root of the mean squared standard differences of successive normal-normal RR intervals
RAS	Renin-angiotensin system
SDNN	Standard deviations of all normal-normal RR intervals

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8

Heart Rate Variability and Blood Pressure Variability in Obstetrics and Gynecology

Dietmar Schlembach and Manfred G. Moertl

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8.1 Introduction

The maternal cardiovascular system (CVS) undergoes profound changes during pregnancy, to allow the mother to respond to her own increased metabolic needs, as well as to ensure the delivery of adequate oxygenated blood to the fetus (Carlin and Alfirevic, 2008; Chapman et al., 1998; Clapp et al., 1988; Clark et al., 1989; Duvekot and Peeters, 1994; Hunter and Robson, 1992; Magness, 1998; Pirani et al., 1973; Pritchard and Rowland, 1964; Robson et al., 1989b; Rovinsky and Jaffin, 1965; Silversides and Colman, 2007). Changes occur in circulating blood volume (BV), peripheral vascular compliance and resistance, myocardial function and contractility, heart rate (HR) and neurohormonal system (Table 8.1). These changes cause no major problems for healthy women. However, in some women with an underlying disease, the normal physiological changes in pregnancy can compromise the CVS and threaten the lives of both mother and fetus.

The autonomic nervous system (ANS) plays a central role in the adaptation of the CVS to various hemodynamic needs and is the principal system involved in short-term cardiovascular control. In the following sections, we will discuss the gradual hemodynamic changes observed in pregnancy that are caused by adaptive mechanisms, the acute changes that occur during labor and delivery and also the changes in the hemodynamics that are induced by shifts in the position of a pregnant woman that put pressure on the maternal organs. An understanding of these adaptations is crucial, especially to predict and possibly treat women with complicated pregnancies and to monitor women with underlying cardiovascular disorders.

8.2 Physiological Changes in Pregnancy

8.2.1 Cardiovascular and Respiratory Systems: Changes throughout Pregnancy

In normal physiology, the cardiac output (CO; liters per minute) is determined by the product of the stroke volume (SV; the amount of blood ejected by the heart during one

TABLE 8.1
Hemodynamic Changes during Normal Pregnancy and Peripartum

	Pregnancy	Peripartum
Blood volume	↑	↑
Heart rate	↑	↑
Systemic peripheral resistance	↓	↑
Blood pressure	↓	↑
Cardiac output	↑	↑
Stroke volume	↑	↑

contraction) and the HR (beats per minute). Arterial blood pressure (BP) is determined by a product of the CO and systemic vascular resistance (SVR). During pregnancy, an increase in BV, a determinant of SV, and an increase in HR, together bring about an increase in CO. This compensates for the reduction in SVR, which is also observed in normal pregnancy, and helps sustain BP. We examine pregnancy-related changes in each of these factors.

8.2.1.1 Blood Volume

BV increases progressively from week 6 to week 8 of gestation and reaches a maximum of about 50% more than in the pre-pregnant state at approximately 32–34 weeks, with little changes thereafter (Clapp et al., 1988; Clark et al., 1989; Pirani et al., 1973; Pritchard and Rowland, 1964; Rovinsky and Jaffin, 1965). The increase in BV is relatively greater than the increase in red cell mass (20%–30%), resulting in hemodilution, that is, a decrease in hemoglobin concentration (Pirani et al., 1973; Taylor and Lind, 1979). The increased BV delivered to the ventricle during pregnancy increases the preload. Preload is influenced by maternal position: the supine position results in compression of the inferior vena cava by the uterus and, consequently, obstruction of venous return and decrease in CO.

8.2.1.2 Heart Rate

HR rises in pregnancy as a compensatory response to falling SVR (Duvekot et al., 1993), but hormonal effects may also play a role. This rise is seen as early as week 7 of gestation and increases by up to 20% in the third trimester, although there is a wide individual variation (Clark et al., 1989; Hunter and Robson, 1992).

8.2.1.3 Systemic Vascular Resistance

SVR is a measure of the resistance that the heart has to overcome in trying to eject blood into the peripheral circulation. The amount of resistance will depend on the tension of the vascular bed (afterload). When the arteries are dilated, there is less resistance. During pregnancy, the SVR begins to fall by week 5 of gestation and reaches its nadir between weeks 16 and 34. The SVR then slowly increases until term (Torgersen and Curran, 2006). The overall fall in SVR is a result of changes in resistance and flow in multiple vascular beds.

8.2.1.4 Blood Pressure

There is a corresponding initial decrease in the systemic arterial pressure, with the decrease in diastolic BP more pronounced than in systolic BP. BP decreases by approximately 10% by 7–8 weeks of gestation, reaching its nadir at mid-pregnancy (around 24 weeks) (Clapp et al., 1988; Duvekot et al., 1993; Moutquin et al., 1985; Robson et al., 1989b). This probably occurs secondary to peripheral vasodilation (Phippard et al., 1986). Thereafter, the systemic pressure begins to increase again and ultimately reaches or exceeds the pre-pregnancy level. Pregnancy hormones play a role in these changes: progesterone and prostaglandins relax the walls of maternal blood vessels, thereby decreasing the SVR (Meyer et al., 1993). This change, coupled with a major portion of maternal blood flow and CO directed toward the support of the uteroplacental circulation, provides a basis for the decrease in maternal systemic BP.

8.2.1.5 Cardiac Output and Stroke Volume

Systolic and diastolic functions contribute to the overall cardiac performance (Wiederman et al., 1965). CO studies in pregnant women have been, by nature, limited in availability and number. Small study populations, variation in timing of measurements and the methodology used and the possible effects of aortocaval compression have all made a precise interpretation difficult. CO is dependent on HR and SV—both of which increase during pregnancy. The general consensus is that CO rises in the first trimester and peaks by the end of the second trimester at approximately 30%–50% of non-pregnant values (Bader et al., 1955; Clark et al., 1989; Duvekot et al., 1995; Easterling et al., 1987; Hansen and Ueland, 1974; Katz et al., 1978; Robson et al., 1989b; Rubler et al., 1977; Ueland et al., 1969). The rise in CO occurs as early as week 5 of gestation, increasing steadily and reaching a plateau at 32 weeks. Thereafter, CO remains unchanged to term or decreases slightly near term. SV is also increased by 8 weeks of gestation, reaching a plateau at 16–20 weeks. Although most of the increase in CO results from the increase in SV, increased HR also contributes. This becomes more important later in pregnancy when the SV plateaus while the HR continues to rise (Mabie et al., 1994; Robson et al., 1989b).

8.2.1.6 Aortocaval Compression (Supine Hypotension)

In the supine position, the enlarged uterus compresses the inferior vena cava, reducing venous return to the heart, which decreases SV and CO. Not only is the inferior vena cava compressed in the supine position, the uterus may also obstruct the abdominal aorta and the iliac arteries (Bieniarz et al., 1969). This latter effect is seldom observed before week 24 and is most pronounced in late pregnancy. Approximately 1 in 10 pregnant women becomes symptomatic with pallor, sweating, nausea and hypotension, accompanied by profound bradycardia and a fall in cerebral blood flow, resulting in unconsciousness if not corrected (Pirhonen and Erkkola, 1990). Shifting to the left lateral decubitus position usually relieves this compression. The decreased CO that occurs in the supine position can be as high as 25%–30% and is usually compensated by an increase in supine SVR. The “supine hypotensive syndrome of pregnancy” (or inferior vena cava syndrome) occurs when there is an inferior vena cava obstruction, possibly further exacerbated by an underdeveloped paravertebral collateral system, and an insufficient increase in the SVR or HR.

8.2.1.7 Respiratory Changes

The respiratory tract undergoes many changes during pregnancy, mediated initially by changes in the endocrine system and later by the enlarging uterus, in order to provide oxygen for the increased maternal demands and for the fetus. Minute ventilation increases during pregnancy because of the increases in tidal volume, whereas the respiratory rate does not change. The functional residual capacity decreases and, along with the increased oxygen consumption, results in less oxygen reserve. Furthermore, as pregnancy progresses, the uterus expands upward and changes the chest shape. The lower ribs “flare” due to looser ligaments. The thoracic circumference increases by 8%, and both the transverse and the anteroposterior diameters increase (Contreras et al., 1991). These changes increase the chest excursion and result in an elevation of the diaphragm (Elkus and Popovich, 1992). Lung compliance is unchanged, but chest wall compliance decreases.

8.2.2 Changes in the Peripartum and Post-Partum Periods

Stress, caused by pain, anxiety and uterine contractions, alters the hemodynamic performance of the CVS at the time of labor and delivery (Robson et al., 1987a). Increases in CO, HR and BP may possibly stress a marginally compensated woman with heart disease and may lead to decompensation.

During the first stage of labor, uterine contractions can increase central BV by as much as 500 mL, the so-called "autotransfusion" (Ueland and Hansen, 1969). The basal BP increases during labor and further increases with each uterine contraction. HR increases during labor secondary to increased circulating catecholamines. The changes in the HR are variable among individuals, dependent mainly on position (more pronounced in the left lateral decubitus position) and anesthesia (reducing pain and thereby anxiety). As a result of the increased HR and SV, basal CO increases during labor by about 10% and furthermore with each contraction (Robson et al., 1987a).

During and after the third stage of labor, large fluid shifts occur within the first 24 h. Hemodynamics are significantly altered due to blood flow from the uterus back to the heart, relief of vena cava compression and fluid shifts from the extravascular to the intra-vascular compartment.

After delivery, hemodynamic parameters return to baseline values, but full resolution may take as long as 6 months. Thus, studies investigating the hemodynamic and ANS have to take into account the fact that parameters investigated post-partum may not have fully recovered to normal non-pregnant values. Usually, BV decreases by 10% within the first 3 days after delivery. BP usually declines within the first 2 days following delivery and thereafter increases to values not significantly different from those recorded at the end of pregnancy and usually returns to pre-pregnancy levels about 12 weeks post-partum (Robson et al., 1989a). Within 2 weeks post-partum, SVR is reported to increase by 30% (Robson et al., 1987b). Maternal HR slowly returns to baseline level over the next 2 weeks. CO peaks by as much as 80% within 10 min following delivery (Hansen and Ueland, 1974; James et al., 1989; Ueland and Hansen, 1969) and remains elevated for about 24 h, followed by a decrease over the next 24 weeks (Capeless and Clapp, 1991; Robson et al., 1987b). Similarly, SV decreases during the first 24 weeks after delivery.

8.2.3 Neurohormonal Factors

Numerous endocrine and metabolic alterations occur during pregnancy, which principally affect the neurohormonal system and the CVS (Cunningham et al., 2010a,b; Walfisch and Hallak, 2006). Both corticotropin and cortisol levels are elevated in pregnancy. The decrease in BP and changes in uterine and renal blood flow initiate additional baroreceptor-mediated neurohormonal events, including activation of the renin-angiotensin-aldosterone (RAAS) and ANS and the release of natriuretic peptides. The activation of the ANS typically occurs in response to a decrease in BP. Conversely, plasma volume expansion suppresses catecholamine levels.

Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) are involved in the integration of the cardiovascular and renal functions and are released in response to volume overload states. In healthy pregnant women, ANP and BNP levels increase during the course of pregnancy (Yoshimura et al., 1994). An impairment in the production of such vasodilators, along with overactivity of the ANS and RAAS, have been implicated in

the pathogenesis of hypertensive pregnancy, intrauterine growth restriction (IUGR) and preterm delivery (Nisell et al., 1986, 1988; Rondó et al., 2003).

8.3 Heart Rate Variability and Blood Pressure Variability in Normal Pregnancy

Heart rate variability (HRV) and blood pressure variability (BPV) are generated by the rhythmic actions of cardiovascular hormones and neuronal pathways on effector organs, such as the heart, kidneys and blood vessels. The rhythm of the heart is further modulated by a combination of sympathetic and parasympathetic inputs, resulting in short-term and long-term variations in the HR. HRV provides a non-invasive window through which the autonomic outflow to the CVS can be studied.

HRV has been used as an indicator of cardiovascular health. A reduced HRV, reflecting a shift in the cardiac sympathovagal balance from parasympathetic to sympathetic control of the heart rhythm, is a predictor of all-cause mortality, arrhythmic events and sudden death after an acute myocardial infarction, as well as in the general population (Bigger et al., 1993; Tsuji et al., 1996). During pregnancy, another source of variability comes from the predictable pattern of BP changes during pregnancy (Ayala et al., 1997; Hermida et al., 2000). Similarly, sinoaortic baroreflex sensitivity (BRS), which is one of the primary mechanisms that regulates BP, is correlated with the incidence of pathophysiological conditions (Bristow et al., 1969; Gribbin et al., 1971).

The brain is involved in setting BP and HR. A study of 31 stroke patients found a significant suppression of HRV as a manifestation of cardiovascular autonomic failure in a hemispheric brain infarction. The impairment of HRV correlated with the severity of the neurological deficits. HRV was absent in five patients with increased intracranial pressure due to large brain infarction, suggesting the important role of the brain in HRV (Korpelainen et al., 1996). The molecular mechanisms involved in the regulation of BPV and HRV or BRS are only poorly understood. Initial analyses of gene-manipulated animals suggest that genes involved in cardiovascular regulation and that are expressed in the central nervous system may be interesting candidates for the molecular regulation of BPV and HRV (Mansier et al., 1996; Uechi et al., 1998; Wickman et al., 1998; Zohn et al., 1998).

8.3.1 Baseline HRV and BPV

On the one hand, autonomic nervous function can be altered by the physiological changes in pregnancy, as discussed in Section 8.3, but on the other hand, regardless of pregnancy, ANS plays a central role in the adaptation of CVS to various hemodynamic needs and is the principal system involved in short-term cardiovascular control (Ekholm and Erkkola, 1996; Lucini et al., 1999). Although significant adaptations of the maternal CVS are known to occur during normal pregnancy, our knowledge of the maternal HRV and BPV during pregnancy is still limited. Most of the studies performed have used frequency domain parameters, such as low-frequency (LF) oscillations, high-frequency (HF) oscillations, normalized units of both frequencies (LF_n, HF_n) and the LF/HF ratio (Akselrod et al., 1987). The term “sympathovagal balance” has been used extensively in the literature and has frequently been characterized by the LF/HF ratio or the %LF power. However,

there are those who disagree that HRV-based measures quantify sympathovagal balance (Goldberger, 1999).

8.3.1.1 Heart Rate Variability

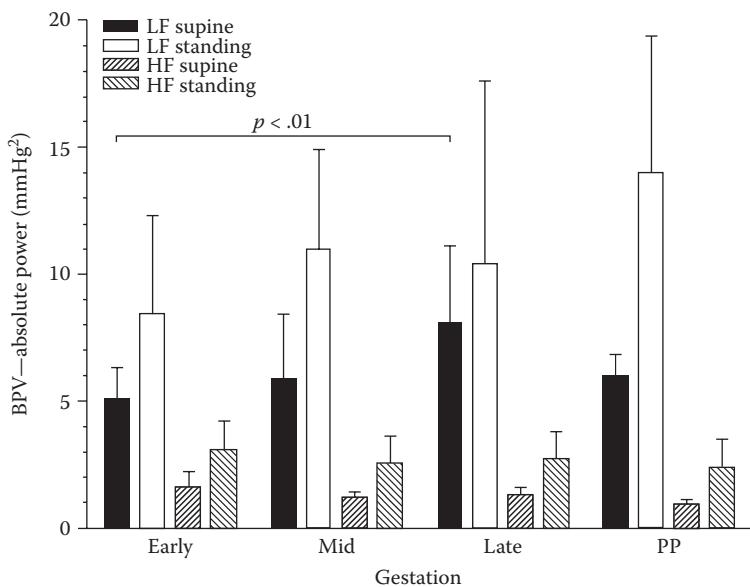
In the 1990s, Ekholm et al. (1993) reported on HRV and HR responses to postural changes and the Valsalva maneuver to be blunted in mid-pregnancy and concluded that parasympathetic cardiovascular control was reduced in pregnant women compared with non-pregnant controls. The beginning of pregnancy is associated with sympathetic reactivity and the latter half is characterized by an increased hemodynamic stability and a significantly reduced HRV (Ekholm and Erkkola, 1996). In a subsequent study, the same researchers investigated the circadian rhythm of frequency domain measures (Ekholm et al., 1997a). Compared to non-pregnant women, pregnancy was associated with an overall reduction in HRV, most markedly in the LF component, suggesting an altered baroreflex or a sympathetic modulation of HR. The HF component was lower at night compared to the non-pregnant controls, but similar in daytime, suggesting a decreased vagal activation at night. Subsequently, Stein et al. (1999) performed a longitudinal study in healthy volunteers, performing measurements before and during pregnancy, and were able to show that an alteration of the ANS in pregnancy occurs in early pregnancy, with a significant decrease in LF power and a further significant decline in late pregnancy. Antonazzo et al. (2004) investigated women within the first trimester (between 6.0 and 12.5 weeks) with a subsequent normal pregnancy outcome and reported LFnu to be lower and HFnu to be higher compared to non-pregnant controls.

Blake et al. (2000) examined women longitudinally throughout gestation in two different positions. They could not detect any change during pregnancy in the total supine HRV or in the LF component, whereas the absolute supine HF component decreased significantly throughout gestation. In the standing position, no overall change was observed in total HRV power, although both the LF and HF frequencies increased with time. The LF/HF ratio increased significantly with gestation in the supine position, whereas in the standing position, no change could be observed with advancing gestational age.

In a cross-sectional study, Voss et al. (2000) investigated the influence of maternal age and gestational age on HRV and BPV. Maternal age was significantly correlated with LFnu power in HRV in non-pregnant women. Interestingly, a higher gestational age was correlated only with an increase in the power within the ultralow-frequency band. In comparing pregnant women with non-pregnant women, subdivided into subclasses of maternal age of less than 28 years or older than 28 years, considerable differences in the HRV were found. Both LF and HF were significantly decreased in pregnant women. In agreement with Voss et al., we also could not find significant changes in HRV in 20 healthy pregnant women monitored longitudinally throughout pregnancy (Moertl et al., 2009).

8.3.1.2 Blood Pressure Variability

Although hypertension is a serious complication of pregnancy, studies on BPV in pregnancy are sparse, especially those using devices that are capable of continuous measurement. Time domain and frequency domain measures of BPV cannot be obtained easily without a device such as Portapres (Finapres Inc., Amsterdam, the Netherlands), which can record BP continuously as Holter ECG monitors do and perform a Fourier

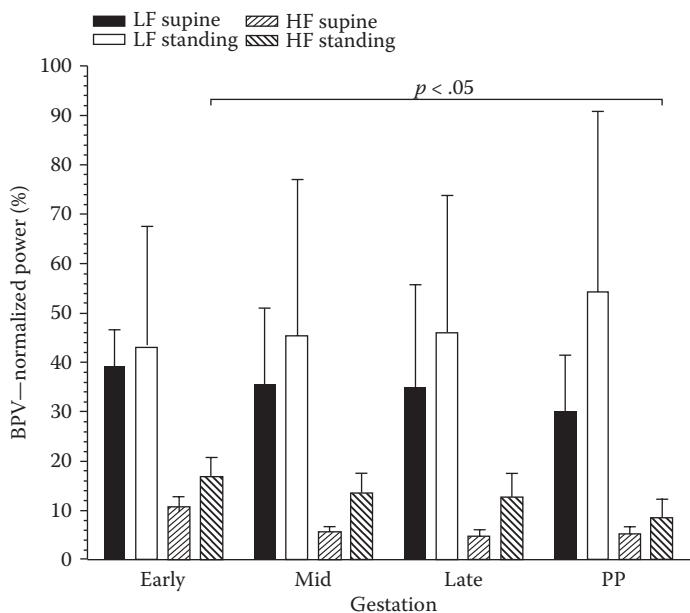
**FIGURE 8.1**

Changes in the BPV during pregnancy (LF and HF absolute powers). (Data from Blake, M.J., Martin, A., Manktelow, B.N., Armstrong, C., Halligan, A.W., Panerai, R.B. and Potter, J.F., *Clin. Sci. (Lond.)*, 98, 259–268, 2000.)

transform on the collected data. Hermida et al. measured BPV using an ambulatory measurement device that measured BP every half hour during the daytime and hourly at night, and they reported a steady decrease in BP up to 20 weeks of gestation, followed by an increase in BP until delivery (Ayala et al., 1997; Hermida et al., 1998, 2000, 2001, 2003, 2004).

Blake et al. (2000) measured BP in 16 normotensive pregnant women and in 10 normotensive non-pregnant controls, using a non-invasive beat-to-beat BP recording device. Total supine BPV was significantly altered during pregnancy, increasing by 79% between early (16 ± 2 weeks) and late (36 ± 1 weeks) gestation, whereas no such changes in BPV were detected when measured in the standing position. Looking at the different power spectral components, in the supine position, LF changed with time, with a significant increase in variability of 68% between early and late gestation (Figure 8.1). No overall change was reported in standing BPV during pregnancy and post-partum period. When the data were normalized to eliminate variations due to the very-low-frequency (VLF) band, there was an overall increase in standing LFnu variability with time, but the HFnu variability decreased, with a significant fall between early gestation and post-partum period (Figure 8.2). In contrast to the changes reported by Blake et al., Voss et al. and our group were unable to find any differences in the BPV in pregnant women with uncomplicated pregnancies (Voss et al., 2000; Moertl et al., 2009).

Interestingly, Matsuo et al. reported differences in the LF/HF ratio depending on the duration of labor. The LF/HF ratio was significantly higher in the longer labor group (duration of labor ≥ 13 min) of primiparous women (Matsuo et al., 2007). In addition to post-partum hormonal changes, the relief of the aortocaval compression following delivery is believed to be the main cause for the return of autonomic activity 3 months after delivery to non-pregnant levels (Chen et al., 1999b).

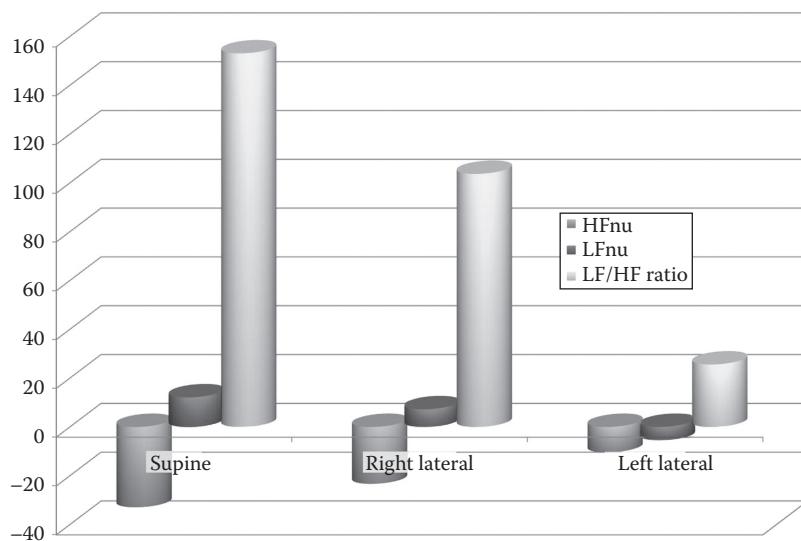
**FIGURE 8.2**

Changes in the BPV during pregnancy (LF and HF normalized powers). (Data from Blake, M.J., Martin, A., Manktelow, B.N., Armstrong, C., Halligan, A.W., Panerai, R.B. and Potter, J.F., *Clin. Sci. (Lond.)*, 98, 259–268, 2000.)

8.3.2 HRV and BPV Depending on Maternal Position

As mentioned earlier, with increasing gestational age, the enlarged uterus compresses the inferior vena cava, reducing the venous return to the heart (Bieniarz et al., 1969). This is called “supine hypotensive syndrome of pregnancy” (or inferior vena cava syndrome). The diminished preload causes the ANS to counteract. Several groups have studied the effects of aortocaval compression and maternal position during pregnancy and after delivery (Chen et al., 1999a,b; Kuo et al., 1997, 2000; Matsuo et al., 2007; Speranza et al., 1998). It is commonly accepted that the left lateral position is accompanied by the least change in HRV compared to the right lateral or supine position (Chen et al., 1999b; Kuo et al., 1997; Speranza et al., 1998). Kuo and coworkers reported percentage changes in the measures of HRV in pregnant women in three positions compared to non-pregnant women: HFnu decreased by 32.9% in the supine position, 23.3% in the right lateral position and 10.4% in the left lateral position. LFnu increased by 12.1% (supine) and 7.23% (right lateral) and decreased by 5.44% (left lateral) in the different positions described earlier. The corresponding LF/HF ratios changes were 153.1%, 103.7% and 25.6%, respectively (Figure 8.3) (Kuo et al., 1997).

In a cross-sectional study, this group consecutively examined the effect of maternal position in all trimesters of pregnancy (Chen et al., 1999a; Kuo et al., 2000). The HFnu component and the LF/HF ratio increased significantly in the supine position in the first trimester and then decreased progressively with advancing gestation. When the position was changed from supine to the right lateral position, the percentage of changes correlated significantly with the decrease in the HFnu component. They concluded that the ANS activity is shifted toward a lower sympathetic and higher vagal modulation in

**FIGURE 8.3**

Changes in the frequency domain components of the HRV in pregnant women, depending on the position. (Data from Kuo, C.D., Chen, G.Y., Yang, M.F. and Tsai, Y.S., *Anaesthesia*, 52, 1161–1165, 1997.)

the first trimester and changed toward a higher sympathetic and lower vagal modulation in late pregnancy. The aortocaval compression caused by the uterus may be a possible explanation for this shift.

8.4 Heart Rate Variability and Blood Pressure Variability in Hypertensive Pregnancy

8.4.1 Preeclampsia: A State of Sympathetic Overactivity?

Hypertensive disease occurs in approximately 12%–22% of all pregnancies, and preeclampsia, a severe hypertensive pregnancy disorder with an incidence of 3%–8% worldwide, is still a leading cause of fetal and maternal morbidity and mortality. Preeclampsia accounts for 42% of all maternal deaths per year and is associated with 15% of all preterm deliveries (Noris et al., 2005; Roberts et al., 2003; Sibai et al., 2005). The severe early-onset form of preeclampsia (<34 weeks of gestation) complicates about 2% of all pregnancies. The diagnosis of hypertensive disorders and especially preeclampsia is based on the measurement of BP (i.e., BP \geq 140/90 mmHg) and proteinuria ($>$ 300 mg/day) (ACOG, 2002).

Despite intensive research efforts, the pathogenesis of the disease remains to be elucidated (Gilbert et al., 2008; Noris et al., 2005; Schlembach, 2003), but it is commonly accepted that preeclampsia is characterized by endothelial dysfunction and a marked increase in SVR (Gilbert et al., 2008; Poston, 2006; Redman and Sargent, 2005; VanWijk et al., 2000). Since vascular tone is largely determined by the activity of the ANS, it has been investigated whether an increase in sympathetic vasoconstrictor activity may be an important mechanism in mediating the increase in peripheral vascular resistance in preeclampsia.

Schobel et al. (1996) measured postganglionic sympathetic nerve activity in the blood vessels of skeletal muscles by means of intraneuronal microelectrodes. The rate of sympathetic nerve activity in patients with preeclampsia was higher by threefold compared to normotensive pregnant women. They concluded that preeclampsia is a "state of sympathetic overactivity," which reverts to normal after delivery. Furthermore, this group was able to show that all women at risk for preeclampsia were invariably characterized by a pregnancy-induced increase in muscle sympathetic nerve activity, which normalized after delivery (Fischer et al., 2004). They named this phenomenon "pregnancy-induced sympathetic overactivity" (PISO). Interestingly, PISO was not necessarily associated with peripheral vasoconstriction and hypertension and only a subset of patients developed preeclampsia later on. The authors hypothesized that PISO constitutes a precursor of preeclampsia, which is physiologically compensated by vasodilatory mechanisms, leading to the disorder only when they fail.

In addition, using microneurography, Greenwood et al. (1998, 2001) showed that central sympathetic output was increased in women with normal pregnancy and was even greater in hypertensive pregnant women, although preeclampsia was not associated with greater sympathetic overactivity than pregnancy-induced hypertension (PIH) (Greenwood et al., 2003).

Unfortunately, muscle sympathetic nerve activity is measured by an invasive method and is therefore of limited clinical use. Furthermore, it is debatable if the increased sympathetic activity measured by microneurography truly represents an overall increase in sympathetic activity in preeclamptic women. Consequently, only a non-invasive assessment of the ANS in women with hypertensive disorders has been performed.

8.4.2 HRV and BPV in Hypertensive Pregnancy Disorders

Non-pregnancy-related hypertension is attributed, in part, to autonomic dysregulation (i.e., decreased parasympathetic and increased sympathetic cardiac modulations), which results in an increase in HR, as well as in an enhanced vasomotor sympathetic modulation that causes vasoconstriction (Dabrowska et al., 1996; Guyenet, 2006; Pagani and Lucini, 2001). Moreover, the baroreceptor-HR reflex is impaired in patients with hypertension (Parati et al., 1988). Studies on HRV and BPV in hypertensive pregnancy disorders are scarce and not easy to compare due to differences in the definition of disease, number of patients examined, study design and performance of the test methods.

8.4.2.1 Chronic Hypertension

A maternal BP measurement of $\geq 140/90$ mmHg on two occasions before 20 weeks of gestation, or persisting beyond 12 weeks post-partum, indicates chronic hypertension (ACOG, 2002). About 1%–5% of pregnant women or more than 100,000 pregnant women each year in the United States have chronic hypertension (Joint National Committee, 1997). Women with chronic hypertension have an increased risk for superimposed preeclampsia and placental abruption as well as for life-threatening maternal complications, such as pulmonary edema, hypertensive encephalopathy, retinopathy, cerebral hemorrhage and acute renal failure.

It has been shown that essential hypertension leads to a reduction in HRV, depending on the degree of severity (Guzzetti et al., 1988; Iwane et al., 2000; Mussalo et al., 2001). However, so far, only two research groups have investigated HRV in pregnant women

with chronic hypertension (Faber et al., 2004; Khlybova et al., 2008; Walther et al., 2005). Walther et al. examined the hypothesis that chronic hypertension during pregnancy had an impact on the adaptation of the autonomic control during pregnancy based on HRV analysis. Beginning at 20 weeks of gestation, 16 pregnant women with chronic hypertension and 35 healthy pregnant women serving as controls were monitored longitudinally every 4 weeks until delivery (Walther et al., 2005). No significant HRV differences between both groups could be observed. Longitudinal variations were detectable in normal pregnancies and also, albeit to a lesser degree, in chronic hypertensive pregnant women. Throughout gestation, a decreased HRV was observed, but it was more pronounced in healthy pregnant women. The LF/HF ratio was increased in both groups due to a decrease in HF and thus a significant increase in LFnu. However, VLF (power of the VLF range) increased exclusively in the normotensive pregnancies. They concluded that patients with long-term hypertension are still able to respond to the physiological changes that occur during pregnancy. By contrast, Khlybova et al. (2008) reported increased HF and LF powers and LF/HF ratio in women with chronic hypertension compared to healthy pregnant women and concluded that the changes in HRV indicate an increased ANS activity in pregnant women with chronic hypertension (Khlybova et al., 2008).

8.4.2.2 Gestational Hypertension

Gestational hypertension or PIH is defined as the onset of hypertension ($\geq 140/90$ mmHg) in pregnancy without proteinuria after 20 weeks of gestation (ACOG, 2002).

BP and SVR are increased in women with gestational hypertension, the BV is smaller and BP and HR responses to various provocations are different compared to those of normotensive pregnant women (Airaksinen et al., 1985; Ekhholm and Erkkola, 1996; Ekhholm et al., 1994, 1996; Heiskanen et al., 2008; Kammerer et al., 2002; Nisell et al., 1985a,b, 1987; Rang et al., 2002; Woisetschläger et al., 2000), although the results are inconsistent (Rang et al., 2002).

Ekhholm et al. (1997b) have examined the association of cardiovascular changes in gestational hypertension with the increase in sympathetic control of hemodynamics and change in sympathovagal balance. They found that HRV and systolic BPV were significantly increased in women with gestational hypertension. This increase was greatest in the HF component of HRV. Furthermore, the HF variability of systolic BP was also significantly increased in women with gestational hypertension compared to normotensive pregnant subjects. As a result, Ekhholm et al. could show that the neural control of HR and BP is disturbed in gestational hypertension, as shown by an increased HRV and BPV. Both the sympathetic and the parasympathetic controls of HR and BP appeared to be increased.

Faber et al. (2004) analyzed HRV and BPV in 81 pregnant women with various hypertensive disorders (19 with chronic hypertension, 18 with gestational hypertension and 44 suffering from preeclampsia) and in 80 healthy pregnant women. Whereas frequency domain parameters of HRV were unaltered in hypertensive women compared to normotensive women, BPV was markedly altered in all three hypertensive groups compared to healthy pregnancies, with the changes most pronounced in preeclamptic patients. Patients with gestational hypertension and preeclampsia were characterized by a significant increase in the LF component compared to the controls, whereas the HF component was elevated in all three hypertensive groups. The LF/HF ratio was not statistically different between the groups. No single BPV parameter was able to discriminate between the hypertensive

groups. Interestingly, the increase in BPV in preeclamptic patients did not lead to an elevated baroreflex activity, while BPV changes in both the other hypertensive groups were paralleled by alterations in baroreflex parameters. As some parameters of HRV, BPV and BRS differed between the various hypertensive pregnancy disorders, Faber et al. concluded that distinct clinical manifestations of hypertension in pregnancy may have different pathophysiological, regulatory and compensatory mechanisms.

8.4.2.3 Preeclampsia

Preeclampsia is characterized by the development of hypertension (BP $\geq 140/90$ mmHg) and proteinuria (>300 mg/day) after 20 weeks of gestation (ACOG, 2002). Currently, the only curative treatment available is delivery and thereby removal of the placenta. In preeclampsia, the hemodynamic and vascular adaptations to pregnancy are disturbed. Women who subsequently develop preeclampsia have an increased CO throughout pregnancy (Easterling et al., 1990). However, after development of preeclampsia, CO has been reported to be decreased (Kuźniar et al., 1982), normal (Assali et al., 1964; Lees, 1979) or increased (Benedetti et al., 1980; Mabie et al., 1989). These different findings probably reflect the heterogeneity of preeclampsia and/or the different methods used (for estimating CO) and the patient populations studied (Yang et al., 1996). Late hemodynamic changes in preeclampsia are characterized by increased BP, reduced plasma volume, increased SVR and vasoconstriction (Visser and Wallenburg, 1991).

Additionally, preeclampsia is associated with autonomic nervous dysfunction (Airaksinen et al., 1985; Schobel et al., 1996), particularly decreased vagal control of the heart (Eneroth-Grimfors et al., 1994; Swansburg et al., 2005; Yang et al., 2000). During pregnancy, the power within the maternal HR spectrum is markedly depressed (Eneroth and Storck, 1998). However, when comparing the alterations in frequency domain parameters in preeclamptic women with normotensive pregnant control women, the results are inconsistent: Eneroth and Storck (1998) could not detect any difference, whereas Yang et al. (2000) reported HF to be lower and LF/HF ratio to be higher in preeclampsia compared to normal pregnant or non-pregnant women, concluding that the changes in the ANS activity occurring in normal pregnancy are further enhanced in preeclampsia (Yang et al., 2000).

In most cases, the clinical symptoms resolve during the post-partum period. Nevertheless, it has been shown that in normotensive, formerly preeclamptic women, a subnormal plasma volume coincides with a higher sympathetic activity in the BP regulation and a reduced BRS. Whether these alterations in the autonomic control mechanisms are a cause or an effect of the subnormal plasma volume remains to be elucidated (Courtar et al., 2006).

8.5 HRV and BPV and Cardiovascular Reflex Tests in Normal and Hypertensive Pregnancies

In addition to power spectral analysis of spontaneous HRV and BPV in the resting condition, various cardiovascular challenge tests for evaluating the ANS control and response can be performed (Ekholm and Erkkola, 1996; Ekholm et al., 1994, 1996; Heiskanen et al., 2008; Kammerer et al., 2002; Nisell et al., 1985a,b, 1987; Rang et al., 2002; Woisetschläger

TABLE 8.2

Non-Invasive Methods and Challenge Tests for Autonomic Nervous System Testing

Test Method	ANS Level Tested
Power spectral analysis	<ul style="list-style-type: none"> • Efferent (para)sympathetic control • Overall baroreflex sensitivity
Orthostatic stress test	<ul style="list-style-type: none"> • Overall baroreflex integrity
Valsalva maneuver	<ul style="list-style-type: none"> • Overall baroreflex integrity
Isometric hand grip test	<ul style="list-style-type: none"> • Efferent sympathetic pathway
Cold pressure test	<ul style="list-style-type: none"> • Efferent sympathetic pathway
Deep breathing test	<ul style="list-style-type: none"> • Efferent vagal pathway

et al., 2000) (Table 8.2). Given the important physiological changes that accompany pregnancy, the performance of laboratory challenges on pregnant women constitutes a way of determining how this unique group reacts to stressors.

These studies of physical cardiovascular challenge tests in normotensive and hypertensive pregnancies have been summarized in two extensive and critical reviews by Rang et al. (2002) and De Weerth and Buitelaar (2005). We summarize some of the results next.

8.5.1 Orthostatic Stress Test

After a total of 5–10 min of supine rest, the patient is instructed to stand up and remain in an upright position for at least 2 min, causing the blood to pool from the thorax into the veins. This consecutively diminishes preload, followed by a decline in SV and CO.

Short-term adjustments to orthostatic stress can be distinguished in an initial reaction (first 30 s) and an early steady-state response (after 1–2 min standing). On standing, the HR initially rises rapidly by an exercise reflex, then more gradually due to the dual effect of cardiac vagal inhibition and sympathetic activation. The subsequent rapid decrease in HR is associated with the recovery of the arterial pressure and is due to rapid vagal inhibition mediated through the baroreflex. The arterial BP increases due to muscular compression of the vessels of the legs directly after standing up and due to an increase in abdominal pressure, resulting in a shift of blood toward the heart. This causes a reflex release of vasoconstrictor tone and hypotension. This drop in the BP induces sympathetically mediated vasoconstriction, whereby BP recovers and sometimes overshoots. After approximately 1 min, circulatory readjustment has been achieved (Wieling and Shepherd, 1992; Wieling et al., 1991).

The HR response to orthostatic stress is mainly vagally mediated and can be used as a measure of cardiac vagal integrity. BP maintenance after 1 and 2 min of standing (early steady state) depends predominantly on the increased activity of the sympathetic system. The HR increase at that moment gives an indication of the decreased vagal and increased sympathetic efferent inputs to the sinus node (Wieling et al., 1991).

During the initial phase of the stress test, the bradycardic response to orthostatic stress in pregnant women is diminished compared to non-pregnant women. Preeclamptic women showed no differences in HRV and BPV compared with healthy pregnant women. When compared to resting conditions, in the steady state, there is a higher diastolic BP difference in normal pregnant women compared with non-pregnant women.

The responses were similar for preeclamptic women compared with normal pregnant women (Rang et al., 2002).

In 2008, Heiskanen et al. (2008) studied the cardiovascular autonomic responses to the head-up tilt test (HUT) in 28 pregnant women at third trimester and 3 months postpartum, using a tilting table. In the horizontal position, all frequency components of HRV were lower during pregnancy than at 3 months after parturition, while pregnancy had no influence on normalized LF and HF powers. During pregnancy, hemodynamics were well balanced with only minor changes in response to postural change, while the hemodynamic responses to HUT were more remarkable after parturition. In pregnant women, HRV, especially the VLF component of HRV increased in response to HUT, whereas 3 months after parturition, HRV decreased in response to HUT. They concluded that parasympathetic deactivation toward term in pregnant women was likely to contribute to an increased HR and CO at rest, whereas a restored sympathetic modulation with modest responses to stimulation may result in stable peripheral resistance and sufficient placental blood supply during HUT.

8.5.2 Valsalva Maneuver

In the Valsalva maneuver, the intrathoracic pressure is increased abruptly by forced expiration against a resistance. The closure of the glottis is prevented and thus the pressure is transmitted to the chest. The increased intrathoracic pressure causes a decrease in venous return to the right atrium, which leads to a fall in BP. A serious hypotension is prevented by a baroreflex-mediated vasoconstriction due to increased sympathetic activity. The HR increases to preserve the CO, where the former is mediated by both vagal withdrawal and increased sympathetic outflow to the sinus node. Despite the tachycardia, CO and BP fall. The sympathetic activity is amplified and raises SVR, which leads to progressive BP recovery toward the end of the strain. After the strain, the venous inflow to the heart increases and SV and CO become normalized. As the normal SV of the heart is ejected into a vascular bed that is still constricted, there is an overshoot of the mean arterial pressure, and secondary to this, a vagally mediated bradycardia results (Smith et al., 1996). Elevation of BP after the straining phase of the Valsalva maneuver provides an estimate of the sympathetic nerve responses and the integrity of the arterial baroreceptor-sympathetic control mechanisms (Smith et al., 1996). The HR response to Valsalva straining is higher in pregnancy compared with non-pregnant values, but it is not influenced by preeclampsia (Rang et al., 2002).

8.5.3 Isometric Handgrip Test

During the isometric handgrip test, the patient squeezes a pressure-gauging device with the dominant hand for 3 min using 30% of the predetermined maximum voluntary force. During such an isometric exercise, systolic and diastolic BPs and HR gradually increase. Immediately after cessation of the exercise, BP and HR fall abruptly to their basal levels (Lind et al., 1964).

Two mechanisms are responsible for the cardiovascular adjustments to this static exercise. The increase in BP occurs mainly by an increase in sympathetic activity to the blood vessels, whereas the increase in HR occurs mainly by a decrease in parasympathetic activity at the sinus node (Iellamo et al., 1999). In normotensive as well as in hypertensive pregnant women, HRV and BPV are not influenced by isometric handgrip test (Rang et al., 2002).

8.5.4 Cold Pressor Test

The cold pressor test is performed by immersing the patient's hand to the wrist in ice water (0°C – 4°C) for 2 min, causing an immediate local and generalized vasoconstriction of the skin and the skeletal muscle, which is not only due to a direct effect of cold on the local skin vessels, but also due to pain, which activates the spinal and hypothalamic reflexes. The HR increases, peaking at about 30 s in the cold pressor test, and returns to control values during the second minute. Due to an increase in SVR, the arterial pressure increases with a maximum in the second minute.

The activation of sympathetic vasoconstrictor outflow to the skeletal muscle is an important component of the pressor response to this test. The increased HR is mediated by sympathetic activation rather than by parasympathetic withdrawal.

In normal pregnant women, a change in systolic BP to cold exposure is smaller compared to non-pregnant women. For preeclamptic women, BPV during cold exposure is highly variable, while HRV is not influenced by pregnancy or preeclampsia (Rang et al., 2002). It has been suggested that the hypothalamic–pituitary–adrenal axis becomes hypo-functional to natural stressors at the end of pregnancy (Kammerer et al., 2002).

8.5.5 Deep Breathing Test

For this test, the patient is asked to breathe deeply and evenly at 6 breaths/min. This produces a maximum variation in HR. The respiratory fluctuations in HR are likely to be mediated primarily by parasympathetic efferent pathways. The respiratory sinus arrhythmia can thus be used as a measure of cardiac vagal modulation (Ewing et al., 1985). Using the deep breathing test, no differences could be observed between normotensive pregnant versus non-pregnant women and also between normotensive versus hypertensive pregnant women (Rang et al., 2002).

8.5.6 Mental/Psychological Stress Test

As maternal psychological stress and distress have been shown to be of predictive value for pregnancy complications (Rondó et al., 2003), it may be interesting to investigate the responses to psychological challenge tests in pregnancy. Various mental stress tests, such as serial subtraction, mirror-image tracing or the standardized Trier Social Stress Test, can be used for the psychological challenge of the ANS (Klinkenberg et al., 2009; Matthews and Rodin, 1992).

Matthews and Rodin (1992) reported a diminished BP response to serial subtraction and mirror-image tracing in pregnancy. Klinkenberg et al. (2009) examined 55 healthy pregnant women (28 women at the second trimester and 27 in or close to the third trimester) and compared them with 24 non-pregnant women. The ANS activity (i.e., the HF and LF frequencies) during the psychological stress decreased with advancing gestational age, whereas the subjective stress perception did not show significant changes.

8.6 Values of HRV and BPV for Prediction of Pregnancy Complications

The development of preeclampsia is thought to be a consequence of an impaired trophoblast invasion of the maternal spiral arteries and their conversion from narrow muscular vessels into wide non-muscular channels (Pijnenborg et al., 1980; Redman and

Sargent, 2005). In many cases of preeclampsia, trophoblast invasion is inhibited, the arteries are poorly remodeled and the capacity of the uteroplacental circulation is too small. This is called poor placentation, and it occurs before 20 weeks, predating the appearance of the clinical signs of preeclampsia (Redman, 1991). This implies that the pathophysiological origin of preeclampsia is already established early in pregnancy before the onset of clinical symptoms and in some patients, the disorder progresses rapidly. Therefore, an accurate prediction of preeclampsia and IUGR is crucial to allow the judicious allocation of resources for monitoring and preventive treatment to improve the maternal and perinatal outcomes (Cnossen et al., 2008).

The physiological process of trophoblast invasion is reflected in the observation from Doppler ultrasound studies that impedance to flow in the uterine arteries decreases with gestation between 6 and 24 weeks and remains constant thereafter. However, the screening performance of Doppler sonography is insufficient, because only a proportion of women with disturbed uterine perfusion develop complications related to pregnancy, such as pre-eclampsia, PIH or IUGR (Cnossen et al., 2008).

Considering that sympathetic activity slowly increases in the third trimester in a normotensive pregnancy and that the aforementioned alterations in the ANS in preeclampsia (i.e., a decreased vagal control and a sympathetic overactivity) also appear in the third trimester, it has been suggested that changes in HRV and BPV, as well as in BRS, in early pregnancy can be used to predict the development of pregnancy complications. A study by Antonazzo et al. demonstrated that assessment of short-term analysis of HRV in high-risk and IVF pregnancies was significantly different from that observed in normal pregnancies. These differences were more significant in those pregnancies with an adverse outcome (Antonazzo et al., 2004). These results suggest that analysis of short-term HRV performed in early pregnancy may facilitate the identification of women at risk for the most common complications, such as gestational hypertension, preeclampsia and IUGR, before they become clinically apparent (Antonazzo et al., 2004).

Rang et al. (2004) have proposed that a serial assessment of cardiovascular control in the form of baroreflex gain, HRV and BPV can identify early signs of preeclampsia. These results were confirmed by Pal et al., (2009), who investigated the role of spectral analysis of HRV in the early prediction of gestational hypertension. They observed an increased LF/HF ratio, the most sensitive indicator of the sympathovagal balance, from early pregnancy (12 weeks) in high-risk women, who subsequently developed PIH (Pal et al., 2009), suggesting that the predictive knowledge of the sympathovagal imbalance should be utilized in designing the prevention and management of PIH.

The possibility of combining this technique (HRV) with uterine artery Doppler sonography to improve the prediction of preeclampsia and other pregnancy complications was considered (Voss et al., 2006; Walther et al., 2006). Voss et al. monitored 19 women with abnormal uterine perfusion and subsequent pregnancy complication (hypertensive disorder or IUGR), 16 women with abnormal uterine perfusion and subsequent normal pregnancy outcome and 32 healthy pregnant women as controls. The women were recruited at 20 weeks of gestation and were followed longitudinally every 4th week until delivery. In the control group, pregnancy-induced adaptation of the cardiovascular control could be detected. On the contrary, no changes during the second half of pregnancy could be observed in pregnancies with abnormal perfusion. HRV and BPV parameters were significantly altered in women with abnormal perfusion compared with normal pregnancy, whereas these changes were more pronounced in women with subsequent pregnancy complication compared to normal outcome patients (Voss et al., 2006). They examined 58 pregnant women with abnormal uterine perfusion compared to 44 normal pregnancies in

the second trimester (18–22 weeks) and identified a combination of three variability and baroreflex parameters to best predict preeclampsia several weeks before clinical manifestation: The HF component in diastolic BP (HF-dBP), the total power normalized VLF component in HRV (VLFn-HRV) and the number of tachycardic baroreflex events in the range of 4–6 ms/mmHg (Walther et al., 2006). The discriminant function of these three parameters classified patients with subsequent preeclampsia with a sensitivity of 87.5%, a specificity of 83.7% and a positive predictive accuracy of 50.0%. Combined with the Doppler investigations of the uterine arteries, the positive predictive accuracy increased to 71.4% (Malberg et al., 2007; Walther et al., 2006).

As the pathophysiological mechanisms of preeclampsia take place in early pregnancy, the usefulness of such combined screening is limited by the fact that the aforementioned studies were performed within the second trimester, thereby making treatment or sufficient prophylaxis impossible. To achieve this goal, this and other screening models should be performed during early pregnancy.

8.7 Discussion

Decreased HRV is a marker for an increased risk of death among patients with heart disease and other clinical conditions, whereas a decrease in HRV (mainly in the HF component) during pregnancy represents a normal physiological response. It is likely, however, that the change in HRV during complicated pregnancies differs from the normal pattern. Such patterns present as variations in the HRV-related parameters or as an inability to evolve with time. Often, the direction the parameter changes does not follow the “normal” course seen in healthy pregnant women. Methodological limitations may be the cause of such variations. In this section, we explore the reasons for large variations in the autonomic studies reported in the literature on pregnant women and potential solutions. Recommendations for a sound design of stress test protocols are presented (De Weerth and Buitelaar, 2005).

Often, the ANS response to certain tests in hypertensive pregnancies can be a source of debate. For example, the “state of sympathetic overactivity” detected with invasive microneurography (Fischer et al., 2004; Greenwood et al., 1998, 2001, 2003; Schobel et al., 1996) could not be reproduced using non-invasive measures of continuous HR and BP analysis. A possible explanation for this discrepancy is that the increased sympathetic activity, which was observed by microneurography, may not truly represent an overall increase in sympathetic activity in preeclamptic women. Microneurography measures the sympathetic outflow to the skeletal muscle, but sympathetic activity in the skeletal muscle may not reflect sympathetic activity in other organs, such as the heart or the kidneys. Furthermore, since microneurography is an invasive procedure causing anxiety and pain, it may be possible that the observed sympathetic activation is mainly caused by the procedure itself.

Since these abnormalities in hemodynamic adaptations to pregnancy can be detected in the first trimester, it is likely that abnormal HRV responses in early pregnancy could help discriminate and provide insight into subsequent complications, such as preeclampsia and/or IUGR (Antonazzo et al., 2004; Rang et al., 2004; Pal et al., 2009).

Given the important physiological changes that accompany pregnancy, the performance of laboratory challenges to pregnant women constitutes a way of determining

how this unique group reacts to stressors. Important basic questions are whether the physiological stress reactivity of a pregnant woman is comparable to that of a non-pregnant subject, or whether pregnant women display heightened or dampened reactivity to stress. Unfortunately, the results of challenge tests during pregnancy are either conflicting or are inconclusive (Rang et al., 2002). These may be due to methodological factors, differences in definitions of disease or study design and performance of the testing procedures.

For a proper analysis of HRV and BPV to different stimuli, continuous recording of BP and HR must be used, which has not been performed in all studies. Most studies are cross-sectional and only a few are longitudinal and are conducted with a relatively small sample size. In addition, relatively few researchers have included control groups for comparison. Only a few studies performed measurements before the onset of the hypertensive disorder and also before pregnancy. A longitudinal repeated testing approach involving higher-risk populations of pregnant women is extremely important as it can reveal information about how pregnancy affects the autonomic reactivity in these sub-groups of individuals. In the specific case of post-natal reactivity, we believe that it is advisable to test women at least 6–12 months after childbirth, in order to ensure full recovery from pregnancy.

The differences in design make comparison between studies quite difficult and could very well account for at least some of the variation in the results. The duration of the stressful challenge presented varies greatly among the studies and even within the same study. Thus, even when autonomic challenge tests carry the same name, the protocol followed can be quite different. A further probable source of inconsistency in the results is the lack of standardization in the physical and psychological testing environment. It is evident that these differences in protocol could at least be partly responsible for the differences in results between various studies.

It has to be emphasized that standardization is crucial and of utmost interest, since several parameters for quantifying the ANS are very sensitive. This is supported by a study by Linden (1991), in which subtle changes in the arithmetic stress test protocols were investigated. The author concluded that certain aspects of the laboratory testing, such as vocal delivery of the results versus written delivery, could significantly influence the magnitude of the autonomic responses (De Weerth and Buitelaar, 2005; Linden, 1991). Next, women should be allowed to adjust to the test environment before taking any measurements, a precaution that has not been taken in many studies. The rest period before beginning the measurements should be sufficiently long so as to ensure that the patient is accustomed to the testing environment and is relaxed. It has been recommended that the patient be allowed to relax in a comfortable position for about 30 min before starting the measurements (De Weerth and Buitelaar, 2005). In addition, the very first time a measurement is made, the patient will find the procedure unfamiliar, and in longitudinal studies, the second and later measurements may reveal more stable results, as the patient becomes accustomed to the laboratory environment. For this reason, it may be helpful to perform one "pretest" to help the patient become familiar with the test before starting longitudinal measurements. The time of day that the autonomic tests take place should also be standardized, in order to account for the circadian neurohormonal rhythm and the natural circadian variations in the physiological variables being measured.

Another reason for the large inter-individual variability may be inherent in the non-invasive test methods themselves. Although the physiological reactions to stressors are apparently attenuated in pregnancy, most studies report large standard deviations in their reactivity data, indicating that individuals vary greatly in the magnitude of their

reactions (De Weerth and Buitelaar, 2005). This implies that in cross-sectional studies, the variation within subgroups may be so large that differences between the groups may not be detected, thereby limiting the clinical use of these tests in discriminating normal from pathological pregnancies. By contrast, as a research tool, various stress tests can help distinguish between groups of women with different patterns of stress reactivity during pregnancy, thereby providing more information on how these patterns can affect pregnancy outcome.

The similar test results between healthy and preeclamptic pregnant women (Rang et al., 2002) may, in part, be explained by the different study designs, but may also presume an intact reflex response and a sound efferent pathway. The non-invasive test methods that have been evaluated may seem to be directed purely at efferent pathways, but they involve reflex arcs and hence central and afferent connections are also involved (Ekholm and Erkkola, 1996; Rang et al., 2002). Afferent sensitivity could be changed due to resetting of the baroreceptor sensitivity. A decreased BRS in preeclamptic women relative to healthy pregnant women has been reported by Molino et al. (1999) and Silver et al. (2001). As in other hypertensive conditions, the baroreflex seems to be reset toward the elevated BP, implying that this mechanism acts to maintain BP, rather than opposing the BP elevation (Rang et al., 2002). The increased resting sympathetic activity demonstrated by microneurography in preeclampsia might be caused by a compromised central control or a change in afferent sensitivity.

Finally, the results of autonomic cardiovascular control in pregnancy, based on studies by Voss et al., support the conclusion that due to the complexity of cardiovascular control, an optimal analysis needs to involve a combination of linear and non-linear, as well as univariate and multivariate, approaches (Voss et al., 1996, 1998).

8.8 Future Research

Although, as of now, the clinical use of HRV and BPV analysis in obstetrics seems to be of limited use, it is clear that analysis of ANS activity with continuous non-invasive devices represents a useful research tool in the study of the role of the ANS in maternal adaptation to pregnancy. This applies to studies investigating the normal physiological adaptation to pregnancy as well as to complications during pregnancy. Moreover, the feasibility of predicting clinical outcomes in pregnancy using HRV warrants further investigation. It would be extremely useful, if it were possible, to discriminate as early as in the first trimester women at risk for pregnancy complications, in order to facilitate a timely prophylactic intervention. In addition, effects of cardiovascular active drugs, such as antihypertensive, tocolytic or uterotonic medications, may be monitored by means of non-invasive measurements of the cardiovascular response.

HRV and BPV are significantly influenced by breathing (Bernardi et al., 2001), an effect that, with the exception of the standardized conditions, cannot be controlled during daytime.

For further research, it is of utmost importance to have a proper study design with regard to patient numbers and groups, definitions of disorders, longitudinal monitoring and, most of all, a well-defined standardization of the test environment and of the tests themselves.

8.9 Conclusion

During pregnancy, HRV is reduced mainly due to a decrease in vagal autonomic modulation. A proper ANS function is essential for the CVS to adapt to the maternal hemodynamic changes that occur in pregnancy. As gestational age advances, aortocaval compression becomes more frequent. ANS activity is altered in late gestation by maternal position, with the supine position causing the most marked changes. Poor adaptation of maternal hemodynamics can affect uteroplacental circulation and the subsequent course of pregnancy and fetal development. Women with reduced uterine perfusion were found to have a reduced HRV with subsequent pregnancy complications, such as hypertensive disorders or IUGR. In hypertensive disorders, especially preeclampsia, the changes in HRV and BPV are more pronounced compared to normal pregnancy, meaning that vagal modulation is further reduced. The results of cardiovascular stress tests in pregnancy are inconclusive mainly due to the inconsistency in results between studies. In women who subsequently develop pregnancy-related complications, alterations of the ANS response have been observed as early as the first trimester, suggesting a possible tool for early prediction of such complications.

Abbreviations

ANP	Atrial natriuretic peptide
ANS	Autonomic nervous system
BNP	Brain natriuretic peptide
BP	Blood pressure
BPV	Blood pressure variability
BRS	Baroreflex sensitivity
BV	Blood volume
CO	Cardiac output
CVS	Cardiovascular system
HF	High frequency
HR	Heart rate
HRV	Heart rate variability
HUT	Head-up tilt
IUGR	Intrauterine growth restriction
LF	Low frequency
PIH	Pregnancy-induced hypertension
PISO	Pregnancy-induced sympathetic overactivity
RAAS	Renin-angiotensin-aldosterone
SV	Stroke volume
SVR	Systemic vascular resistance
VLF	Very low frequency

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10

Heart Rate Variability and Sleep

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10.1 Introduction

The simple observation that humans and many animals spend about one-third or more of their lifetime sleeping (Chou et al., 2003; Saper et al., 2005a) speaks directly and strongly about the importance of this physiological process.

Although an extensive literature has been published on the possible biological meanings and functions of this fundamental process, there are still many unanswered questions. Indeed, the observation that chronic sleep deprivation in laboratory animals is capable of inducing death highlights the fact that sleep is essential for life and that alterations of one or more of the mechanisms regulating the sleep–wake cycle could lead to an increased morbidity and mortality both in animals and in humans.

The sleep onset, wake–sleep cycles, transitions between different sleep stages and circadian rhythms are complex physiological processes that involve several neural structures, from the cortex to the forebrain and the medulla through the hypothalamic and thalamic relay neurons. These neural structures interact to regulate the physiological sleep process according to a range of hormonal, local and external factors, such as melatonin and orexin, adenosine accumulation and light–dark cycles (Saper et al., 2005b). These neural mechanisms affect and are affected by the autonomic nervous system (ANS), which represents the primary interface between sleep and homeostatic cardiovascular circulatory control.

10.1.1 Normal Sleep: Macrostructure and Microstructure

After the discovery of rapid eye movement (REM) sleep in the 1950s, it became clear that sleep is characterized by two discrete physiological states, non-rapid eye movement (NREM) sleep and REM sleep. NREM sleep can be divided into two physiological states, light sleep (Stages 1 and 2, N1 and N2) and deep sleep (Stage 3, N3). Deep sleep is more commonly called slow-wave sleep (SWS). These stages are characterized and defined by specific features of the electroencephalogram (EEG) that records the cortical activity of the brain and other characteristics including eye movements and muscle tone.

During quiet wakefulness, with eyes closed, the EEG activity is characterized by the presence of high-frequency, low-voltage waves called α -rhythm, with a frequency band between 8 and 12 Hz. With the onset of sleep, the cortical rhythm slows and is characterized by the presence of a θ -rhythm (3.5–7.5 Hz) alongside the α -rhythm, which then disappears as sleep becomes deeper. Stage 2 is associated with a complete loss of the α -rhythm and the emergence of the θ -rhythm. This stage is also characterized by the presence of two peculiar EEG features, K complexes and spindles. K complexes are waveforms with a first negative high-voltage peak followed by a slower positive complex and a final negative peak. The rate of their occurrence is approximately every 1–2 min. The other typical waveform is the spindle, originating in a burst of brain activity and characterized by a high-frequency waveform (12–14 Hz) lasting more than 0.5 s. The further transition to SWS is associated with the emergence of high-voltage, low-frequency waves called δ -waves, with a voltage greater than 75 μ V and a frequency between 0.5 and 3 Hz. This stage represents the period of highest synchronization of neural activity in the brain and is accompanied by low muscle activity and almost absent REMs. REM sleep, however, is characterized by low-voltage, high-frequency and desynchronized activity, accompanied by complete muscle atonia and REMs.

In the last few years, it has been observed that NREM is not a homogeneous state but is characterized by the presence of spontaneous and physiological fluctuations in the EEG, known as cycling alternating patterns (CAP). In 1985, Terzano et al. (1985) described for the first time the presence of a continuing periodic activity characterized by specific EEG patterns with a periodicity of 20–40 s. Specifically, this activity is formed by the repetitive oscillatory elements (Phase A) and intervals that interrupt these repetitive elements (Phase B), named cycling alternating patterns. This phenomenon represents a periodic sequence of spontaneous phasic events that occur within NREM sleep as a prolonged oscillation of the arousal level and that are, therefore, expressions of the arousal system.

10.1.2 Wakefulness–Sleep Transitions

Sleep onset is a relatively rapid process, if we consider that it lasts no more than 1 min in humans (Takahashi et al., 2010).

The physiological transitions among sleep stages are not unidirectional, from wake through light and deep sleep to REM sleep, but instead vacillate between different sleep stages (e.g., from NREM to REM and vice versa) with rapid changes in the EEG wave characteristics, sometimes interrupted by sporadic arousals (Saper et al., 2010). Thus, transitions may occur, for instance, from N2 to N3 or from N2 to REM directly.

These transitions from wake to sleep and across the sleep stages are regulated by a complex network of neurons in the medulla and in the cortex. For example, one of the mechanisms that is considered essential in the wake–sleep transition is the reciprocal interaction between monoaminergic neurons and hypothalamic neurons (Saper et al., 2010).

These monoaminergic neurons are located in the pons with projections to the locus coeruleus (noradrenergic nucleus) and to the serotonergic and dopaminergic neurons in the raphe. During wake period, the activity of these monoaminergic nuclei inhibits neurons that are located in the ventrolateral preoptic nucleus (VLPO), and also those that are responsible for the transition to REM, thus limiting any direct shift from wake to REM sleep. Vice versa, during sleep, the VLPO neurons increase their firing activity, inducing an inhibitory effect on the monoaminergic neurons, thus decreasing inhibitory effects of the latter and triggering sleep onset. This mechanism, the so-called “flip-flop switch model” (Saper et al., 2010), is essential for the wake–sleep transition and is capable of producing rapid state shifts.

10.1.3 Circadian Rhythms in Sleep Regulation

Although circadian rhythms play a key role in mechanisms regulating the wake–sleep transition, a precise description and an understanding of all control systems that are involved in sleep onset and sleep duration are still lacking. Sleep homeostasis, or “sleep pressure,” probably derives from the interaction of several control mechanisms, such as genes, hormonal and metabolic factors and neuronal pathways. There is growing interest, in particular, in the genetic and molecular mechanisms that are responsible for the circadian rhythm. In fact, several genes, the so-called “clock genes,” such as the period genes (Per1, 2 and 3) and the cryptochrome genes (Cry1, 2) that are activated by two proteins CLOCK and BMAL1, play a key role in circadian rhythms, along with other genes that have been discovered more recently (Lamont et al., 2007; Travnickova-Bendova et al., 2002; Franken and Dijk, 2009). Interestingly, PER3 polymorphisms have recently been associated with different sleep phenotypes and also neurovegetative profiles (Viola et al., 2008).

10.2 Heart Rate Variability and Sleep

10.2.1 Heart Rate Variability as a Window over Autonomic Cardiovascular Control

The analysis of heart rate variability (HRV) can be performed in time and frequency domains. A detailed description of these techniques is given elsewhere in this book. Application of a spectral analysis of the HRV and the blood pressure variability (BPV) in healthy subjects and in several cardiovascular and non-cardiovascular diseases has been a non-invasive tool for the evaluation of the alterations of the autonomic cardiovascular control in health and diseases, the reliability of which is directly dependent on the rigor of the experimental models and the analytic techniques used (Malliani et al., 1991; Task Force, 1996; Montano et al., 2009).

10.2.2 Normal Sleep

Sleep and the ANS interact at multiple levels. Specifically, different sleep stages are characterized by important modifications in autonomic cardiovascular regulation. Conversely, changes in the sympathovagal balance can alter the physiological sleep process.

Intense physical exercise or intense mental or emotional stress characterized by an increased sympathetic activity can lead to difficulty in falling asleep or arousals during

sleep if it occurs just before sleep. For example, Hall et al. (2004) reported that an acute psychophysiological stress before sleep reduced the parasympathetic modulation during NREM and REM sleep and increased the LF/HF ratio, an index of the sympathovagal balance.

There has been increasing interest in the assessment of the autonomic cardiovascular control during physiological sleep. Different sleep stages are associated with the changes in heart rate (HR), blood pressure (BP) and muscle sympathetic nerve activity (MSNA) (Somers et al., 1993). Progressive decreases of HR, BP and MSNA were observed during NREM sleep, with a greater decrease observed in SWS. On the contrary, the transition to REM was characterized by a noticeable increase in the MSNA, at levels similar to, or even higher than, those observed during wakefulness. These measures, together with an assessment of HRV, BPV and baroreflex sensitivity (BRS), provide important information regarding autonomic control during sleep.

The classical studies on the HRV during sleep reveal that light sleep, SWS and REM are associated with different profiles of the autonomic cardiovascular regulation. The transition from NREM to REM is accompanied by a rapid increase in HR, while in the frequency domain the overall HRV progressively decreases in NREM sleep and increases during REM, with an increasing trend across the next REM stages (Cajochen et al., 1994). The transition from wake to SWS is characterized by a progressive increase in the parasympathetic modulation and a parallel decrease in the sympathetic modulation. However, the abrupt shift toward REM sleep is characterized by a change in the sympathovagal balance, with a sympathetic predominance and a vagal withdrawal (Baharav et al., 1995; Busek et al., 2005; Crasset et al., 2001; Trinder et al., 2001; Elsenbruch et al., 1999; Versace et al., 2003; Berlad et al., 1993; Vaughn et al., 1995).

Spectral analysis of HRV in normal subjects during sleep revealed an increase in the high-frequency (HF) component, a marker of vagal modulation, during NREM, compared to wake and REM sleep, while this oscillation is markedly reduced during REM (Busek et al., 2005). By contrast, the low-frequency (LF) component, a marker of sympathetic modulation, progressively decreases with the deepening of sleep from wake to SWS, while the transition to REM sleep is associated with an abrupt increase in the sympathetic modulation to levels similar to that seen during wakefulness. The LF/HF ratio, a marker of sympathovagal balance, progressively decreases during SWS and rapidly increases during REM to wakefulness levels, suggesting a vagal predominance during SWS and a sympathetic predominance during REM. It is worth noting that changes in the autonomic cardiovascular variability observed during REM sleep (namely, the increase in sympathetic modulation) begin in NREM sleep, minutes before the beginning of REM sleep and usually persist beyond the end of the REM period (Bonnet and Arand, 1997).

Interestingly, it has been observed that the LF/HF ratio is much higher during N2 preceding REM sleep, than it is during N2 preceding N3, thus suggesting that autonomic control undergoes a specific and variable regulation throughout the entire duration of the sleep cycle (Busek et al., 2005). These HRV and BP changes seem to occur abruptly at sleep onset, but then a relatively constant trend of autonomic fluctuations over time is usually maintained (Trinder et al., 2001). In addition, a study evaluating the differences between the genders showed that males had a higher increase in the LF/HF ratio during REM compared to females, thus suggesting that factors such as hormones and metabolic influences may contribute to the oscillatory adjustments of the autonomic profile across various sleep stages.

Not only is REM sleep associated with a marked sympathetic predominance, but when considering different sleep stages throughout the entire sleep cycle, later periods of REM sleep also seem to be characterized by a higher sympathetic predominance when

compared to other REM stages of the same sleep cycle, thus suggesting a possible relationship between this enhanced sympathetic drive in REM at the end of sleep and the increased incidence of cardiovascular events occurring in the early morning (Scholz et al., 1997; Muller et al., 1995; Murali et al., 2003; Verrier and Josephson, 2009). While studying the sleep-to-wake transition, it has also been demonstrated that wake periods are different in terms of the autonomic control, depending on the sleep stage that preceded the wakefulness. In fact, HR and BP are higher when waking from N2 than from REM sleep (Goff et al., 2010).

As for the assessment of BRS, REM seems to be characterized by a higher BRS than nocturnal wakefulness (Monti et al., 2002). Similar to measures of HRV, BRS also changes across the sleep cycle. The first sleep cycle is characterized by an increased BRS during NREM compared to wakefulness and REM. However, in the last sleep cycle before waking, BRS is increased during REM compared to wake and SWS. These results suggest that baroreflex control is more efficient in blunting REM sympathetic surges, especially during the late sleep cycles (Legramante et al., 2003).

In addition to the assessment of the HRV during sleep, there has been interest in the relationship between the HRV changes and the sleep microstructure. The sleep microstructure is characterized by the CAP, a nocturnal arousal rhythm that occurs during NREM. An evaluation of the autonomic cardiac modulation during CAP in N2 and N3 revealed that during these periods, autonomic control shifted toward a sympathetic predominance, as suggested by an increase in the LF component and LF/HF ratio and a decrease in HF oscillation (Ferri et al., 2000). Similarly, a significant increase occurs in the LF component of BPV, an index of vascular sympathetic modulation, during CAP compared to non-CAP periods, while BRS during the CAP was as high as during REM sleep, suggesting that CAP, like REM, can be considered a phase characterized by sympathetic activation (Iellamo et al., 2004).

An important physiological condition associated with sleep and autonomic changes is aging. In fact, we know that the aging process is associated with a reduction in the overall cardiovascular variability (Kuo et al., 1999; Bonnemeier et al., 2003) and that sleep architecture undergoes important changes throughout life, such as reduced total sleep time, decreased sleep quality and alteration of the normal respiratory pattern, with an increased prevalence of periodic breathing (Brandenberger et al., 2003).

An analysis of HRV in older subjects revealed that the overall variability was significantly reduced in older subjects in all sleep stages and that aging caused an attenuation of autonomic cardiovascular modulation across different sleep stages, with a predominant loss of parasympathetic modulation occurring during SWS (Crasset et al., 2001; Brandenberger et al., 2003).

10.2.3 Sleep-Disordered Breathing: Obstructive Sleep Apnea

Sleep-disordered breathing (SDB) refers to a group of diseases characterized by alterations of breathing control mechanisms and breathing patterns during sleep. Four main diseases can be clearly identified: (1) snoring, (2) upper airway resistance syndrome (UARS), (3) central sleep apnea syndrome (CSA) and (4) obstructive sleep apnea syndrome (OSA), where apnea is a transient cessation of breathing. There can be considerable overlap and transition between these conditions within the same subject. A description of the first two entities is outside the scope of this chapter. However, a brief description of mechanisms underlying the apnea syndromes will be useful in understanding their cardiovascular consequences.

The CSA is characterized by apneic episodes secondary to the transient cessation of central neural command to the respiratory muscles. This condition is associated with several neurological diseases and is also often seen in congestive heart failure patients, in whom it is a strong and independent predictor of mortality (Lanfranchi et al., 1999). OSA is characterized by the occurrence of repetitive episodes of apnea during sleep due to the partial or complete collapse of the upper airway during inspiration. Obstructive apneas are associated with movements of the thorax and abdomen, which attempt to overcome the resistance created by the collapse of the upper airway, and are followed by a fall in oxygen saturation and arousals from sleep. These recurrent apneic episodes lead to two main consequences: first, alteration of gas exchange with consequent hypoxemia, hypercapnia, arousals and sleep fragmentation during the night, and second, sleep deprivation that causes excessive sleepiness, irritability and reduced cognitive performance during the day.

The prevalence of OSA is estimated at approximately 2%–4% in the middle-aged population, although it often remains undiagnosed. The severity of the disease is evaluated by the presence of apneas (defined as a cessation of the airflow lasting 10 or more seconds) and hypopneas (a reduction of the airflow greater than 50% lasting 10 s with an oxygen desaturation of more than 4% from baseline). The apnea/hypopnea index (AHI) is defined as the number of apneas and hypopneas per hour of sleep: AHI 5–15 identifies mild OSA, AHI 15–30 is moderate OSA and AHI >30 is severe OSA.

OSA is associated with increased cardiovascular morbidity such as hypertension, ischemic heart disease, congestive heart failure, cardiac arrhythmias, cerebrovascular disease and cardiovascular mortality (Kales et al., 1984; Hung et al., 1990; Dyken et al., 1996; Blwise et al., 1988; McNicholas et al., 2007; Parish and Somers, 2004; Somers et al., 2008). It has been hypothesized that ANS (sympathetic activation) plays an important role in linking OSA to cardiovascular morbidity and mortality (Somers et al., 1995; Narkiewicz and Somers, 2001).

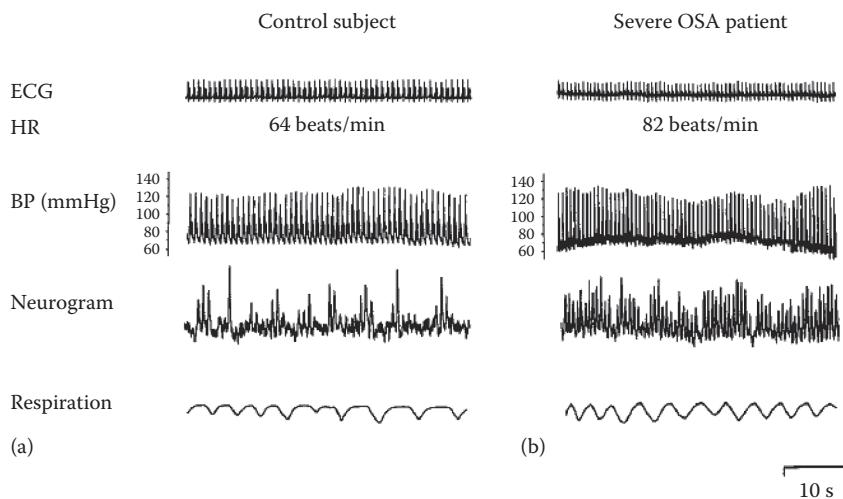
Other pathways have also been reported to be altered in OSA, such as an increase in the prothrombotic and proinflammatory factors, endothelial dysfunction, an increased activity and aggregation of platelets, leukocyte adhesion and accumulation on endothelial cells (Dyugovskaya et al., 2002; Parish and Somers, 2004; Narkiewicz and Somers, 2003). These mechanisms may also predispose OSA patients to increased cardiovascular risk.

10.2.4 Autonomic Control in OSA

Chronic intermittent hypoxemia following repetitive apneic episodes and cyclic disruption of the sleep architecture caused by the arousals induce a complex series of both acute and chronic changes (see Figure 10.1).

Changes in HR and BP are acute changes and those have been described in the literature (Vanninen et al., 1996; Smith et al., 1998). The chronic consequences primarily involve the baroreflex and chemoreflex control mechanisms, with a higher sympathetic modulation and a blunted parasympathetic control of HRV (Smith et al., 1998). It has been suggested that the two main determinants of the HRV changes in OSA are (1) an alteration of central cardiac-respiratory coupling, which is significantly impaired in OSA; and (2) an attenuation of the BRS, compared to normal subjects (Jo et al., 2005).

The hemodynamic alterations in OSA patients during the apneic episodes are a strong indicator of the cardiovascular “storm” that is associated with each apneic event. Physiologically, lung inflation inhibits the sympathetic activity. However, during apnea,

**FIGURE 10.1**

The HR, blood pressure, MSNA and respiration in a control subject (a) and a patient affected by severe OSA (b). The OSA patient shows a higher HR, blood pressure variability and MSNA. (From Narkiewicz, K., Montano, N., Cogliati, C., van de Borne, P.J., Dyken, M.E. and Somers, V.K., *Circulation*, 98, 1071–1077, 1998. With permission.)

this reflex-mediated sympathoinhibitory mechanism is lacking, thereby leading to a marked sympathetic activation resulting in acute cardiovascular effects, such as a marked elevation in the BP and bradycardic/tachycardic events (Somers et al., 1991, 2008).

The apneic events are also associated with an increased sympathetic modulation, as demonstrated by the increase in LF/HF ratio (Vanninen et al., 1996). This sympathetic overdrive is highest when hypoxemia and hypercapnia reach maximal levels at the end of an apnea. The subsequent airway reopening is associated with a large increase in the BP, primarily due to the synergistic effect of the peripheral vasoconstriction, increased venous return and thus cardiac output. The arterial pressure rise activates the baroreflex control mechanisms, thereby inducing a temporary shutdown of the sympathetic overactivity (Narkiewicz and Somers, 2001). This apnea–breathing cycle and the hemodynamic and autonomic alterations can occur hundreds of times through the night. Moreover, hypoxemia induces chronic intermittent activation of chemoreceptors and this can lead to coactivation of both the sympathetic and the vagal autonomic branches, resulting in profound changes in HR. This vagally mediated bradycardia during apnea needs to be taken into consideration during frequency domain analysis and interpretation of the HRV during apneas.

In summary, the repetitive apneic episodes that induce hypoxemia, hypercapnia and alterations of neural circulatory activation are responsible for an enhanced sympathetic drive during sleep cycles.

However, increased cardiovascular risk may also be related to the possibility that OSA subjects have a sympathetic overdrive even during normoxic wakefulness, when the typical breathing pattern and the altered blood gas exchange observed during sleep cannot be acutely responsible for the hemodynamic and autonomic alterations. In fact, several studies report that OSA patients have a higher sympathetic activity even during the wake period compared to controls (Somers et al., 1995). This increase may be unrelated to BP values, as they are similar in normotensive and hypertensive subjects (Carlson et al., 1993).

Once alterations of autonomic control have been clearly established, an assessment of HRV and BPV in OSA patients helps provide further information regarding neural control mechanisms that are altered in OSA and the possibility that particular autonomic components may serve as indices of OSA severity and as possible markers for risk stratification in these patients.

Narkiewicz et al. (1998), in a study of OSA patients without any overt cardiovascular disease, reported that during daytime in supine resting conditions, patients with moderate-to-severe OSA had higher HR and MSNA, as well as an increased BPV, in comparison to subjects with mild OSA and controls, all of whom had a BP similar to that of severe OSA patients (see Figure 10.2). As for HRV measures, total power and HF component, expressed in normalized units (nu), were decreased, while a clear predominant sympathetic control was observed, as indicated by a greater LF (nu) oscillation and a greater LF/HF ratio. Interestingly, while HR was similar to that of controls in the mild OSA group, overall variance was significantly lower and similar to that of moderate-to-severe OSA group, suggesting that a change in overall variability preceded changes in HR, as observed in several other disease, such as diabetes (Pagani et al., 1988) and hypertension (Lucini et al., 2002). These autonomic alterations have been observed during both

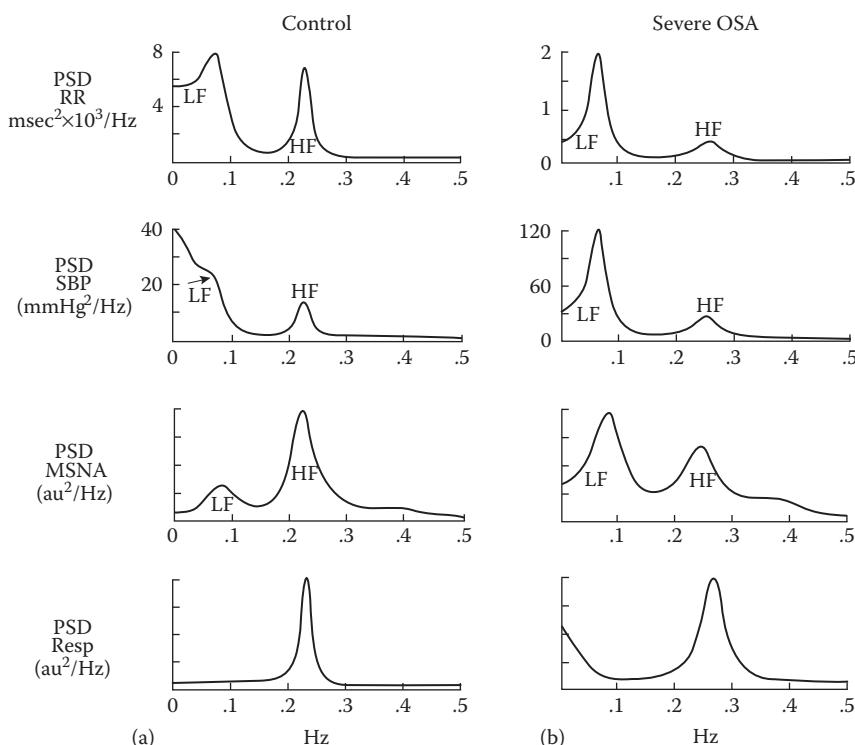


FIGURE 10.2

The power spectrum of the HR, systolic arterial pressure, MSNA and respiration in a normal subject (a) and a subject with severe OSA (b). The OSA patient shows a decreased HR variability, with an increased blood pressure variability. The LF component is predominant in the HR, blood pressure and MSNA in the OSA patient. PSD: power spectral density; au, arbitrary units. (From Narkiewicz, K., Montano, N., Cogliati, C., van de Borne, P.J., Dyken, M.E. and Somers, V.K., *Circulation*, 98, 1071–1077, 1998. With permission.)

wake (Khoo et al., 1999; Narkiewicz et al., 1998) and sleep (Shiomi et al., 1996; Vanninen et al., 1996).

An autonomic profile characterized by sympathetic predominance was suggested by other studies comparing OSA with control subjects, demonstrating an increase in the LF, LF/HF ratio, HR and BPV, with a reduction in total HRV (Vanninen et al., 1996; Kesek et al., 2009; Parish and Somers, 2004; Narkiewicz and Somers, 2003; Smietanowski et al., 2006). These alterations have also been confirmed when evaluating the dynamic changes in the cardiac autonomic control during controlled breathing, a maneuver inducing an increased parasympathetic modulation, and during passive head-up tilt test, a provocative test leading to sympathetic activation. In fact, compared to controls, OSA patients showed a reduced vagal modulation at rest, during controlled breathing and after head-up tilt (Wiklund et al., 2000) and a significant reduction in the HR recovery at 1 min after exercise, a measure considered to be a marker of vagal modulation (Maeder et al., 2008). An assessment of BRS to evaluate the dynamic responses of HR and BP revealed that severe OSA is characterized by a lower BRS compared to moderate OSA and control subjects and that this reduction seems to be more evident during SWS and nocturnal wakefulness (Parati et al., 1997; Ryan et al., 2007).

Thus, the assessment of autonomic cardiovascular alterations in OSA patients during wakefulness not only provides information on the mechanisms underlying the cardiovascular alterations of this disease, but may also contribute to the identification of markers that correlate with the severity of the disease.

As to the assessment of HRV during sleep, several studies have performed this analysis. However, the results are often questionable, as some have conducted HRV analysis on the overall polysomnographic recording, notwithstanding the presence of the apneic events that, of course, can introduce a "rhythmic" biological noise, impinging on HRV.

It was reported that the HR and LF/HF ratio better correlate with the degree of the AHI in OSA (Park et al., 2008; Kesek et al., 2009) and that higher levels of the AHI are associated with an increased parasympathetic control during NREM sleep (da Silva et al., 2009) and with a more evident cardiopulmonary coupling at the LF oscillation frequency (Thomas et al., 2005). However, contrary to expectations, although moderate OSA was characterized by clear sympathetic overactivity, severe OSA was associated with a lower sympathetic modulation, as indicated by the reduction of LF/HF ratio, as well as the reduced ability of this index of sympathovagal balance, to increase during REM (Kesek et al., 2009; Gula et al., 2003). Khoo and co-workers suggested an explanation for the finding that severe OSA may be paradoxically associated with a reduction in HRV parameters, especially the sympathetic modulation. They hypothesized that the huge alteration in the breathing pattern caused by repetitive apneic episodes could per se be an important confounding factor when analyzing HRV. In OSA patients, they corrected the HRV measures for the presence of breathing patterns and the number of apneas and they calculated that the HRV corrected for respiratory patterns was higher than the non-corrected HRV measures in OSA patients (Khoo et al., 1999); in addition, the corrected LF and HF components and the LF/HF ratio correlated with the severity of the disease. These results suggest that spectral analysis performed during sleep in patients with severe OSA is affected by the non-neural oscillations due to the periodic repetition of apneic episodes, thereby confounding the HRV parameters (Wang et al., 2008).

Recently, interesting results have been obtained by an analysis of the QT interval variability (QTV). QTV is a measure of the variability of cardiac repolarization duration and has been shown to be a strong predictor of risk for sudden cardiac death in patients with mild ventricular dysfunction (Piccirillo et al., 2007). OSA patients exhibit important

modifications of the QTV during sleep, independently of sleep stages, and this measure has been reported to be correlated with the severity of the disease (Baumert et al., 2008), thereby supporting the hypothesis that OSA is associated with an increased arrhythmic substrate during sleep, possibly predisposing these patients to sudden death during sleep (Gami et al., 2005). The HR turbulence, one of the newer HRV measures, was used to probe the possible cause of sudden cardiac death that occurs during sleep (Gami et al., 2005) in a population of patients with coronary artery disease and no suspected sleep disorders. More than 40% of the patients were found to have an AHI >15, indicating the high incidence of OSA in patients with coronary artery disease. The patients with an AHI >15 were found to have a greater number of ventricular premature contractions (a ventricular arrhythmia that can trigger fatal arrhythmias, leading to sudden cardiac death) during REM sleep than during the waking state. The oxygen desaturation duration was longer during REM than during NREM sleep over all patients, and HR turbulence values were correlated with oxygen desaturation duration/apnea event, in that their values were more abnormal (indicating a higher sympathetic activity or a reduced parasympathetic activity) in patients whose oxygen desaturation duration/apnea event was longer (Watanabe et al., 2008).

Finally, it is worth noting that snoring and OSA represent important health problems even during childhood, since snoring may affect 10% of children. A HRV analysis revealed that children diagnosed with OSA have an impaired autonomic modulation with a sympathetic overdrive and a lower parasympathetic modulation (Liao et al., 2010a). In addition, the transition from SWS to REM seems to be related to a more pronounced reduction of parasympathetic modulation, as indicated by the HF component, while REM sleep is characterized by a weaker parasympathetic modulation, compared to normal children (Liao et al., 2010b). Also, a baroreflex analysis revealed that the BRS is decreased during nighttime, associated with an increase in BPV (McConnell et al., 2009) compared to healthy subjects.

10.2.5 Effects of CPAP Therapy on Autonomic Control in OSA Patients

Continuous positive airway pressure (CPAP), when tolerated, is the most effective therapy for OSA patients, and it significantly reduces the recurring apneic episodes by preventing the upper airways inspiratory collapse. CPAP is associated, in a short term, with a significant reduction in the hypoxicemic-hypercapnic stress, sleep fragmentation and arousals; it is also responsible for an improvement of daytime symptoms due to arousals, such as excessive sleepiness, irritability and mood alterations and perhaps also in cardiovascular morbidity and mortality (Marin et al., 2005).

CPAP acutely affects ANS control, lowering MSNA during sleep (Somers et al., 1995), and it also reduces daytime urinary norepinephrine levels (Minemura et al., 1998) and MSNA (Narkiewicz et al., 1999).

CPAP also influences the autonomic cardiovascular variability, reducing such variability during sleep and improving the BRS, even after one night of treatment (Bonsignore et al., 2006). In addition, it has been suggested that CPAP may normalize the enhanced chemoreflex response to hypoxia, thereby leading to a reduced sympathetic response to this stimulus in OSA patients treated with CPAP therapy (Imadogemu et al., 2007).

On a longer time scale, after 1–3 months, CPAP therapy improved arterial stiffness, as indicated by the brachial–ankle pulse wave velocity, independently of BP and endothelium status (Shiina et al., 2010). CPAP also reduced insulin resistance and total cholesterol. It decreased inflammation by lowering the TNF- α (Dorkova et al., 2008) and the soluble

tumor necrosis factor- α receptor 1 (Arias et al., 2008). It also partially decreased platelet aggregation (Shimizu et al., 2002).

In addition, chronic treatment with CPAP may significantly improve the autonomic deregulation that characterizes OSA patients: a HRV analysis during CPAP revealed that during sleep, CPAP reduced the sympathetic cardiovascular modulation, as indicated by a decrease in the LF component and the LF/HF ratio (Roche et al., 1999) and an improved vagal modulation in awake patients both in the supine and standing positions (Khoo et al., 2001). This sympathoinhibitory effect may conceivably be due to the normalization of the chemoreceptor response, as well as to an improved BRS (Ryan et al., 2007).

An alternative to the CPAP treatment is the autoadjusted continuous positive airway pressure (AutoCPAP or APAP), where the pressure provided by the machine is not continuous, but is supplied when a sensor deduces a change in the pressure in the airway due to its collapse. APAP is increasingly prescribed for OSA due to the reported increase in patient compliance and possible reduction in the costs due to elimination of the titration procedure. However, between the two treatments, although both significantly reduced apneas and daytime sleepiness, only the CPAP, not the APAP, was able to reduce arterial BP and the homeostatic model assessment index (Patruno et al., 2007). Interestingly, the comparison between APAP and CPAP for evaluating whether these two therapies could similarly affect autonomic cardiovascular modulation revealed that the HRV measures, such as LF and HF oscillations and the LF/HF ratios, were significantly improved by the CPAP therapy, while the APAP seemed not to affect them (Bianchi et al., 2005; Karasulu et al., 2010).

10.3 Summary and Conclusion

Sleep control mechanisms are important in both health and disease. An assessment of autonomic cardiovascular control during wakefulness and sleep, using linear and non-linear methods, could provide useful tools for the evaluation of the neuroregulatory control during different sleep stages in physiological and pathological conditions. In doing this, it is important that a careful and rigorous experimental approach is taken, to avoid confounding of analysis and interpretation by other factors, such as irregular respiratory patterns.

As evident in OSA, alterations of autonomic cardiovascular control, with sympathetic overdrive both during daytime and nighttime, enhanced cardiac vagal modulation during apneas and blunted BRS, may play key roles as possible links to cardiovascular morbidity and mortality. Whether altered autonomic control, in turn, potentiates sleep disorders needs further investigation.

Abbreviations

AHI	Apnea/hypopnea index
ANS	Autonomic nervous system
BRS	Baroreflex sensitivity
CAP	Cycling alternating patterns

CPAP	Continuous positive airway pressure
CSA	Central sleep apnea syndrome
EEG	Electroencephalogram
HRV	Heart rate variability
MSNA	Muscle sympathetic nerve activity
NREM	Non-rapid eye movement
OSA	Obstructive sleep apnea syndrome
REM	Rapid eye movement
SDB	Sleep-disordered breathing
SWS	Slow-wave sleep
VLPO	Ventrolateral preoptic nucleus

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Section III

Clinical Applications of Heart Rate Variability—Acute Care

11

Heart Rate Variability in the Intensive Care Unit

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11.1 Introduction

Patients with critical illnesses are managed in intensive care units (ICUs), which are specialized hospital areas that provide advanced life support (i.e., ventilatory support, hemodynamic support and kidney support). These patients are by definition, unstable and their clinical conditions can change rapidly and, at times, unpredictably. The response to treatment is also very complex due to the speed of physiological change and interactions between multiple treatments and pathological processes. The management of patients in the ICU does not follow strictly defined rules, as the physician has to make decisions on incomplete information.

In order to follow the effects of pathological processes and clinical interventions, patients admitted to the ICU are monitored by a team of health-care personnel. Physiological variables are recorded continuously, including hemodynamic (heart rate [HR], blood pressure and central venous pressure), respiratory (rate, arterial oxygen saturation and end-tidal CO₂) and renal (urine output) parameters. However, primary clinical decisions are often based on a few point estimates of these parameters, a situation that is changing due to the rapid development of computer-based automation. Considerably more information can be extracted from these continuously recorded physiological variables, many of which are regulated by the autonomic nervous system (ANS). The heart rate variability (HRV) has been used as a convenient measure for assessing the balance between sympathetic and parasympathetic activities within the ANS. It is very common to see

autonomic dysfunction in ICU patients with a severe brain injury, systemic infection, organ failure, neurological illness (e.g., Guillain–Barré syndrome), cardiovascular disease (e.g., myocardial infarction) and more. Research indicates that HRV can be used as a biomarker to assist a physician in the ICU in making clinical decisions. In this chapter, we will review the research on HRV, which is used as a major source of diagnostic and prognostic information in ICU patients with major trauma, severe infection and multiple organ dysfunction syndrome (MODS), as well as to assist with the process of weaning from mechanical ventilation.

11.2 Major Trauma

Trauma or injury results in debilitating health or death and constitutes an economic burden on society (Riordan et al., 2009). Trauma is the sixth leading cause of death worldwide and has a severe effect on socioeconomic infrastructure. Effective management of critically injured patients in both military and civilian settings is essential to reduce mortality and morbidity. Appropriate timing and correct treatment of trauma patients early during their pre-hospitalization or hospitalization can contribute to short-term as well as long-term positive outcomes (Brattstrom et al., 2010). For severely injured patients in the ICU, sepsis, septic shock, multiple organ failure and acute lung injury (ALI) are some of the most common causes of morbidity and mortality during the next phase of treatment (Ciesla et al., 2006; Dewar et al., 2011). An increased and continuous knowledge about severely injured patients would also increase their chances of survival (Brattstrom et al., 2010; Nast-Kolb et al., 2001; Miller et al., 2002; Osborn et al., 2004; Norris et al., 2006).

Several scoring systems are used to help predict prognosis and to evaluate the effects of treatment. One of the most widely used injury measurement tools is the abbreviated injury scale (AIS), published by the Committee on Automation Safety (AMA Committee, 1972), which provides a severity scale of 1 (minor injury) to 6 (non-survivable injury) for each possible injury. One drawback is that it fails to provide a single unified score for a patient suffering from multiple injuries; however, this is provided by the Injury Severity Score (ISS) (Baker et al., 1974) and the New Injury Severity Score (NISS) (Osler et al., 1997). The ISS and the NISS are the only anatomical scoring systems currently in use, and they correlate linearly with mortality, morbidity and the length of hospital stay. The Glasgow Coma Score (GCS), a neurological scale, is also used in the ICU to stratify critically ill/injured patients. There are other scoring systems, such as the Acute Physiology and Chronic Health Evaluation II (APACHE II), which is calculated during the initial 24 h after admission into the trauma unit and the Sequential Organ Failure Assessment (SOFA) Score, which aims to quantify daily organ dysfunction of critically ill/injured patients. All scoring systems and assessment tools have their limitations. Almost all scales used for scoring critically ill patients (Norris et al., 2008b) summarize and interpret physiological signs through a manual, intermittent and subjective process. They make no attempt to utilize the vast amount of second-by-second physiological data captured in a trauma unit or the ICU. It is also known that most of these scoring systems have a limited prognostic ability (Norris et al., 2006).

In this context, a compromised HRV signal computed from a continuous electrocardiogram (ECG) has been accepted as an indicator of an autonomic dysfunction in

many pathological states (Proctor et al., 2007). The HRV is potentially useful as a tool for pre-hospital triage, initial patient stratification and evaluation of treatment in critically ill/injured patients. It has even been suggested (Morris and Norris, 2005; Norris et al., 2005) that HRV could be a "new vital sign" used to predict the outcome in critically injured patients. A reduced HRV during the initial 24 h in the ICU correlates with increased morbidity and mortality (Norris et al., 2005, 2006, 2008a). Other studies have shown that a decreased HRV or absence of HR complexity is an early indicator of brain death (Goldstein et al., 1998b; Biswas et al., 2000). In addition, research has established that a diminished HRV is a predictor of death, irrespective of the cause, throughout the whole ICU stay (Norris et al., 2006; Grogan et al., 2004, 2005) and correlates with well-known physiological surrogates of shock such as acidosis, coagulopathy and temperature extremes (Morris et al., 2006).

Despite the potential of HRV as a useful tool in the management of critically ill patients, it is yet to be used routinely in clinical decision making (Proctor et al., 2007). Even though we can associate a reduced HRV with a poor outcome in trauma patients, the underlying mechanisms contributing to this observation are not well understood. Currently, there are no specific guidelines or treatment regime to treat the underlying injury that results in reduced HRV (Huikuri et al., 1999). In addition, a pathological diagnosis or a prediction of outcome does not solely depend on parameters that are computed from the HRV signal. It is confounded by many other physiological parameters, such as blood pressure and respiratory rate (Fathizadeh et al., 2004), as well as clinical variables, including severity of the condition, medications and demographic factors such as age (Norris et al., 2006). Currently, there is no unique way to measure and report HRV-based indices that can be used as routine clinical variables. In general, HRV can be quantified using at least one of three analysis methods: time domain, frequency domain and non-linear techniques. The time domain and frequency domain procedures for HRV are the most commonly reported methods of analysis in the literature (Norris et al., 2005; Grogan et al., 2004). However, non-linear or complexity analysis is gradually gaining acceptance because non-linear measures, such as the multiscale entropy (MSE), show reproducible patterns and responses to interventions (Norris et al., 2008b). In this section, we will examine investigations that have reported the usefulness of HRV recorded from patients who are admitted to the ICU following critical injuries.

Grogan et al. (2004) have recorded continuous physiological data including HR, from patients admitted to the trauma center at Vanderbilt University Medical Center for a study entitled Signal Interpretation and Monitoring (SIMON). They defined a new parameter, called integer HRV (HRVi), by computing the standard deviation of HR signal sampled every 1–4 s over a 5 min interval for each patient (Grogan et al., 2004). Approximately 120 million HR data points were prospectively collected and stored in a relational database from 1316 trauma ICU patients over 30 months. The outcome data were linked to the database and logistic regression models incorporating age and ISS were developed on a test set of patients ($n=923$). The model was validated on 393 patients separately. They found that HRVi identified a subgroup of patients with a high probability of dying. Norris et al. state that HR volatility measured using HRVi can independently and accurately predict mortality and morbidity of trauma patients within the first 24 h in the ICU and that it outperforms any traditional biomarkers (Grogan et al., 2004). In a separate study, they further stated that the predictive power of HRVi increases over time and can independently predict the death of a patient as early as 12 h following admission to the ICU. They also pointed out a limitation of the HRVi, namely, that it cannot be directly associated with autonomic dysfunction. Even though the HRVi has proved useful, it has yet to facilitate

stratification of the patients by therapy, resource utilization and probability of survival (Norris et al., 2005).

In subsequent papers, Norris et al. (Norris et al., 2006; Morris et al., 2006) coined the term “cardiac uncoupling,” which quantifies cardiac volatility-related dysfunction in the time domain. Cardiac uncoupling is defined as the percentage of time HRV of a patient falls within a critically low range (0.3–0.6 bpm) (Norris et al., 2006; Morris et al., 2006) when computed over a 24 h period. They concluded that cardiac uncoupling is an independent predictor of death throughout the ICU stay in a predictive window of 2–4 days. Increased uncoupling has been associated with diminished physiological reserve (defined as acidosis, coagulopathy and hemorrhage severity, sepsis, multiple organ failure and mortality). Continuous tracking of cardiac uncoupling shows a unique pattern of injury and identifies the onset of complications. An increase in the median cardiac uncoupling can stratify patients with traumatic brain injury (TBI) into survivors and non-survivors early in their ICU stay and can also be used to forecast death due to sepsis at day 6 of the ICU stay (Norris et al., 2006).

Proctor et al. (2007) proposed a new algorithm using the standard deviation of normal RR intervals (SDNN) and the square root of the mean squared difference of successive normal RR intervals (RMSSD) to predict the presence of abnormal findings on head computed tomography (CT) in trauma patients. The new algorithm compensates for some of the variables that reduce the specificity of HRV measurements. These variables include anesthetics, sedatives, analgesics and neuromuscular blocking agents. The authors found that the specificity and the efficiency of identifying abnormal CTs in trauma patients improve after factoring in these variables (Proctor et al., 2007). In another study on patients with severe head injury, it was also noted that HRV-based indices could be used to identify patients who had a greater propensity for brain death (Rapenne et al., 2001).

A majority of the studies in the TBI field have employed time and/or frequency domain methods for HRV analysis. Many studies have concluded that for patients with a TBI, decreased low frequency (LF), high frequency (HF), LF/HF ratio and total power (TP) are correlated with brain death and increased mortality (Rapenne et al., 2000, 2001; Winchell and Hoyt, 1997; Papaioannou et al., 2006). Researchers have also observed that patients with decreased frequency domain parameter values of HRV post-injury take a longer time to recover from TBI (Keren et al., 2005).

Most recent studies on prognosis in trauma patients utilize non-linear methods for analyzing HRV. Batchinsky et al. (2009) used approximate entropy (ApEn), sample entropy (SampEn) and similarity of distributions for rapid prediction of the survivability in trauma patients (Batchinsky et al., 2009). They concluded that these non-linear HRV parameters can stratify trauma patients between survivors and non-survivors using ECG records with only 800–1000 beats.

Norris et al. (2008b) compared the predictive powers of HRVi and MSE. They found that even though both HRVi and MSE could identify trauma patients at risk of hospital death within first 24 h of admission, MSE tended to improve the identification of patients at risk compared to HRVi (Norris et al., 2008b). In another study, Norris et al. (2008a) found that MSE can predict death in trauma patients using as little as 3 h of data. In a subsequent study, MSE was used to predict mortality regardless of the mechanism, anatomic location or severity of the injury (Riordan et al., 2009). The study also concluded that MSE could provide unique information on critical care patients and is independent of the probability for survival and provides new information for early patient stratification.

11.3 Sepsis and Septic Shock

Sepsis, in the narrow sense, refers to the presence of infectious organisms in parts of the body that are normally free of bacteria and viruses, such as the bloodstream and within tissues. Sepsis can also result in an immune and/or inflammatory response of the whole body. Decreased oxygen delivery and/or reduced perfusion can occur in a specific organ system or to all organ systems (septic shock). Acute tubular necrosis (ATN) in kidneys and acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) are manifestations of acute sepsis in individual organs. On the other hand, a systemic inflammatory response syndrome (SIRS) can result in MODS. Characterization of autonomic dysfunction and loss of autonomic balance during sepsis have been demonstrated to predict the mortality and morbidity in ICU patients with sepsis.

Sepsis is a leading cause of death among critically ill patients. The mortality rate due to severe sepsis or septic shock has been estimated to be 30%–50% among all patients (Dellinger, 2003; Friedman et al., 1998). The mortality rate is 14% or higher due to sepsis among ICU patients (Smith et al., 1998). The septic response is an extremely complex chain of events that involves both inflammatory and anti-inflammatory processes, humoral and cellular reactions and circulatory abnormalities (Hotchkiss and Karl, 2003; Gullo et al., 2006). Sepsis alters homeostasis, thus affecting sympathovagal balance. Even though various aspects of host response to severe sepsis and septic shock are well documented, there is a lack of understanding of the interactive and dynamic nature of factors contributing to sepsis.

The diagnosis of sepsis in its early stages is complicated by the dynamic behavior of various signs and symptoms of sepsis (Lever and Mackenzie, 2007). Despite this difficulty, researchers have developed numerous biomarkers for diagnosing sepsis and its states, which help identify the presence and severity of sepsis (Atkinson et al., 2001; Marshall and Reinhart, 2009), and for differentiating bacterial sepsis from viral sepsis as well as systemic sepsis from local infection. Biomarkers can also play a role in patient care for determining prognosis, guiding therapy, tracking response to a given therapy and predicting complications leading to organ dysfunction (Pierrickos and Vincent, 2010). However, it is not yet clear how various biomarkers could be used in effective management of patients with sepsis (Dellinger et al., 2008).

In a recent comprehensive review, Pierrickos and Vincent (2010) enumerate 178 different biomarkers used for identifying sepsis. However, their list does not include HRV as a distinct biomarker of sepsis. Their study has concluded that, while there are many biomarkers for sepsis, none of them has the specificity and sensitivity to be routinely used in clinical settings. According to this review, even procalcitonin and C-reactive protein, the two most widely used biomarkers, have a limited ability to distinguish sepsis from other inflammatory conditions or to predict outcome. They suggest that a combination of biomarkers could be a more effective strategy for the clinical management of the patient with sepsis.

Sepsis can stay in a mild self-limiting state or become more severe (hypoperfusion, multiple organ failure and death) (Ferguson and Brown, 1996; Bone, 1996). In the earlier stages of sepsis, it may be difficult to identify patients with the highest risk of deterioration. The vital signs (fever and tachycardia) may show mild abnormalities (Barnaby et al., 2002). Global tissue hypoxia is a key indicator that is keenly observed by the ICU physician in patients with sepsis. The transition time during which sepsis becomes a critical condition has been termed the “golden hour,” when positive identification and effective therapy would confer the maximal benefit (Rivers et al., 2001). The timing of appropriate resuscitation in

patients with sepsis makes a huge impact on mortality, morbidity, length of ICU stay and health-care expenses (Ferguson and Brown, 1996; Rady, 1996; Rivers et al., 2001; Barriere and Lowry, 1995; Nguyen et al., 2000).

It has been observed that early goal-directed therapy targeted at normalizing hemodynamic parameters and reversing hypoxia within the first 6 h of an ICU stay produces significant benefits with respect to outcome in patients with severe sepsis and septic shock (Rivers et al., 2001). The problem lies with reliably finding patients who have sepsis and who present the greatest risk of subsequent deterioration (Chen and Kuo, 2007).

Current available means to diagnose sepsis is to identify an increase beyond a pre-defined threshold value for one or more of vital signs, in conjunction with results from the laboratory tests (Ahmad et al., 2009a). These approaches lack sensitivity and specificity, and it may take a longer time to obtain laboratory results (Ahmad et al., 2009b). Seely and Christou (2000) hypothesize that the systemic host response to trauma, shock or sepsis should be evaluated as a complex non-linear system. They state that the host response to sepsis is a non-linear dynamical system as it involves an interaction between organs, cells, mediators, molecules, nerves and genes (Seely and Christou, 2000) and that an analysis of HRV may provide a novel avenue of evaluation. A study of the variation or fluctuation of HRV over time has been shown to provide useful, but otherwise hidden, clinical data about the homeostatic state of a patient (Ahmad et al., 2009b). HRV depicts a complex system, showing the effects of coupling between the heart, ANS and other organs (Ellenby et al., 2001). Therefore, a reduction of HRV represents the process of decomplexification and points to a diminished interaction between different components that contribute to homeostasis (Seely and Christou, 2000; Kleiger et al., 1992; Pincus, 1994). In certain diseases where heart is the end organ, HRV has been successful in identifying deleterious effects of an autonomic imbalance (Task Force, 1996; Kleiger et al., 2005; Pomeranz et al., 1985). Thus, HRV is a readily available tool to evaluate non-linear dynamic relationships between different organs.

Goldstein et al. (1995) have shown that, when endotoxin is administered to an animal model of infection and sepsis, HRV decreases rapidly. In humans, endotoxemia or sepsis results in a decreased beat-to-beat variation of the HR, indicating an uncoupling of the ANS and cardiovascular system (Godin and Buchman, 1996; Godin et al., 1996). Research from Godin's and other laboratories supports the hypothesis that a decreased variability is a result of an impaired sympathetic regulation of the HR (Godin and Buchman, 1996; Godin et al., 1996; Piepoli et al., 1995).

HRV is depressed in the presence of a systemic infection (Chen and Kuo, 2007; Piepoli et al., 1995; Korach et al., 2001; Annane et al., 1999) and corresponds to the severity of infection (Garrard et al., 1993; Barnaby et al., 2002). An impaired sympathetic modulation has been used as a predictive biomarker for MODS in patients with sepsis (Pontet et al., 2003). In addition, a diminished sympathovagal balance, as suggested by a low LF/HF ratio, might occur prior to the clinical deterioration seen in ICU patients (Barnaby et al., 2002). A diminished sympathetic and compromised sympathovagal balance has been linked to significant morbidity and mortality in patients with septic shock (Barnaby et al., 2002; Chen and Kuo, 2007). Much of the work in this area, as pointed out by Ahmad et al. (2009b), has been done in neonates and infants (Griffin et al., 2003, 2004, 2005a,b; Griffin and Moorman, 2001; Moorman et al., 2006). In their pioneering studies on neonates, Moorman et al. have used a novel parameter of HRV, called the heart rate characteristics (HRC). It has been shown that a decreased and decelerated HRC precedes sepsis in neonates/infants (Griffin et al., 2003, 2004, 2005a,b; Griffin and Moorman, 2001; Moorman et al., 2006, 2011a,b).

The most commonly used method of HRV analysis in sepsis patients is frequency domain Fourier spectral analysis (Ahmad et al., 2009b; Randall et al., 1991; Saul, 1990; Peng et al., 1995a,b). A reduced LF/HF ratio is a common feature in sepsis (Godin et al., 1996; Piepoli et al., 1995; Annane et al., 1999; Garrard et al., 1993). Similarly, an altered sympathetic modulation of cardiac activity could be an early indicator of impending septic shock for patients in the ICU (Annane et al., 1999; Goldstein et al., 1995).

Ahmad et al. (2009a) analyzed results of multiple HRV techniques for early diagnosis of sepsis in adult bone marrow transplant (BMT) patients, a group at high risk of developing sepsis. They continuously monitored 17 BMT patients, beginning a day before cell infusion, until their recovery. The study was unique because they employed several methods for analyzing the HRV, including time domain and frequency domain methods, wavelet analysis, and algorithms derived from chaos theory, such as detrended fluctuation analysis (DFA), SampEn and MSE. Their study demonstrated that for 12 out of 14 patients, who were later diagnosed with sepsis, all HRV parameters, except the power law parameter, dropped 25% below the baseline prior to the clinical detection of sepsis. Of these, a wavelet-based HRV parameter dropped 35 h prior to sepsis.

Chen et al. (2008) utilized both time domain and frequency domain HRV parameters to identify mortality in 132 ICU patients with sepsis, of whom 10 patients did not survive. Their study concluded that the SDNN, TP, very low frequency (VLF), LF and LF/HF ratio of the non-survivors were significantly lower than those of the survivors and HF power was significantly higher in non-survivors. They identified a diminished SDNN and an increased HF power as the most significant independent predictors of ICU mortality in sepsis patients.

There is another significant finding from Chen's study (Chen et al., 2008). It was postulated that the RMSSD could be used as a short-term predictor but it is not as useful for long-term prediction of outcome. This finding was presented as further analysis of a study (Chen and Kuo, 2007) done by the same group. In that study, they concluded that sepsis patients who are at risk of an impending septic shock within first 6 h of an ICU visit show impairment in autonomic nervous modulation, including altered sympathovagal balance with sympathetic suppression. They also suggest that RMSSD might be a good early predictor of septic shock.

In a study on septic patients, Pontet et al. (2003) examined the hypothesis that HRV can be used to predict MODS and found that both RMSSD and LF power were diminished in septic patients who subsequently developed MODS. The authors preferred the LF HRV, which strongly correlates with sympathetic branch of the ANS (Goldstein et al., 1998a; Toweill et al., 2000), as it is a better biomarker for a quicker and easy prognosis of MODS in septic patients.

Tateishi et al. (2007) examined correlations between systemic inflammatory response and autonomic dysfunction in septic patients. Because hypercytokinemia plays an important role in sepsis, Tateishi et al. (2007) investigated the relationship between a depressed HRV and blood level of interleukin-6 (IL-6), an indicator of cytokine network activation, in 45 patients who were admitted to the ICU with sepsis. HRV indices, namely, the frequency domain parameters, were used as an indicator of autonomic dysfunction. On admission, the IL-6 blood level exhibited significant negative correlations with LF power ($r=-0.76$; $p<.01$) and HF power ($r=-0.53$; $p<.01$). The study found that even though IL-6 blood level and HRV indices, namely, LF power, were not significantly different between the groups of survivors and non-survivors on admission, IL-6 blood level tended to remain high and LF power was low in non-survivors during the ICU stay. Similarly, the study found that with a depressed LF power, changes in blood pressure become greater, suggesting that a

reduced HRV is associated with a loss of circulatory homeostasis. These observations support the hypothesis that there is a significant relationship between cytokines and blood pressure homeostasis, mediated by the ANS in patients with sepsis.

11.4 Multiple Organ Dysfunction Syndrome

Failure of several organs, more commonly referred to as MODS, is usually triggered by severe sepsis, but it could also be preceded by trauma, cardiogenic shock, pneumonia and acute renal or liver failure (Singh and Evans, 2006; Baue et al., 1998; Medina et al., 2001; Schmidt et al., 2005b). Organ failure, which usually lags these triggering events by a period of days to weeks, often begins with the respiratory system and is followed by failure of gastrointestinal, hepatic, renal and hematologic systems and finally, the cardiac failure. The exact order of failure may vary according to the nature of the triggering event (Seely and Christou, 2000). It has been shown that a septic patient has a better chance of survival if the infection has not evolved into MODS (Baue et al., 1998; Medina et al., 2001). MODS is identified as the most common cause of sepsis-related death (Singh and Evans, 2006). Mortality in MODS is strongly correlated with the number of organ system failures, age and duration of organ failure (Ahmed et al., 1995). Despite advances in the knowledge of underlying causes and treatment, the mortality rate and cost of treating MODS in ICU remain high (Moerer et al., 2002; Angus et al., 2001). If MODS is present, the mortality rate of sepsis patients steeply increases from 5%–30% to 100% (Medina et al., 2001) and accounts for 50%–80% of total deaths in the ICU (Deitch, 1992).

In 1994, the European Society of Intensive Care Medicine created the SOFA system to quantify organ dysfunction/failure, that is, MODS, in the ICU (Vincent et al., 1998). The SOFA scoring involves six organ systems: respiratory, cardiovascular, renal, coagulation, hepatic and neurological. Although SOFA is used extensively in the ICU, it has several limitations. A SOFA score is recorded once each day, for a patient, throughout the ICU stay. Each SOFA score represents the severity of a patient's state. Even though a relatively high SOFA score represents a poor eventual outcome for a patient, the once-a-day SOFA score is too coarse a measure of an ICU patient's status when the time scale of deterioration of a patient's physical condition is in minutes or hours. This makes it inadequate for planning suitable and a timely treatment to the patient.

The development of MODS is associated with SIRS and subsequent cell damage of parenchymal organs. Autonomic dysfunction is a part of severe SIRS, and disturbances of neurally mediated organ interactions could contribute to the development of MODS (Godin and Buchman, 1996). Thus, researchers have proposed viewing MODS as a phenomenon of "*decomplexification*" (Goldstein et al., 1998a) or "*uncoupling*" (Godin and Buchman, 1996). One of the basic features of a healthy human body is a continuous interaction ("*coupling*") between all vital organs through the mediation of the ANS (Godin and Buchman, 1996; Godin et al., 1996; Toweill and Goldstein, 1998). Godin and Buchman (1996) proposed uncoupling, or isolation of the organs, which begins with a single organ dysfunction and results in MODS (Godin and Buchman, 1996). Thus, an investigation into the impaired or blunted inter-organ communication through signal analysis of HRV as an index of the ANS function could provide diagnostic and prognostic power for detecting MODS (Godin and Buchman, 1996; Seely and Christou, 2000; Hoyer et al.,

2006; Tibby et al., 2003; Schmidt et al., 2001, 2004, 2005a, 2008). An examination of the literature reveals that time domain, frequency domain and non-linear measures have been employed to identify those patients in the ICU who develop MODS (Schmidt et al., 2005b, 2008; Seely and Christou, 2000; Papaioannou et al., 2006; Norris et al., 2006; Pontet et al., 2003; Hoyer et al., 2006) or to predict mortality (Schmidt et al., 2005b; Seely and Christou, 2000; Papaioannou et al., 2006).

In order to identify critical variables that provide clinically useful information, Schmidt et al. (2005b) measured HRV, baroreflex sensitivity and chemoreflex sensitivity to quantify the ANS function in 90 consecutive patients who were admitted to the ICU and diagnosed with MODS. It was found that both SDNN and VLF were the two key variables derived from HRV that predicted 28-day mortality more accurately. In a subsequent study, Schmidt et al. (2008) state that the VLF is not only the best predictor of 28-day mortality in MODS patients, but also of longer-term mortality of 2 months. Schmidt et al. (2005b) concluded that the VLF band not only contains parasympathetic outflow (Stauss, 2003), but also reflects other physiological influences, such as that due to hormones, temperature and vasomotion (Schmidt et al., 2005b; Taylor et al., 1998) and could be a medium for parasympathetically regulated inter-organ communication. They also found that mechanical ventilation lowered pNN50, RMSSD, HF, LF and VLF, but did not significantly alter SDNN, SDANN, LF/HF ratio or baroreflex or chemoreflex sensitivities. Whereas age had an additional confounding effect on a decreased autonomic function, the latter was influenced more by the disease severity than by age.

Pontet et al. (2003) used HRV as an early marker of MODS in septic patients. The authors studied 46 septic patients with no MODS at the time of ICU admission. At the time of admission, the APACHE II scores for subsequent MODS group and non-MODS group were similar. However, most HRV indices were significantly reduced for the MODS group. According to the results of the study, LF component of HRV was the strongest predictor of MODS in septic patients.

Schmidt et al. (2008) have indicated that fractal scaling and non-linear dynamics of HRV could provide new insight into the HR dynamics. Papaioannou et al. (2006) used non-linear properties of HR signals to link 53 critically ill patients with a concomitant deterioration of organ dysfunction and high mortality. The non-survivors had a lower ApEn mean (a greater periodicity in their signals) and minimum values compared to survivors. Patients in better condition with a SOFA of less than 7 (mean value) had a higher variance and ApEn (more variable, less periodic signals) than those with a SOFA of 7 or higher. The α_2 exponent and variance were correlated with the length of stay and the minimum ApEn with mortality.

Norris et al. (2006) characterize a low HRV as cardiac uncoupling. In a study of 2808 patients admitted to the ICU, they found cardiac uncoupling in 63.5% of all patients. They also found that a low HRV/cardiac uncoupling (1) is an independent predictor of death throughout the ICU stay, (2) has a predictive window of 2–4 days and (3) appears to increase in response to inflammation, infection and multiple organ failure.

11.5 Weaning from Mechanical Ventilation

Mechanical ventilation is a common intervention used by clinicians for ICU patients. Yet, deciding when to discontinue mechanical ventilation remains a major challenge.

Discontinuation of mechanical ventilation is commonly termed “*weaning*,” which is a protocol-guided process requiring a gradual reduction of ventilation support and which may not be applicable to all ICU patients (Frazier et al., 2006). There are several factors that contribute to an unsuccessful weaning. Reasons for the failure of a successful transition to spontaneous ventilation include oxygenation failure, respiratory muscle dysfunction, psychological dependence and cardiovascular dysfunction (MacIntyre et al., 2001; Marini, 1986).

There is a complex connection between the respiratory/ventilation system and cardiovascular system. This complex inter-link is the reflection of an interaction between myocardial reserve, ventricular pump function, circulating blood volume, blood flow distribution, autonomic tone, endocrinologic responses, lung volume, intrathoracic pressure (ITP) and surrounding pressures for the remaining part of circulation (abdominal and intrapleural pressure). It is not surprising that patients with unsuccessful discontinuation of mechanical ventilation may display impaired baseline cardiovascular performance (Lemaire et al., 1988) but regularly show signs of heart failure during weaning (Pinsky, 2005). Cardiovascular dysfunction could also be a sign of prolonged dependence on mechanical ventilation, which is associated with an increased risk of mortality (Ingersoll and Grippi, 1991; Jayr et al., 1993; LoCicero et al., 1992), increased morbidity (Jayr et al., 1993; LoCicero et al., 1992; Cheng et al., 1996), a longer stay in the ICU (Ingersoll and Grippi, 1991; Jayr et al., 1993; Cheng et al., 1996) and a diminished functional capacity after discharge (Spicher and White, 1987). Cardiovascular dysfunction is also correlated with reintubation after extubation (Frazier et al., 2006). Thus, an evaluation of the ANS function before and during the discontinuation of mechanical ventilation could provide useful information about cardiovascular dysfunction (Frazier et al., 2006). Despite this evidence, autonomic tone as a function of the cardiovascular status is not systematically explored in mechanical ventilation weaning studies. Many researchers who have suggested that a cardiac dysfunction could be a cause of the unsuccessful discontinuation of mechanical ventilation have most often studied patients with known cardiac diseases. On the contrary, an undetected cardiac dysfunction could be the primary reason for many patients in the ICU not being able to respond to hemodynamic changes produced by a discontinuation of the ventilation (Frazier et al., 2006).

Shen et al. (2003) employed HRV analysis to characterize a cardiovascular dysfunction during ventilation weaning in patients recovering from respiratory failure. The study used frequency domain parameters for HRV analysis of 24 patients receiving mechanical ventilation. The TP, HF and LF components of HRV were measured in three stages: assist/control mandatory ventilation (ACMV), pressure support ventilation (PSV) and spontaneous breathing trial (SBT). The study found that HRV parameters were not significantly altered during the shift from ACMV to PSV, in all patients. But, during the shift from PSV to SBT, the parameters significantly decreased in the group of patients who failed in comparison to the group who were successful in weaning. The authors also found that reduced HF component was a better marker than reduced LF component to identify patients who were prone to failure following weaning from mechanical ventilation. Thus, a reduced HRV or vagal withdrawal signified by a diminished HF is a major signature of patients with weaning failure.

In a recent study, Papaioannou et al. (2011) similarly measured the HRV in patients during weaning from mechanical ventilation. They used both the linear (LF and HF) and the non-linear (DFA, SampEn and MSE) techniques of HRV on 32 patients who were mechanically ventilated for at least 48 h. The measurements were taken in two phases: during PSV and SBT with low-pressure support. The patients in the study did not have any known

cardiovascular diseases. The authors found that patients who failed weaning exhibited significantly lower SampEn, LF, HF and α_1 exponent than patients who successfully weaned from the mechanical ventilation. They also concluded that non-linear methods of HRV analysis performed better than linear methods of HRV analysis for weaning outcome assessment.

Frazier et al. (2008) studied the ANS function in 43 ICU patients receiving mechanical ventilation, as well as during a continuous positive airway pressure (CPAP) weaning trial. The study concluded that patients who failed their initial CPAP weaning trial showed a significant decrease in HRV during baseline mechanical ventilation in comparison to patients who succeeded. During the CPAP trial, HRV further diminished for the failure group. This study has the limitation of having a small patient population.

11.6 Autonomic Dysfunction in ICU Patients

The evaluation of impairment of sympathetic and parasympathetic balance in critically ill patients has been shown to provide useful information about the prognosis, pathogenesis and treatment strategies in disorders of ICU patients, which we have examined in this chapter (Schmidt et al., 2001). While recent studies have focused on quantifying the autonomic function/dysfunction in ICU patients, the use of HRV as a tool in the ICU for clinical care is not yet common.

One of the important tasks of ANS is the uninterrupted coordination of cardiorespiratory interaction in maintaining oxygen delivery to tissues (Schmidt et al., 2001). The ANS achieves this through processing information received from baroreceptors, chemoreceptors, atrial receptors, ventricular receptors and from respiratory, vasomotor, renin-angiotensin-aldosterone, thermoregulatory and other systems (Cooke et al., 1998). The ANS also plays a vital role in inter-organ communication (Hoyer et al., 2006). This continuous interaction of ANS modulation can be characterized by mathematical models of non-linear dynamics (Towlell and Goldstein, 1998; Godin and Buchman, 1996; Godin et al., 1996). An evaluation of ANS function also provides important prognostic power related to adrenal insufficiency and Guillain–Barré syndrome (Schmidt et al., 2004; Morris et al., 2007; Winchell and Hoyt, 1996; Flachenecker and Reiners, 1999). The loss of autonomic tone is also correlated with brain death and increased mortality (Hoyer et al., 2006; Rapenne et al., 2000, 2001; Winchell and Hoyt, 1997; Papaioannou et al., 2006).

Age is an important factor when evaluating the autonomic function. It is well established that HRV declines with age (Colosimo et al., 1997; Pikkujamsa et al., 1999). There is a shift of autonomic balance toward sympathetic predominance in patients belonging to higher age groups, thereby limiting the ability of the cardiovascular system to adjust to different demands and thus increasing the risk of developing tachyarrhythmias (Boettger et al., 2010).

11.7 Conclusions

The analysis of continuously obtained physiological data, especially that of the HRV signal, is a relatively recent innovation that can provide an insight into pathological

processes of critically ill patients. Several measures of HRV correlate with subsequent development of infection and mortality. One use of HRV analysis is to examine these parameters as a measure of the state of the system (i.e., to quantify the integrated function and/or dysfunction of the whole organism). Our evaluation of the literature suggests that a reduced HRV is likely due to an alteration in the function of any organ system, which may explain relative usefulness of these HRV-based measures in prognosis. However, a major limitation of these techniques is that it is not clear how they can be applicable when studying the function of an individual organ. Further, while most studies have focused on the prediction of mortality, such information does not necessarily help while treating a particular patient.

In a clinical setting, especially an ICU, much progress needs to be made before HRV can be employed to direct therapy. Further areas of research may be directed toward analyzing other continuous physiological parameters and examining interactions/associations between these variables. To observe how these interactions contribute to clinical outcomes and response to treatment is an obvious extension of this field of research. Researchers have yet to determine and arrive at a consensus on whether there is an optimum set of HRV parameters that can provide a summary of the state of ANS of a patient at any time during their stay in the ICU. Effects of various interventions on the HRV need to be elucidated and documented.

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Conflicts of Interest

Dr. Seely is founder and chief science officer of Therapeutic Monitoring Systems Inc., which is developing a clinical decision support software to perform continuous individualized multiorgan variability analysis (CIMVA), in order to improve the care for patients at risk or with an existing critical illness.

Abbreviations

AIS	Abbreviated injury scale
ALI	Acute lung injury
ANS	Autonomic nervous system
APACHE II	Acute physiology and chronic health evaluation II
ARDS	Acute respiratory distress syndrome

CT	Computed tomography
DFA	Detrended fluctuation analysis
ECG	Electrocardiogram
GCS	Glasgow coma score
HF	High frequency
HRC	Heart rate characteristics
HRV	Heart rate variability
HRVi	Integer HRV
ICU	Intensive care unit
IL-6	Interleukin-6
ISS	Injury severity score
LF	Low frequency
MODS	Multiple organ dysfunction syndrome
MSE	Multiscale entropy
RMSSD	Square root of the mean squared difference of successive normal RR intervals
SBT	Spontaneous breathing trial
SDNN	Standard deviation of normal RR intervals
SIRS	Systemic inflammatory response syndrome
TBI	Traumatic brain injury
TP	Total power
VLF	Very low frequency

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12

Heart Rate Variability and Cardiovascular Dynamic Changes during Local Anesthesia

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12.1 Cardiovascular and Heart Rate Variability Changes during Local Anesthesia in Animal Studies

The effect of different anesthetic drugs on cardiovascular hemodynamics has been studied since the 1960s (Lal et al., 1969; Taylor et al., 1965a,b,c). However, most of these studies focus on the effect of local anesthetic drugs on heart rate (HR), blood pressure (BP) and other cardiovascular and hemodynamic parameters, without any in-depth investigation of their effects on heart rate variability (HRV) and/or blood pressure variability (BPV). This could represent a major drawback, as small transient changes that occur due to the application of local anesthetic drugs could be missed if the aforementioned global variables alone are examined. Nevertheless, these studies are useful in providing some indication of hemodynamic and cardiovascular effects caused by the administration of local anesthesia (LA), some of which are summarized in Table 12.1.

Stewart et al. (2010) used HRV analysis to study the role of autonomic nervous system (ANS) in mediating eye temperature responses during painful procedures (sham handling or surgical castration) using 34-month-old bull calves. The maximum eye temperature, HR and HRV were recorded continuously from 25 min before to 20 min after the castration. The results showed that LA reduced but did not eliminate all three responses to the painful procedure. It was concluded that HR, HRV and infrared thermography measurements when used together could provide a non-invasive means to assess the ANS responses as indicators of acute pain.

TABLE 12.1

Animal Studies Involving Different Local Anesthetic Drugs

References	Animal Model	Local Anesthesia (LA)	Summary
Fogarty et al. (1970)	Rabbits	Pentazocine	Transient increase and subsequent decrease in arterial pressure. Abnormalities of the QRST complex
Basil et al. (1973)	Guinea pigs, cats and dogs	Hydrochloride (M&B 17,803A)/ practolol and propranolol	Propranolol more potent than M&B 17,803A and practolol
Munson et al. (1975)	Rhesus monkeys	Etidocaine, bupivacaine and lidocaine	Central nervous toxicity of lidocaine four times less than that of etidocaine and bupivacaine
Kotelko et al. (1984)	Sheep	Bupivacaine and lidocaine	Arrhythmias more common in the animals that received bupivacaine
Hotvedt et al. (1985)	Dogs	Bupivacaine	Bupivacaine can enhance susceptibility to re-entrant arrhythmias
Gerard et al. (1989)	Mongrel dogs	Bupivacaine and/or diazepam	Diazepam blunts the compensatory effects of bupivacaine on cardiac function and decreases the margin of safety during a major neural blockade
Edouard et al. (1991)	Dogs	Lidocaine after an intravenous bolus of bupivacaine or normal saline with concurrent 40 min infusions of equihypotensive doses of verapamil	Regional anesthesia should be applied with caution in patients treated with calcium entry blockers
De Kock et al. (1991)	Rats	Bupivacaine: 5 µg/kg intravenous digoxin or saline	The threshold doses of bupivacaine toxic effects and its serum concentrations were lower in the digoxin group
Pitkanen et al. (1992)	Rabbits	Ropivacaine, bupivacaine and lidocaine	Bupivacaine is a cardiac depressant and arrhythmogenic
Freysz et al. (1995)	Pigs	Bupivacaine	Bupivacaine should be used with caution in the condition of ischemia
Oliveira et al. (2003)	Rats	Prilocaine chloridate (alone and mixed with felypressin and epinephrine)	Epinephrine must be used with prilocaine

12.2 Effects of Local Anesthesia on HRV in Dentistry

The effects of anesthetic drugs given during dental procedures can vary significantly, depending on the condition of the patient. Due to the highly vascular nature of the application area, the use of LA during oral surgery could significantly affect cardiovascular dynamics. Consequently, a significant amount of literature exists on the use of LA in dentistry, some of which is discussed in this section. Table 12.2 summarizes some of the key studies that describe the cardiovascular and/or hemodynamic changes that could occur during dental anesthesia.

The reports in Table 12.1 focused on the changes in BP and HR that occur during dental LA, rather than on HRV. Kawano (1990) studied the changes occurring in parasympathetic

TABLE 12.2

Effects of Anesthetic Drugs in Dentistry

References	Study	Summary
Hasse et al. (1986)	LA during dental treatment in patients with and without cardiac disease	Cardiac patients demonstrate significantly higher ST segment depression during tooth extraction
Cintron et al. (1986)	Cardiovascular effects and the safety of dental anesthesia in patients with a recent myocardial infarction	Limited dental anesthesia and dental interventions were tolerated by patients with a recent myocardial infarction
Rengo et al. (1989)	Effect of LA (mepivacaine hydrochloride 2% plus adrenaline 1:200,000) on patients with cardiac disease	HR, systolic BP and diastolic BP significantly increased during tooth extraction
Davenport et al. (1990)	Hemodynamic effects of 2% lidocaine with and without epinephrine 1:100,000 on patients with cardiovascular disease	The cardiac effects of local anesthetics containing epinephrine are small and can be safely used in patients with a stable cardiovascular disease
Goldstein et al. (1982)	The effects of sedation with intravenous diazepam and of the inclusion of epinephrine with the local anesthetic during molar extraction	Increase in HR (25%), systolic BP (13%) and cardiac output (34%). Diazepam sedation abolished the norepinephrine response without significantly affecting the HR or systolic BP responses. Cardiac output and mean plasma epinephrine were increased fivefold with the inclusion of epinephrine
Chernow et al. (1983)	Hemodynamic effects of LA following an inferior alveolar nerve block with epinephrine- and norepinephrine-containing lidocaine hydrochloride	Lidocaine administered alone caused no change in mean arterial pressure (MAP) or HR. Lidocaine with epinephrine caused a transient increase in HR and no change in MAP
Knoll-Köhler et al. (1989)	Cardiovascular risk due to the presence of epinephrine in LA, 2 mL 2% lidocaine with and without 20 or 80 µg epinephrine	Lidocaine caused no changes. Lidocaine with 20 µg epinephrine caused an increase in the plasma epinephrine concentration and HR and a decrease in MAP. Similar changes occurred earlier with 80 µg of epinephrine
Hempenstall et al. (1986)	Comparison of LA and general anesthesia (GA) in dental surgery	Plasma growth hormone and prolactin increased in the LA group, while GA increased all other parameters

activity due to LA in 52 patients undergoing dental treatment. The coefficient of variation of the RR interval (CVR-R = SD/mean × 100%) was used as an index of parasympathetic activity. Comparisons were made between a control group and another group receiving atropine sulfate. The results showed consistently low CVR-R values, higher systolic BP, diastolic BP and HR; and longer recovery time in the atropine sulfate group compared to the control group.

Matsumura et al. (1998) also studied the changes caused by LA (2% lidocaine containing 1:80,000 epinephrine) in HR, BP and HRV in 40 patients (mean age ± SD: 42.7 ± 3.0 years) who underwent tooth extraction. A Holter monitor was used to record the electrocardiogram (ECG). The power in the low-frequency (LF = 0.041–0.140 Hz) region, the power in the high-frequency (HF = 0.140–0.50 Hz) region and the total power (TP = 0.000–4.000 Hz) were calculated, and the ratio of power between the LF and the HF regions (LF:HF) and the normalized power in the HF region (%HF = HF/TP × 100) were used as the indices of sympathetic and parasympathetic activities, respectively. The results showed that after the administration of the local anesthetic, both BP and pulse rate increased. Patients aged 40 years or older experienced an increase in their BP, while the LF:HF ratio decreased. By contrast, in patients aged

<40 years, the %HF decreased and the LF:HF ratio increased, indicating that the regulation of the ANS during dental surgery differed between younger and older patients.

In another study, Carrera et al. (2000) compared three anesthetics drugs in combination with different vasoconstrictors in the surgical removal of lower third molars. The study consisted of three groups ($n = 15$) split according to the anesthetic solution and the associated vasoconstrictor administered, namely, 4% articaine + epinephrine 1:200,000, 3% mepivacaine without vasoconstrictor and 3% prilocaine + felypressin 1:1,850,000. The HR, systolic BP, diastolic BP and oxygen saturation were recorded at different times before, during and at the end of surgery. It was found that the study variables were more stable with articaine + epinephrine 1:200,000, although there were no significant hemodynamic changes compared to the baseline values.

Miura et al. (2000) compared changes in cardiovascular dynamics in 18 hypertensive patients with the changes in an age- and sex-matched group of normotensive patients, during dental surgery. The HR, BP and HRV were monitored before and during dental surgery. From HRV analysis, the LF, HF and TP spectral powers were calculated, and the ratio of the powers (LF:HF) and %HF were used as indices of sympathetic and parasympathetic activities. The increase in BP during tooth extraction did not differ significantly between the two groups. The administration of anesthesia significantly decreased the %HF in normotensive patients (before vs. after anesthesia; 22.3 ± 2.4 vs. $13.8 \pm 2.7\%$, $p < .05$). By contrast, the LF:HF ratio significantly decreased during LA and tooth extraction in hypertensive patients.

Ishida et al. (2001) studied the effects of LA and periodontal surgery on autonomic nervous activity by measuring HR, BP and HRV in 10 patients undergoing periodontal surgery. It was observed that the LF:HF ratio increased significantly before and during LA, about 3 min after LA and before surgery. The peak of the plasma epinephrine concentration occurred almost simultaneously with the increase in the LF:HF ratio after the administration of an LA containing epinephrine. Mental stress was the contributing factor in the increase in the LF:HF ratio before anesthesia, while the later increase was due to physical stress and presence of epinephrine in anesthesia. However, there were no significant changes in the power of the HRV bands during periodontal surgery.

Nakamura et al. (2001) also studied changes in HRV and BP in 11 normotensive patients (mean age \pm SD, 22.5 ± 0.7 years) during dental surgery. The baseline readings of these variables were measured 3–7 days prior to surgery, every 30 min over a 24 h period. The anesthesia was applied using 2% lidocaine with 1:80,000 adrenaline. Nakamura et al. (2001) observed that during dental surgery, there was a significant increase in systolic BP ($+10.8 \pm 3.5$ mmHg), but it was not correlated with the baseline systolic BP or with the 24 h averaged BP, LF:HF ratio or HF power. Hence, they concluded that ambulatory measurements of BP and HRV over 24 h could not predict the responses of BP during dental surgery.

Gedik et al. (2005) also analyzed BP, HR and temperature variability during periodontal surgery in 127 healthy patients (43 males and 84 females mean age of 26 ± 12 years). The patients were divided into four groups (gingivectomy, periodontal flap surgery, frenectomy and curettage) and were anesthetized using Ultracain DS containing 0.06 mg adrenaline. A significant decrease was observed in all parameters studied (BP: systolic 111.3 ± 20.1 , diastolic 67.7 ± 13.1 ; pulse rate: 87.8 ± 14.9 ; temperature: 36.3 ± 0.3) for all patients. However, after the surgery, the changes in the parameters decreased significantly (BP: systolic 105.9 ± 19.7 , diastolic 62.6 ± 11.3 ; pulse rate: 84.01 ± 13.1 ; temperature: 36.2 ± 0.3). The female patients, without age differentiation, showed statistically significant decreases in all of the parameters ($p < .05$).

Neves et al. (2007) analyzed the effect of epinephrine in local dental anesthesia in 62 patients (mean age \pm SD: 26 \pm 12 years) with coronary artery disease. The anesthesia was applied using 2% lidocaine with epinephrine ($n = 30$) and without epinephrine ($n = 32$). The results showed that there were no significant differences between the two groups with respect to BP, HR and the number of arrhythmic episodes. It was concluded that epinephrine could be employed safely during dental anesthesia for patients with coronary artery disease.

More recently, Alemany-Martínez et al. (2008) studied hemodynamic changes during the surgical removal of lower third molars in 80 (40 females and 40 males) normotensive patients. LA was applied using 4% articaine adrenaline (1:100,000). The systolic BP, diastolic BP, HR and oxygen saturation (SpO_2) were measured. Patient anxiety was also determined using Corah's Dental Anxiety Scale (Corah, 1969) and Kleinknecht's Dental Fear Scale (Kleinknecht et al., 1973), and the level of pain experienced was assessed by means of a visual analog scale. Their results suggest that female patients demonstrate higher levels of anxiety. The HR and BP did not change significantly during molar extraction. The SpO_2 values showed no significant changes. These results showed that most of the cardiovascular changes could be associated with anxiety and stress induced by surgery. A comparison between 2 mL of 2% lidocaine with clonidine (15 $\mu\text{g}/\text{mL}$) and 2 mL of 2% lidocaine with epinephrine (12.5 $\mu\text{g}/\text{mL}$), used for the extraction of the upper third molar, was also carried out by Brkovic et al. (2008) in 40 patients. The results showed that 10 min after surgery, the HR and systolic BP decreased significantly in the lidocaine + clonidine group, while HR increased significantly in the lidocaine + epinephrine group. Changes in all other hemodynamic parameters were similar in both groups. Therefore, it was concluded that a lidocaine + clonidine combination could safely replace a lidocaine + epinephrine combination for intra-oral infiltration anesthesia.

12.3 Comparison of Cardiovascular and Hemodynamic Effects of Local versus General Anesthesia

Due to its perceived advantages such as faster recovery time, fewer requirements for post-operative analgesia, cost-effectiveness and more stable cardiovascular and hemodynamic conditions, LA has been preferred to general anesthesia (GA) in many surgical procedures. This section focuses on some of the studies carried out to compare the hemodynamic and cardiovascular changes caused by LA and GA.

Takolander et al. (1990) studied 75 patients to compare the autonomic and cardiovascular changes caused by LA and GA during carotid surgery. Arterial plasma catecholamines, BP and HR were determined before, during and after carotid endarterectomy. The patients were divided into three groups. The LA group ($n = 28$) received LA given as a cervical block with skin infiltration containing 200 μg adrenaline. The GAs group (s for skin, $n = 32$) received nitrous oxide, fentanyl and isoflurane with skin infiltration containing 200 μg adrenaline, and the GAo group (o for no skin, $n = 15$) received GA without skin infiltration. The results showed that the plasma noradrenaline (P-NA) levels were significantly higher in the LA group ($p < .05$) during anesthesia and surgery, while they decreased in the GAo group ($p < .01$) and remained unaltered in the GAs group. Incidences of a hypotensive BP reaction (systolic BP < 100 mmHg; LA vs. GAo, $p < .001$) were higher in the GAs group (eight patients) as compared to the LA group (two patients) and the GAo

group (seven patients). Ten patients in the LA group also showed a hypertensive BP reaction. Thus, both types of anesthesia have certain disadvantages in patients who have an increased risk for cardiovascular morbidity/mortality.

Campbell et al. (1993) performed a comparison between LA and GA during cataract surgery in 169 patients. Parameters such as oxygen saturation, BP and HR were monitored during anesthesia and in the immediate recovery period. The results showed that oxygen desaturation occurred at least once in 19% of the patients in the GA group compared to none in the LA group. In the GA group, 61% of the patients also experienced more than 30% decrease in the systolic BP. The authors concluded that there was no significant difference between the performance of LA and the performance of GA in cataract surgery.

Demirtas et al. (2005) also studied the hemodynamic effect of pre-operative stressor events during rhinoplasty in 50 healthy adult patients. An ambulatory Holter ECG recording was carried out for 24 h, starting on the day before the operation and continuing throughout the procedure. All patients received 10 mL of 2% lidocaine with 1:80,000 adrenaline 15 min after intubation. The frequency domain HRV parameters, HR and non-invasive BP were measured during the study. Their results showed that mild-to-moderate tachycardia occurred in the majority of the patients before the induction of anesthesia. A similar change was also detected after the infiltration of lidocaine/adrenaline and during lateral osteotomies. However, the pre-operative stressors (with the exclusion of GA induction, intubation and extubation) did not cause any significant changes in the BP. Tachycardia before induction was caused by an increase in the sympathetic activity due to the patient's anxiety. These results show that patients undergoing rhinoplasty would benefit from the routine use of premedications, and a lidocaine/adrenaline combination is a safe addition to GA during this procedure.

In another study, patients' stress response during asleep–awake craniotomy was studied by Conte et al. (2009), who quantified the sympathovagal balance using HRV analysis. Twenty-one patients, aged 22–53 years, undergoing a tumor resection with language testing were recruited for the study. The HR and systolic BP were measured at five time points: T1: preanesthesia; T2: dura mater opening; T3: cortical mapping; T4: subcortical mapping; and T5: dura mater suturing. The patients were anesthetized with a propofol/remifentanil infusion and ventilated via a laryngeal mask during T2 but were awakened for language testing at T3 and T4 and resedated with remifentanil during T5. At each of these five time points, HRV frequency domain parameters of TP; powers in the very-low-frequency (VLF), LF, and HF bands; and LF:HF ratio were estimated. The results showed that compared to T1, significant increases in HR and BP were observed from T3 through T5 ($p < .05$). The LF:HF ratio progressively increased, reaching significant levels ($p < .05$) during T4. However, the ratio values returned to the level of T1 during the T5 period. These results confirmed the presence of a moderate intra-operative stress response, indicating a significant increase in the LF:HF ratio during the awake phase. This information can help individualize the protocol and duration of the awake phase according to the patient's autonomic response.

12.4 HRV and Cardiovascular Effects of Local Anesthesia

LA has been used extensively in numerous surgical procedures. Depending on the site and the technique of application, the anesthetic dose could differ significantly, which

could result in varying cardiovascular and hemodynamic effects during the application of anesthesia. There are many studies in the literature in which different anesthetic drugs and/or anesthetic techniques have been compared. These studies, which will be the main focus of this section, have analyzed the effect of different techniques and/or drugs on HR, BP and HRV.

Barman et al. (1989) undertook a study to determine intra-operatively the hemodynamic effects of LA of the carotid sinus nerve during carotid dissection in preparation for endarterectomy. In a control group ($n = 10$), a saline solution was infiltrated into the carotid bifurcation. In another group ($n = 10$), 5 mL of 2% lidocaine hydrochloride was infiltrated. The HR and BP values were recorded at baseline and inter-operatively every 2 min during a 10 min period. Inter-operatively, the lidocaine group showed a higher increase in the systolic pressure ($p < .0064$) and mean pressure ($p < .0028$). From these results, it was concluded that a local anesthetic injection of the carotid sinus nerve before carotid dissection and endarterectomy was unnecessary when nerve-sparing dissection was performed.

In another study, Keyl et al. (1996) investigated stability in the cardiac autonomic tone after GA or LA in 28 patients undergoing cataract surgery. Group 1 ($n = 14$) received GA (premedication: clorazepate; anesthetic induction: propofol, alfentanil and atracurium; anesthetic maintenance: isoflurane and alfentanil; airway management: laryngeal mask airway) and Group 2 ($n = 14$) received LA (retrobulbar block with bupivacaine/mepivacaine). An HRV frequency domain analysis was carried out intra-operatively and up to 3 h post-operatively. The results showed that in the GA group, only the TP was significantly reduced intra-operatively and increased slowly during the post-operative period. Post-operatively, HR and LF:HF ratio values were significantly increased in the LA group compared to the GA group. From these findings, it is concluded that during ophthalmic surgery, in terms of pre-operative cardiac autonomic tone, GA has no disadvantage compared to LA.

Middlehurst and Coulthard (1999) studied hemodynamic and electrocardiographic responses to LA in 75 patients with heart disease. After dividing patients into two groups, LA was applied using 2% lignocaine, adrenaline 1:50,000 and vasopressin 0.25 IU, either alone or with midazolam sedation. In addition to HR, BP and ECG, the rate-pressure product and the pressure-rate quotient were calculated as indicators for myocardial ischemia. Significant changes were observed in HR, systolic BP and mean BP due to sedation and anesthesia. For the anesthetic group, the maximum value for the rate-pressure product and the minimum value for the pressure-rate quotient were 12,168 (95% CI = 1,368) and 1.39 (95% CI = 0.04), respectively, while for the sedated group, these values were 9,882 (95% CI = 1,226) and 1.13 (95% CI = 0.06), respectively. Based on these results, the authors concluded that sedation was not associated with a significant ischemic risk.

Schwall et al. (2000) also compared the use of total intravenous anesthesia (TIVA) with LA during cataract surgery. The patients were randomly assigned to a peribulbar local block ($n = 10$) or TIVA ($n = 10$). Propofol and alfentanil were used for TIVA. The parameters related to HR, BP and the plasma concentrations of catecholamines, cortisol and glucose were assessed at seven pre-operative, intra-operative and post-operative time points. The results showed that LA caused no significant change in the plasma concentrations of epinephrine, norepinephrine and cortisol, whereas in the case of TIVA, they decreased by approximately 66%, 51% and 61%, respectively. The BP and HR did not change significantly during LA, while the systolic BP decreased by 30% and the HR by 12 beats/min during TIVA. The results presented in this study showed that LA produced the best adrenergic and hemodynamic stability during cataract surgery.

In another study, Dogru et al. (2003) investigated the effect of high/low doses of epinephrine during an axillary brachial plexus block in 60 American Society of Anesthesiologist (ASA) I and II patients, who were divided randomly into three groups. The patients in Group 1 received saline containing 25 µg epinephrine followed by lidocaine; the patients in Group 2 received saline followed by 200 µg of epinephrine mixed with lidocaine; the patients in Group 3 received saline alone followed by lidocaine. All lidocaine solutions were 35 mL at 1.5% concentration. All saline solutions were 5 mL. Starting from the first minute after the axillary injection, the hemodynamic data were measured at intervals of 1 min for a duration of 10 min (10 measurements in total). During the course of the 10 min recording, the HR, systolic BP and diastolic BP were higher in Group 2 compared to Groups 1 and 3 ($p < .05$). From these results, it could be seen that a lower dose of epinephrine provided a more stable hemodynamic profile than a higher dose of epinephrine, without significantly affecting the motor blockade. Therefore, a lower dose of epinephrine may be preferable in patients with a higher risk of tachycardia and/or hypertension.

Aydin et al. (2004) in another study, analyzed the effect of single-dose fentanyl on the cardiorespiratory system in 70 ASA I, II and III elderly patients (>60 years) undergoing cataract surgery with phacoemulsification method. One group ($n = 35$) of patients received fentanyl in bolus doses of 0.7 µg/kg in a 2 mL balanced salt solution, while the other group ($n = 35$) received 2 mL balanced salt solutions without any analgesic drug. The parameters of systolic BP, diastolic BP, mean arterial pressure (MAP), HR, peripheral SpO₂, respiratory rate, end-tidal carbon dioxide (ETCO₂) inspired CO₂ concentration and sedation scores were measured pre-operatively and at 5, 10, 15, 20 and 30 min intra-operatively. The results showed that in the fentanyl group, no significant differences were observed in systolic BP, diastolic BP, MAP, RR or peripheral SpO₂, whereas in the control group, the respiratory rate value was higher than the baseline values at 10, 15 and 20 min and the diastolic BP value was higher than the baseline values at 20 min. From these results, it was concluded that fentanyl (0.7 µg/kg) could improve the comfort levels of elderly patients undergoing cataract surgery with topical anesthesia without any cardio-respiratory side effects.

12.4.1 New Approach to Define LF and HF Boundaries of HRV Signal

It is well documented that the respiratory effect is not necessarily confined to the fixed limits (0.15–0.4 Hz) defined for the HF band of the signal (Beda et al., 2007). In the literature, different approaches have been proposed for the estimation of the boundaries related to HRV signal components (Aydin et al., 2004; Bailon et al., 2007; Goren et al., 2006; Jasson et al., 1997; Keselbrener and Akselrod, 1996). All these definitions take only the peak frequency of the respiration signal into account, and the boundaries are defined without considering any other aspect (e.g., the signal frequency spread) of the respiration signal. In another study (Bailon et al., 2007), the rate of change in respiration frequency was employed to control the length of the time smoothing window used in the smoothed-pseudo Wigner-Ville distribution (SPWVD). The main drawback of this technique is that it might not be applicable with other frequency analysis methods.

In order to consider the large variability that might be present in the respiration signal, Shafqat et al. (2009a) proposed a new method for calculating the variable boundaries associated with the LF and the HF regions of the HRV signal. The HF band boundaries were defined using the cross-spectrum between the HRV signal and the estimated respiration signal. From the cross-spectrum, the center frequency (CF) and the standard deviation spectral extension (SDSE) were estimated using Equations 12.1 and 12.2, respectively:

$$CF = \frac{\int_{lb}^{hb} f P(f) df}{\int_{lb}^{hb} P(f) df}, \quad (12.1)$$

$$SDSE = \left(\frac{\int_{lb}^{hb} (f - CF)^2 P(f) df}{\int_{lb}^{hb} P(f) df} \right)^{1/2}. \quad (12.2)$$

In Equations 12.1 and 12.2, $P(f)$ represents the frequency domain representation and the integral limits hb and lb represent the upper and the lower boundaries of the regions (i.e., LF, HF).

Using the estimate of the CF and the SDSE, the range of the HF band was defined as $CF \pm SDSE$. The CF and the SDSE related to the LF region of the signal were also calculated; however, in this case, the estimation was carried out using the frequency domain representation of the HRV signal. In the case where the lower boundary of the HF component was below 0.15 Hz, this lower boundary was used in the estimation of the LF component CF and the boundaries, otherwise the estimation was done in the frequency range of 0.04–0.15 Hz. The CF and the boundaries were smoothed using a median filter with a length of 10 s to avoid sharp fluctuations in these parameters. Two examples of the LF and the HF boundary estimations along with the corresponding HRV and the estimated respiration signals are shown in Figures 12.1 and 12.2, respectively.

In both cases (Figures 12.1 and 12.2), the estimation was carried out on 5 min segments of data. In the case of Figure 12.1c, the cross-spectrum shows a single well-defined peak at a frequency of 0.3 Hz. This indicates that the power related to the respiration component (HF) is confined to a narrow band that lies within the fixed limits defined for the HF component. Figure 12.1d (the HRV signal spectrum) confirms the information represented by the cross-spectrum and shows a well-defined respiration-related component around 0.3 Hz. In this case, the respiration component is easily distinguishable from the LF

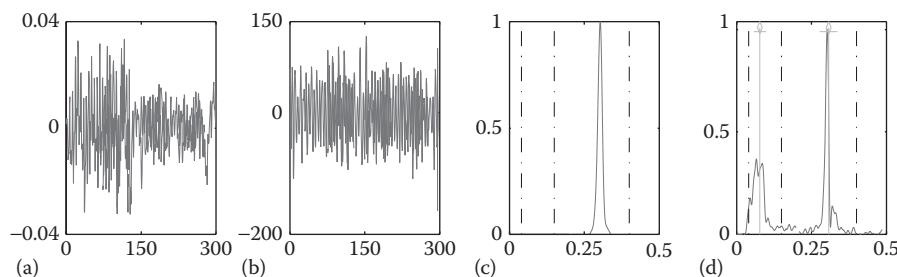
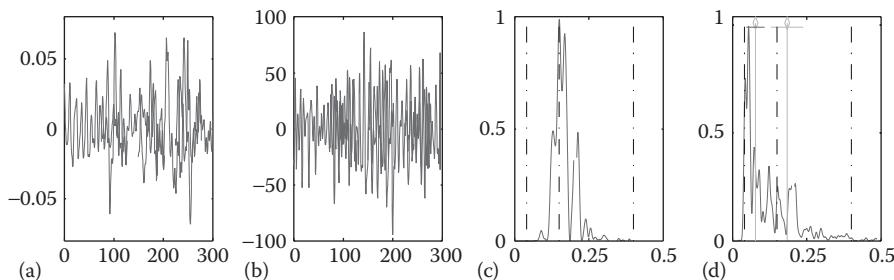


FIGURE 12.1

(a) Boundary estimation example 1: (a) HRV signal; (b) corresponding EDR estimated respiration signal; (c) cross-spectrum between HRV signal and the estimated respiration signal; (d) spectrum of the HRV signal. The dotted lines in part (c) and (d) represent the fixed (classical) boundaries of the LF and the HF regions. The thin lines with a diamond marker in part (d) represent the CF of the LF and HF band while the horizontal thin line (just under the diamond marker) represent the band range as estimated by the variable boundary method $CF \pm SDSE$. Spectral analysis is carried out using non-parametric method.

**FIGURE 12.2**

(a) Boundary estimation example 2; (a) HRV signal; (b) corresponding EDR estimated respiration signal; (c) cross-spectrum between HRV signal and the estimated respiration signal; (d) spectrum of the HRV signal. The dotted lines in part (c) and (d) represent the fixed (classical) boundaries of the LF and the HF region. The thin lines with a diamond marker in part (d) represent the CF of the LF and HF band while the horizontal thin line (just under the diamond marker) represent the band range as estimated by the variable boundary method $CF \pm SDSE$. Spectral analysis is carried out using non-parametric method.

component whose CF is around 0.1 Hz. Figure 12.1d also shows that the range $CF \pm SDSE$ of each band (LF and HF) estimated for the power estimation in the variable boundary method and represented by the horizontal lines quite adequately covers the major parts of the signal in these two regions. The situation is quite different in the second example of the boundary estimation presented in Figure 12.2; in this case, the respiration signal (see Figure 12.2b) shows more complex dynamics as compared to the respiration signal of the first example (see Figure 12.1b). For this reason, the cross-spectrum between HRV signal and the estimated respiration signal shown in Figure 12.2c is spread over a larger frequency range slightly below the fixed lower boundary of the HF region and shows more than one component. By looking at the cross-spectrum shown in Figure 12.2c, it can be seen that if fixed boundaries were used to calculate the power, then some of the power that might be due to the respiration component would be wrongly assigned to the LF region of the signal. However, variable boundary method will be able to take into account the part of the spectrum below the fixed lower boundary of the HF region because, in this case, the range of the HF component is defined by using the cross-spectrum between the HRV signal and the respiration signal. By looking at the horizontal line (in the HF region) in Figure 12.2d, it can be seen that the boundary of the HF region, as defined by the variable boundary method, indeed extends below 0.15 Hz, which is considered to be the lower limit of the HF region in the fixed boundary method. The results from both examples (see Figures 12.1d and 12.2d) show that the major parts of the signal power are covered by the LF and the HF regions as defined by the variable boundary method. Unlike other previously mentioned methods, in this proposed method, the boundary values depend on the characteristics of the HRV and the respiration signals being analyzed. This method represents a major advantage because it takes into account the considerable variations present in respiration signals.

Using this new method of variable boundary estimation, Shafqat et al. have also studied the effect of LA on HRV parameters during an axillary brachial plexus block. Fourteen ASA I and II patients (7 males and 7 females) with a mean age of 50.6 ± 20.7 years and a mean weight of 67 ± 15.3 kg undergoing elective general surgery under LA were recruited for the study. The patients with known cardiovascular and respiratory problems and those suffering from diabetes were excluded from the study. In all cases, the transarterial approach was used for the brachial plexus block. A combination of 30 mL of 1% lignocaine

and 20 mL of 0.5% bupivacaine with 1:200,000 part adrenaline was used as the anesthetic agent. Midazolam was used if extra anesthesia was required during the surgery.

ECG monitoring started about 30 min before the start of the block and was continued for approximately 30 min after the surgery in the recovery ward. The lead II ECG signals were digitized at a sampling frequency of 1 kHz to reduce the error in the estimation of HRV parameters (McSharry et al., 2003; Abboud and Barnea, 1995). The heart timing (HT) signal (Mateo and Laguna, 2000) was used for the HRV signal representation and also for the correction of missing and/or ectopic beats. The VLF component of the signal was removed by detrending the signal using a wavelet packet analysis, which has been validated previously (Shafqat et al., 2007c). The effect of detrending the HRV signal is shown in Figures 12.3 and 12.4. Figure 12.3 shows the time domain representation, while Figure 12.4 shows the spectrum of the same signal used in Figure 12.3, before and after detrending.

The frequency domain analysis of these signals was carried out using non-parametric (Welch's periodogram) method (Shafqat et al., 2007b), parametric (autoregressive modeling) method (Shafqat et al., 2007a), continuous wavelet transform (CWT) (Shafqat et al., 2009b), SPWVD (Shafqat et al., 2009a) and empirical mode decomposition (EMD) (Shafqat et al., 2011). In order to see the effect of variable boundaries on the estimation of the HRV parameters, these quantities were also estimated using the fixed (traditional) range of the LF (0.04–0.15 Hz) and HF (0.15–0.4 Hz) bands. The results obtained in these studies showed that after the application of the local anesthetic drug, the LF:HF ratio increased initially and then decreased, reaching a minimum value. Compared to the variations observed in other parts of the data during this decrease and sometime after reaching the minimum, the variations in the ratio values were significantly low until they recovered from the minimum phase after the block. The decrease in the ratio values was observed in each case within 1 h of the application of the anesthetic block. In addition to the LF:HF ratio value, the normalized LF power decreased significantly and the normalized HF power increased significantly after the application of the anesthetic block. The statistical analysis also showed that similar results were obtained using the fixed (traditional) boundary method and the variable boundary method. The parameter values during the surgery were not included in the statistical analysis because, in this case, it might not be possible to separately identify the changes in HRV parameters due to the local anesthetic drug and changes occurring due to the surgical procedure.

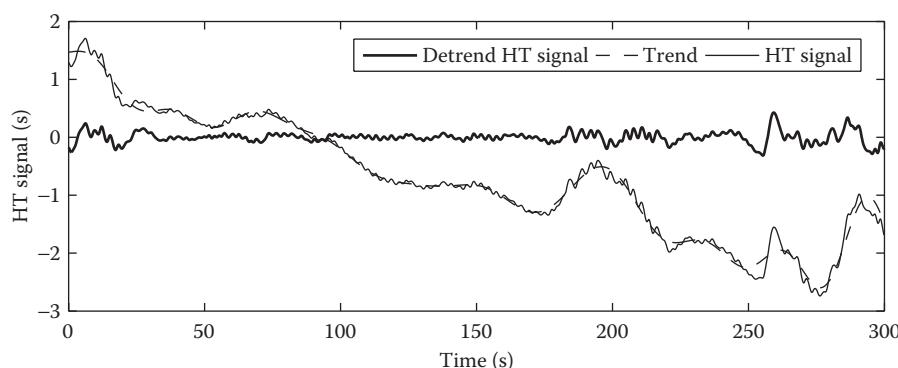
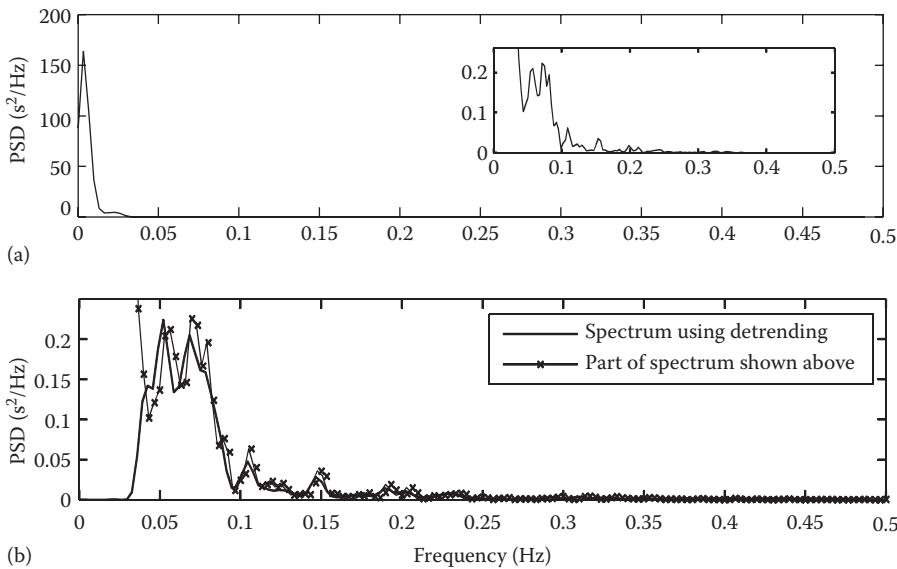


FIGURE 12.3

The result of detrending the “heart timing” signal. The original signal is shown in thin solid black line, while the detrended signal is shown in thick solid black; the thin dashed black line represents the trend that is removed from the original signal.

**FIGURE 12.4**

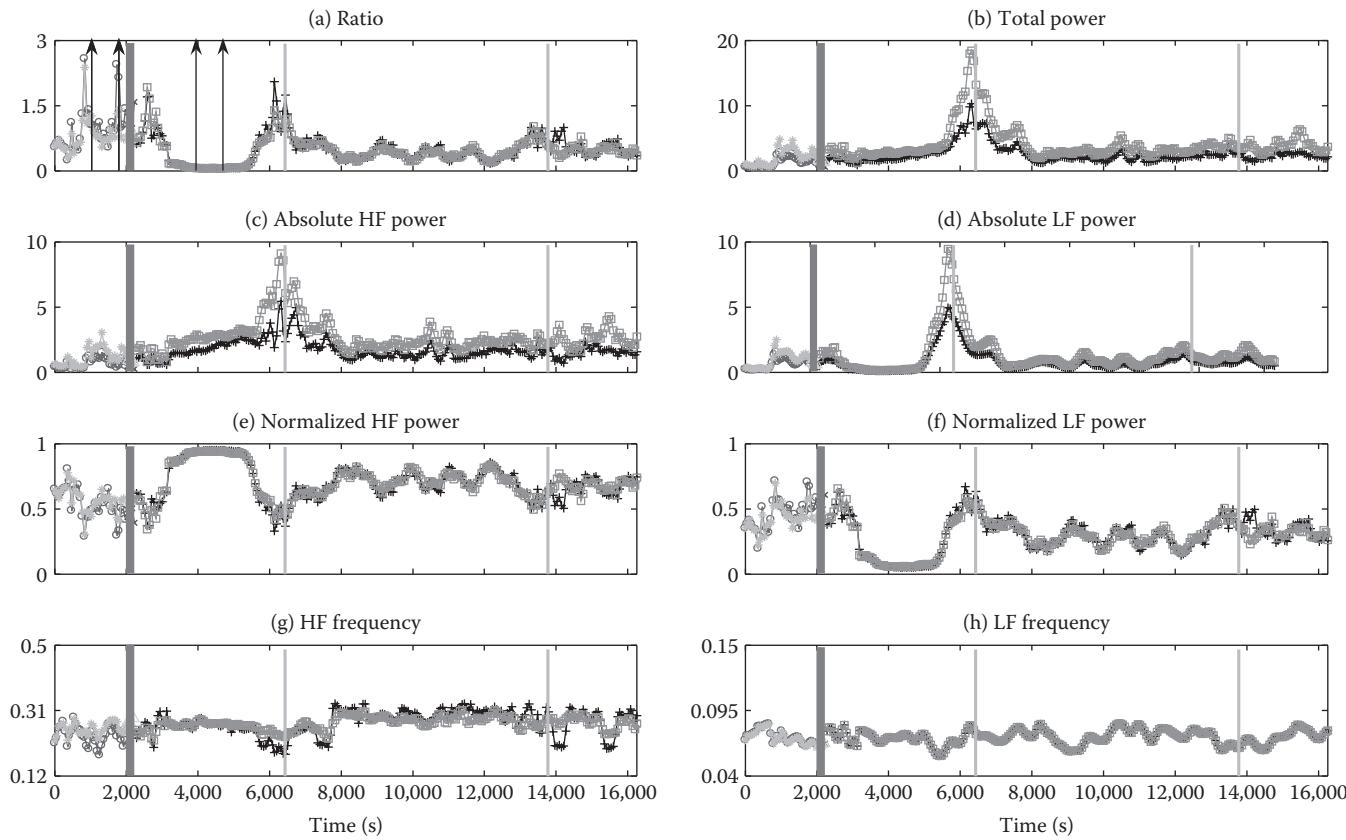
(a) The spectrum of the heart timing signal (used in Figure 12.3) after removing the linear polynomial trend; (b) the spectrum of the same signal after detrending using the wavelet packet method and part of the spectrum shown in (a) (line with cross marks).

The parameters estimated with the CWT data analysis obtained from one of the patients included in the study are presented in Figure 12.5.

Figure 12.5 shows that in most regions, similar changes are observed in the values estimated by both the fixed and the variable boundary methods. However, there are incidences (e.g., around 6000 s) where different values of parameters are obtained from two methods. In all these cases, the CF estimated from the two methods shows more difference between them as compared to other regions of the data. The use of the cross-spectrum between the HRV signal and the estimated respiration signal would allow the variable boundary method to consider the effect of the respiration signal below 0.15 Hz, which is not possible with the fixed boundary method. Due to this difference, when the respiration frequency is close or lower than 0.15 Hz, the parameter estimated from the two methods might be different.

During the analysis of the data from locally anesthetized patients, two distinguishable changes were observed in the LF:HF ratio values after the application of LA. First, the presence of adrenaline in the LA mixture was considered to be the major factor behind a transient short-lived increase in the LF:HF ratio, which was observed in almost all patients included in this study. Second, the anesthetic mixture would cause a sympathetic impairment and/or a vagal enhancement, resulting in a decrease in the LF:HF ratio.

Due to their superior capability of detecting transient changes occurring in the signals, time-frequency methods (CWT, SPWVD and EMD) managed to detect changes in LF:HF ratio values in more patients when compared to parametric and non-parametric methods. The CWT and the EMD were the most successful methods and detected changes in LF:HF ratio values in 13 out of 14 patients included in the study. The performance of the SPWVD method suffered due to the presence of interference terms, because of the bilinear nature of the distribution, which caused an error in the power estimation.

**FIGURE 12.5**

Results obtained from the CWT analysis of a patient undergoing local anesthetic procedure. In each plot, the gray vertical bar (~2000s) represents the time of block (anesthesia) application and the gray vertical lines represent start and end of the surgery. The vertical arrow pairs in part (a) show the data segment before and after the application of block which was used in statistical analysis. Each plot shows the parameter values estimated using both the fixed and the variable boundary method. The light gray lines with start (before the gray vertical bar) and square markers (after the gray vertical bar) represent parameter values before and after the block application estimated using fixed boundary method. The dark gray line with circle markers (before the gray vertical bar) and the black line with plus markers (after the gray vertical bar) represent the parameter values before and after the block application estimated using variable boundary method, respectively. The units on y-axis for the subplots (b, c and d) showing absolute power values are s^2/Hz and for the subplots (g and h) showing frequency values is Hz.

Other researchers have also reported an improved performance of the CWT method compared to the SPWVD method for detecting transient changes occurring in the signal (Faust et al., 2004; Newandee, 2003).

The analysis of the data from locally anesthetized patients showed that during a brachial plexus block using a mixture of lignocaine and bupivacaine, there is a noticeable and almost consistent change in the sympathovagal balance (the LF:HF ratio decreases), which can be detected through an appropriate and structured analysis of HRV.

12.5 Discussion and Conclusions

Due to the high success rate and the low number of serious (life-threatening) incidents that are usually associated with the application of LA, there are not many studies that have analyzed hemodynamic and cardiovascular data, including an HRV analysis, during various procedures involving LA.

The current recommendations regarding the maximum doses of local anesthetics presented in textbooks, or by pharmaceutical industries, are not always determined by randomized and controlled studies. Usually, recommendations are in the form of a total amount of the drug, which does not take into account the patient's body mass index. Also, other factors such as the physical state of the patient and the site of application have a great effect on the dosage of the anesthetic drug. Due to all these uncertainties, the maximum dosage of different anesthetic drugs varies from country to country, as shown in Table 12.3.

The technique of HRV has been applied to many research studies in the field of anesthesia, both general and local; however, so far the technique of HRV has not reached the point of acceptance as a clinical diagnostic tool, as many of the results obtained from such studies are either inconclusive or not in agreement. However, with the continuous advancement of computational and signal processing techniques, there is hope that HRV will be able to provide more robust information that will aid in the better monitoring of patients who are administered anesthetic compounds. Additionally, in order to gain a better understanding of the complex cardiovascular changes that occur due to LA, the information obtained from the linear and non-linear analyses of the HRV signals should be combined with the information obtained from other physiological signals, such as electroencephalogram (EEG) and BPV. Combining information from such physiological signals would allow for a better prediction of the future changes in a patient's cardiovascular state. This would also help in tailoring the delivery and management of anesthesia according to individual patient requirements.

Another issue that impedes more conclusive results in HRV studies during anesthesia is the lack of control in studies involving patients. As a patient's safety during anesthesia is of paramount importance, it is quite difficult to analyze the effect of anesthesia at varying levels of anesthetic dosages. Therefore, attention should be given to animal studies where parameters under study can be controlled in a more systematic manner.

Also, the current availability of extensive computational resources has caused a rapid increase in the number of signal processing techniques available for the analysis of physiological data. This makes the comparison and validation of results from different studies quite difficult. It is essential that the advanced signal processing methods be applied with care as minor changes could cause a great deal of ambiguity and could potentially render the results meaningless. For instance, Deschamps et al. (2004) have observed an increase

TABLE 12.3

Officially Recommended Highest Doses of Local Anesthetics in Finland, Germany, Japan, Sweden and the United States

	Finland	Germany	Japan	Sweden	USA
Chlorprocaine with epinephrine	—	—	—	—	800 mg
Procaine with epinephrine	—	500 mg 600 mg	1000 mg 600 mg (epidural)	—	1000 mg 500 mg
Articaine with epinephrine	7 mg/kg 7 mg/kg	4 mg/kg 4 mg/kg	—	—	—
Bupivacaine with epinephrine	175 mg (200 mg ^a) (400 mg/24 h) 175 mg	150 mg	100 mg (epidural)	150 mg	175 mg 225 mg
Levobupivacaine with epinephrine	150 mg (400 mg/24 h)	150 mg	—	150 mg	150 mg
Lidocaine with epinephrine	200 mg 500 mg	200 mg 500 mg	200 mg	200 mg	300 mg 500 mg
Mepivacaine with epinephrine	—	300 mg 500 mg	400 mg (epidural)	350 mg	400 mg 550 mg
Prilocaine with epinephrine	400 mg 600 mg	—	—	400 mg 600 mg	—
Ropivacaine with epinephrine	225 mg (300 mg ^a) (800 mg/24 h) 225 mg	No mention	200 mg (epidural) 300 mg (infiltr)	225 mg	225 mg (300 mg ^a) 225 mg (300 mg ^a)

Source: Rosenberg, P.H., Veering, B.T. and Urmey, W.F., *Region. Anesth. Pain Med.*, 29, 564–575, 2004.

^a For brachial plexus block in adults.

in the power of the HF band and a decrease in the LF:HF ratio values after the application of LA (20 mL of 0.125% bupivacaine and 50 mg of fentanyl) in patients undergoing epidural anesthesia. Deschamps et al. (2004) have used the wavelet analysis with irregularly sampled signal (tachogram) and have associated coefficients from specific wavelet decomposition levels with HF and LF bands of the HRV signal. Estimating HRV parameters this way could result in an error due to the irregular sampling of data, and there could be a significant overlap of scales (frequencies) between the levels (Milne and Lark, 2009).

Finally, researchers should make every effort to make their data sets available in open-access databases via common Internet protocols. This will allow easier comparison of results obtained from different analysis techniques and facilitate rapid development and better understanding of the effects of LA on HRV and BPV.

Abbreviations

ANS	Autonomic nervous system
ASA	American society of anesthesiologists
BP	Blood pressure

BPV	Blood pressure variability
CF	Center frequency
CVR-R	Coefficient of variation of the RR interval
CWT	Continuous wavelet transform
ECG	Electrocardiograph
EMD	Empirical mode decomposition
ETCO ₂	End-tidal carbon dioxide
HF	High frequency
HR	Heart rate
HRV	Heart rate variability
HT	Heart timing
LA	Local anesthesia
LF	Low frequency
LF:HF	Power ratio between LF band and HF band
MAP	Mean arterial pressure
SDSE	Standard deviation spectral extension
SPWVD	Smoothed-pseudo Wigner–Ville distribution
TIVA	Total intravenous anesthesia
TP	Total power
VLF	Very low frequency

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13

Effect of General Anesthesia on Heart Rate Variability

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13.1 Introduction

Many processes are involved in the modulation of heart rate variability (HRV). For example, seasonal variations are observed in the HRV of hibernating mammals and are related to central temperature variations. The nycthemeral variations are also clearly visible in humans over 24 h and are related to fluctuations in autonomous nervous system (ANS) activity. Changes in endocrine activity produce alterations in HRV over periods of several hours. Epinephrine and norepinephrine plasma level variations related to sympathetic ANS activity produce HRV alterations on the time scale of minutes, while parasympathetic tone variations, mediated by the vagus nerve that directly innervates the sinus node in the heart, produce beat-to-beat variations. Respiratory sinus arrhythmia (RSA) is the oscillation of heart rate (HR) caused by ventilation: HR increases slightly with each inspiratory cycle, due to a transient decrease in the parasympathetic tone. RSA is known to be closely related to the high-frequency (HF) spectral power of HRV (0.15–0.4 Hz), which is under parasympathetic influence only. The cyclic distension of pulmonary stretch receptors by ventilation affects the sinus node via the nuclei in the medulla oblongata of the brainstem (Figure 13.1).

The low-frequency (LF) power (0.05–0.15 Hz) of the HRV spectrum, on the other hand, is under the combined influence of sympathetic and parasympathetic tones. The ventilatory influence is usually not measured in the LF domain if the respiratory rate is higher than 0.15 Hz (9 cycles/min). A very-low-frequency (VLF) power in the frequency range of 0.005–0.05 Hz is influenced by thermoregulatory processes and vascular tone (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996) and requires ECG recordings of several minutes in order to be accurately measured.

The HF/LF ratio has been proposed as a measure of the sympathovagal balance. Methodological caveats, however, have cast a doubt on the clinical interpretation of this measure (Eckberg, 1997).

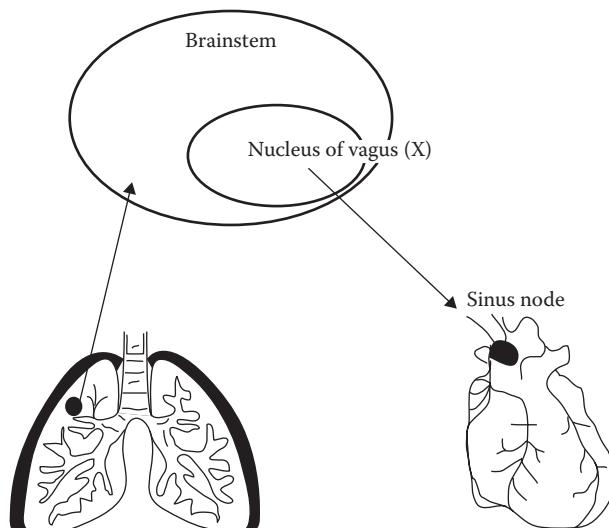


FIGURE 13.1

A schematic figure of the reflex loop between the alveolar stretch receptors and the sinus node via the brainstem.

HRV analysis has been used to characterize the sympathovagal balance during anesthesia. Most studies have essentially focused on the effects of a combination of hypnosis and analgesia or the effect of hypnosis alone and have not yielded results that are useful for clinical situations. During the last few years, we have conducted research to assess the impact of analgesia–nociception balance on HRV. Our hypothesis is that surgical nociceptive stimulation has reproducible effects on some components of HRV and that these effects would be blunted or abolished by adequate analgesia. The reliable assessment of such effects in anesthetized patients would require the following: (1) HRV is combined with an independent assessment of the hypnosis depth and (2) the HRV technique employed tracks transient and rapid changes in ANS activity. Our ultimate goal is to develop a monitor that would enable us to assess the balance between analgesia and nociception in real time using HRV derived from the ECG signal.

13.2 State of the Art: General Anesthesia and HRV Analysis

General anesthesia mainly consists of two components: hypnosis and analgesia. We shall consider the effects of hypnotic and analgesic drugs on HRV as well as those of ventilation on HRV and how HRV has been used for post-operative risk stratification.

13.2.1 RR Series Spectral Analysis

Wavelet transform, a spectral technique that is more recent than the Fourier transform, is better adapted to non-stationary signal analysis and can be used for analyzing the RR series recorded during anesthesia. An advantage of wavelets over Fourier transform is that whereas Fourier analysis cannot detect the time of a particular frequency shift, the wavelet transform shows the actual change of frequency at precisely the time when it takes place (Pichot et al., 1999). This probably constitutes the main advantage of wavelets in situations like those during anesthesia and analgesia–nociception balance monitoring when drug boluses and nociceptive stimuli result in rapid and tremendous changes in ANS sympathetic and parasympathetic tones.

13.2.2 Hypnotic Drugs and Their Effects on HRV

Hypnosis can be described in a broad sense as the loss of consciousness and the absence of recollection of events during that time. It thus provides comfort to the patient during painful surgical procedures. Various pharmacological compounds can be used for the induction and maintenance of hypnosis during general anesthesia. Such drugs are divided into two classes distinguished by the way they are administered: by inhalation (halogenated ethers) or by intravenous administration. All hypnotic drugs have been reported to have a significant effect on the ANS as measured by HRV analysis. Various hypnotic drugs, their administration methods, their typical use and their main mechanism of action are presented in Table 13.1, although the list is not exhaustive.

The main change induced by hypnotic agents on HRV consists of a decrease in the total spectral power that begins with the onset of induction and persists throughout anesthesia. When the patient is aroused following anesthesia, an abrupt shift toward an increased LF power is usually observed, while the full recovery of other autonomic

TABLE 13.1

Typical Hypnotic Drugs Used during General Anesthesia

Hypnotic Drug	Administration	Typical Use	Category
Sevoflurane	Inhalation	Ind and maintenance	Halogenated ether
Desflurane	Inhalation	Maintenance	Halogenated ether
Isoflurane	Inhalation	Maintenance	Halogenated ether
Thiopental	IV	Ind	GABA _A R modulator
Propofol	IV	Ind and maintenance	GABA _A R modulator and Na channel blocker
Etomidate	IV	Ind	GABA _A R modulator
Ketamine	IV	Ind and co-analgesic	NMDA R antagonist
Midazolam	IV	Co-induction	Benzodiazepine

Notes: IV, intravenous; Ind, induction; R, receptor; GABA, γ -aminobutyric acid; NMDA, N-methyl-D-aspartic acid.

functions takes more time, for example, the baroreflex control of HR (Widmark et al., 1998; Nagasaki et al., 2001). Changes of individual components of the power spectrum are dependent on the drug used. Most hypnotic drugs decrease sympathetic activity (as measured by LF power), while their effects on parasympathetic activity (HF power) are variable. The inhaled anesthetics isoflurane, sevoflurane and desflurane inhibit sympathetic activity, but their rapid increase induces, especially in healthy children, an increase in HR by stimulating vascular nervous sympathetic activity and inhibiting cardiac parasympathetic activity (Constant et al., 1999; Kato et al., 1992; Picker et al., 2001; Widmark et al., 1998; Wodey et al., 2003). Barbiturates decrease both the LF and HF powers (Scheffer et al., 1993), while propofol decreases parasympathetic tone to a lesser degree than sympathetic tone, making it more likely for noxious stimuli to be followed by a predominantly parasympathetic reaction of the ANS, which could explain the increased risk for bradycardia during propofol anesthesia (Deutschman et al., 1994; Ebert et al., 1992; Win et al., 2005). Ketamine increases sympathetic activity, as shown by an increase in the LF/HF ratio (Komatsu et al., 1995), and according to Scheffer et al. (1993), etomidate does not change the LF power or the HF power, making these drugs a good choice for patients with hemodynamic impairment. It is hypothesized that the effects of hypnotic agents on ANS activity are due to a combination of inhibition of the baroreflex and lowered consciousness (Latson et al., 1992).

13.2.3 Opioids, Nociception and Their Effects on HRV

Opioids, the most common analgesic drugs used for general anesthesia, are generally administered intravenously, but they can also be administered through the spinal route or through an epidural catheter. The different opioid drugs differ mainly in their duration of action, as measured by their elimination half-time and by their relative potency compared to that of morphine. Other analgesic drugs, called co-analgesics, can also be administered simultaneously with opioids in order to minimize the total amount of opioids used and, therefore, the opioids' side effects. The main opioids and co-analgesics employed during surgery are presented in Table 13.2, along with their elimination half-time, typical use and principal mechanism of action.

Opioids inhibit sympathetic activity but preserve and/or enhance parasympathetic activity (Komatsu et al., 1992; Latson et al., 1992; Zickmann et al., 1996). Among opioids,

TABLE 13.2

Typical Analgesic and Co-Analgesic Drugs Used during General Anesthesia

Analgesic Drug	Administration	Elimination	Typical Use	Category
		Half-Time (h) (Barash et al., 1997)		
Fentanyl	IV	3.1–6.6	Ind and maintenance	Opioid— μ agonist
Sufentanil	IV	2.2–4.6	Ind and maintenance	Opioid— μ agonist
Alfentanil	IV	1.4–1.5	Ind and maintenance	Opioid— μ agonist
Remifentanil	IV	0.17–0.33	Ind and maintenance	Opioid— μ agonist
Clonidine	IV; local	10–20	Co-analgesic	α 2 R agonist
Ketamine	IV	2–4	Ind and co-analgesic	NMDA R inhibitor

Notes: IV, intravenous; Ind, induction; R, receptor; NMDA, *N*-methyl-D-aspartic acid.

remifentanil is known for its strong bradycardiac effect, which can be explained partially by its parasympathomimetic action (Fattorini et al., 2003; Tirel et al., 2005). Latson and O'Flaherty (1993) have shown that surgically induced nociception (activation of pain receptors) increases the total spectral power under propofol anesthesia, but not under isoflurane anesthesia. Propofol and sevoflurane, used in conjunction with remifentanil, have different effects on ANS during nociception, as shown by Ledowski et al. (2005): in both cases, a slight increase in HF and a decrease in LF indicate a shift toward a predominantly parasympathetic tone, but total power is higher during propofol anesthesia than during sevoflurane anesthesia. The level of plasma stress hormones during surgery (catecholamines, adrenocorticotrophic hormone [ACTH] and cortisol) is higher with sevoflurane anesthesia than with propofol anesthesia (Ledowski et al., 2005). These results could be interpreted as a lesser impact of nociception on ANS and on hormonal stress response during propofol anesthesia than during sevoflurane anesthesia.

Typically, epidural or spinal anesthetics are not required during general anesthesia, but they have been shown to be useful adjuncts in order to prevent nociception during general anesthesia and pain during the post-operative period (Duman et al., 2010; Frassanito et al., 2010). Effects of spinal and epidural anesthetics on the ANS are complex and interrelated. Many authors have shown that spinal anesthesia induces a decrease in LF power, an increase in HF power and a decrease in LF/HF ratio, which has been interpreted as a decrease in the sympathetic activity and an increase in the parasympathetic activity (Kawamoto et al., 1993). However, other studies have not found any effect of spinal anesthesia on sympathovagal balance (Cook et al., 1990; Gratadour et al., 1997; Intronà et al., 1995), and some have even shown an increased sympathetic activity during epidural anesthesia (Fleisher et al., 1994). Fujiwara et al. (2009) have explored the effect of intrathecal opioids and found that intrathecal but not intravenous fentanyl prevented a decrease in the LF/HF ratio. Despite these discrepancies between studies, effect of opioids on ANS tends to be an increase in the relative amount of HF power, that is, the parasympathetic activity, and is modulated by the administration of hypnotics.

13.2.4 Frequent Side Effects during General Anesthesia

In the course of general anesthesia, bradycardia and hypotension are the frequent side effects of drugs given for anesthesia. Surgery in an anesthetized patient can result in hypothermia and blood loss, which lead to an impaired hemodynamic status (low blood

pressure). Therefore, general anesthesia is not only performed using hypnotic and analgesic drugs but is also often accompanied by the administration of anticholinergic drugs and catecholamines along with fluid replacement in order to maintain HR and blood pressure.

HRV has been shown to be able to predict hypotension: several studies suggest that a high LF/HF ratio before spinal anesthesia for caesarean surgery is predictive of induced hypotension (Hanss et al., 2005, 2006a,b). Dysautonomia from diabetic or non-diabetic causes, when associated with pre-operative ANS reflex dysfunction, has been shown to be associated with hemodynamic impairment during general anesthesia (Burgos et al., 1989; Latson et al., 1994). A likely explanation for these increased side effects is that ANS dysfunction further inhibits the compensation for the effects of anesthetic drugs on venous return, vascular tone and myocardial contractility, which in turn make bradycardia and/or hypotension more pervasive. HRV analysis can also help us understand the reaction of ANS in cases of blood loss. A decrease in the HF power has been shown to be related to the amount of blood loss in human subjects (Cooke et al., 2008) and animal models (Batchinsky et al., 2007; Porter et al., 2009). Despite growing evidence, a comprehensive monitoring device that could display the ANS status in a simple way has not yet been developed for use in the operating room.

13.2.5 Ventilation and Its Effects on HRV

The role of ventilation during general anesthesia must be emphasized, as it plays a major role in the way the ANS function should be interpreted using HRV analysis (Brown et al., 1993; Schipke et al., 1999). All anesthetic drugs interfere with spontaneous ventilation, leading to bradypnea and apnea, as the administered dose of the drugs increases. For major surgery, the upper airway is secured for ventilation maintenance by an artificial ventilator. Kobayashi (1998) showed that RSA in healthy volunteers was correlated with tidal volume. In conscious volunteers, the arterial CO₂ partial pressure (PaCO₂), which is one of the strongest drivers of the ventilation center in the brainstem, has been shown to influence both LF and HF spectral powers, but not during isoflurane anesthesia. In addition, the respiratory rate has a major influence on the HF power spectrum, in both conscious and anesthetized patients: a reduction of respiratory rate induces a shift of power spectrum toward the LF in both conscious and unconscious patients (Poyhonen et al., 2004).

Anrep et al. (1936a,b) addressed the debate regarding the origin of the ventilation-related fluctuations of RR intervals by showing that RSA was modulated by influences of central and peripheral origins (Anrep et al., 1936a,b). In patients undergoing thoracotomy, during which surgery can only proceed when the lung is deflated, Sato et al. (2000) showed that values of both log(HF) and log(LF) increased simultaneously during ventilation of one lung alone, so that log(HF/LF) did not change. They concluded that there was no overall effect of one lung ventilation on the cardiac ANS (Sato et al., 2000).

Koh et al. (1998) reported that the HF power decreased after the induction of anesthesia and that it decreased further during jet ventilation, thus highlighting the relatively minor role of thoracic stretch receptors in the resultant RSA amplitude. Similar findings were made by Shykoff et al. (1991) in anesthetized dogs. In summary, while the origin of RSA is peripheral or central is still being debated, there is enough evidence to state that it is parasympathetically mediated with a central influence, as suggested by the persistence of HF spectral power in the RR interval series during apnea.

13.2.6 Post-Operative Risk Stratification

Several studies point to a strong relationship between diminished HRV and death related to heart disease (Jouven et al., 2005; Schwartz, 1998; Schwartz et al. 1992). HRV measurements seem to predict an adverse outcome more accurately than any other measure, such as echocardiographic findings. One in three post-operative complications and more than one in two post-operative deaths are related to cardiac complications (Devereaux et al., 2005). Preliminary results seem to indicate that low HRV in surgical patients is related to adverse cardiovascular events and long-term cardiac morbidity and mortality (Laitio et al., 2007).

13.2.7 Interpretational Caveats and Limitations of Computing HRV-Related Indices

General anesthesia employs pharmacological agents that have a significant effect on systems that influence HRV, including consciousness and the ANS. Surgically induced nociception, blood loss and hypothermia also alter the balance between sympathetic and parasympathetic systems. Furthermore, the depth of anesthesia (the plasma concentration of anesthetic agents) and circulating blood volume are not fixed but change minute by minute. Therefore, the interpretation of HRV recorded during surgery is difficult. In such a situation, each method of signal processing has a limitation. In this context, one must note that parametric models require stable conditions in order for such models to predict the ANS status. Non-linear techniques require several minutes' recording to correctly assess the HRV, while the VLF spectral measurements require at least 5 min of ECG recording with a stable HR in order to provide a reliable measurement. Only a short-term power spectral analysis can be performed to compute stable estimates of LF and HF powers, for recording lengths of at least 60 s. Nevertheless, a stable HR remains a prerequisite for Fourier transform, and even if wavelet transform can be applied to a non-stationary RR signal, the power spectral measurements made during a transition phase of rapidly changing HR must be interpreted with caution because of stationarity issues.

Another limitation of HRV analysis during general anesthesia occurs when anticholinergic drugs are used, for example, in order to treat acute bradycardia. The parasympathetic blocking effect of these drugs on the sinus node will result in sinus tachycardia. Tachycardia by itself does not impair HRV measurements, but as shown by Montano et al. (1998), anticholinergic agents blocking cholinergic receptors (and therefore the vagus nerve influence over the sinus node) do annihilate the vagus-mediated modulation of HR. We believe that HRV measurements are not useful in evaluating the effects of anticholinergic drugs when they are used at a dose that generates tachycardia. Lower doses of anticholinergic drugs, however, have been shown to enhance vagal modulation of the heart (Ikuta et al., 1995; Montano et al., 1998).

13.3 From Spectral Analysis to Analgesia–Nociception Balance Monitoring

13.3.1 Introduction

The main changes in HRV during anesthesia consist of attenuation of the total power with a shift toward HF predominance (Galletly et al., 1992, 1994; Howell et al., 1995; Huang

et al., 1997; Kato et al., 1992; Pichot et al., 2001; Pomfrett et al., 1993, 1994; Win et al., 2005). Upon arousal, an abrupt shift toward the LF power is generally observed, but a full recovery to pre-operative status takes several hours, depending on the dosage and the type of anesthetic used. Despite results from various laboratories, which have been in agreement, attempts to derive clinically useful information about the depth of anesthesia from HRV have so far remained inconclusive and HRV was viewed until recently, as being able to discriminate between awake and anesthetized patients at best (Luginbühl et al., 2007; Pichot et al., 2001; Win et al., 2005). This is because only limited data are available on the effects of analgesia–nociception balance on HRV (Latson and O’Flaherty, 1993; Luginbühl et al., 2007). It is highly desirable that some quantitative measure of HRV during anesthesia that could provide information about the adequacy of analgesia in anesthetized patients be developed.

In this section, we describe studies that we conducted at the University Hospital of Lille (France) to test the hypothesis that anesthetic agents have reproducible effects on HRV.

13.3.2 Methods

13.3.2.1 Patients and Anesthetic Protocol

We conducted a study (Jeanne et al., 2009a) that was designed to analyze HRV in patients with stable hypnosis, before and during nociceptive surgical stimulation, in the presence of deep (adequate) and light (inadequate) analgesia provided by various opioids. The power spectral measurements of HRV were made using the wavelet transform technique. Adult patients ($n = 49$) with no ANS-related disease or medication scheduled to undergo general anesthesia for three different types of surgery were studied. All patients underwent the same anesthetic protocol except for the opioid used: sufentanil (Group 1, $n = 19$), alfentanil (Group 2, $n = 18$) or remifentanil (Group 3, $n = 12$) (Figure 13.2). The opioids in Groups 1 and 2 were administered as intravenous boluses, whereas remifentanil in Group 3 was administered continuously using an electric syringe. After induction of anesthesia and tracheal intubation, additional opioid was administered if changes in hemodynamic status or clinical arousal signs were observed, such as a greater than 20% increase in HR or systolic blood pressure (SBP), cough or movement. The ventilation rate was fixed at 10 cycles/min during the whole anesthetic procedure.

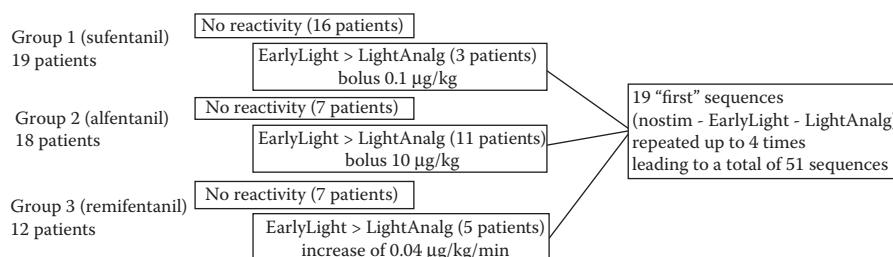


FIGURE 13.2

A flowchart of Groups 1, 2 and 3. Thirty patients remained in deep analgesia (no reactivity) for the entire duration of the surgery. The remaining 19 patients presented with hemodynamic reactivity and required additional opioids. The 10 min period before hemodynamic reactivity was called early light analgesia (10–5 min before reactivity) or light analgesia (5–0 min before reactivity).

13.3.2.2 Monitoring of HRV Analysis

The depth of hypnosis was monitored by the Bispectral index (BIS), which is a widely accepted measure of unconsciousness (Pundjasawadong et al., 2007). A uniformly constant hypnosis was maintained in the recommended 40–60 range by adjusting the propofol target concentration using a TCI-Diprifusor (Zeneca Ltd., Macclesfield, Cheshire, UK), whose inbuilt pK/pD model enables the anesthesiologist to administer propofol so as to maintain its concentration in the brain tissue constant (Swinhoe et al., 1998; Servin, 1998). The ECG was recorded on a microcomputer throughout the periods of anesthesia for off-line analysis. The R waves were detected from the ECG recordings, and power spectral measurements were made using a wavelet transform of the RR series over 256 s, which allows a precise assessment of the rapid changes in ANS activity (Mallat, 1998; Pichot et al., 1999). The power in the LF (wavelet power of levels 6 and 7, corresponding to mid-frequencies of 0.04 and 0.08 Hz) and the HF (wavelet power of levels 4 and 5, corresponding to mid-frequencies of 0.16 and 0.32 Hz) bands in both absolute and normalized units along with the total power were estimated. The normalized HF (HFnu) and LF (LFnu) power spectra were obtained as $\text{HFnu} = \text{HF}/(\text{HF} + \text{LF})$ and $\text{LFnu} = \text{LF}/(\text{HF} + \text{LF})$.

13.3.2.3 Pre-Defined Measurement Periods

HRV measurements were made for pre-defined measuring windows (MWs) where analgesia was defined (post hoc) as “adequate”—consisting of “noStim,” the period before the start of the surgical procedures, and “DeepAnalg,” the period during surgery when no additional bolus of opioid was needed for the following 30 min—or “inadequate”—consisting of “EarlyLightAnalg” and “LightAnalg” periods when deepening of analgesia was needed within the next 10 min. More specifically, the LightAnalg characterized the HRV within the 5 min immediately preceding the additional opioid injection and the EarlyLightAnalg characterized HRV within the 6–10 min preceding the additional opioid injection.

13.3.3 Results

A. HRV measurement comparisons between periods with no nociceptive stimuli (noStim) and periods with nociception inhibited by deep analgesia (DeepAnalg)

Forty-nine patients were included in the study. At the beginning of surgery, 37 patients presented with adequate analgesia (defined by the absence of reactivity during 30 min following measurement), which allowed us to measure 53 DeepAnalg MWs (1–3 per patient) and to compare them with the corresponding noStim MWs before the start of surgery. The results of the HF and LF power spectra are presented as median (interquartile range) seconds squared. The normalized measurements are expressed as percentages (%).

The comparisons between the DeepAnalg MW and the corresponding noStim MW showed the stability of the HRV spectral measurements in these conditions of adequate analgesia before and during surgical nociception: total power (TOT) did not vary significantly from 0.20 (0.63) to 0.27 (0.75) s^2 , the HF remained constant from 0.13 (0.31) to 0.13 (0.39) s^2 and the LF also remained constant from 0.09 (0.25) to 0.11 (0.26) s^2 . These results show that the ANS did not react to the start of surgical nociception during conditions of adequate analgesia.

TABLE 13.3

Heart Rate and Spectral Measurements in 51 Sequences during Anesthesia and Hemodynamic Reactivity

(n = 51)	NoStim	EarlyLightAnalg	LightAnalg	p
HR (bpm)	65 (58–70)	67 (57–74)	71 (65–75)***,****	<.0001
TOT (s ²)	0.30 (0.12–0.40)	0.19 (0.07–0.39)*	0.14 (0.08–0.41)*	.004
HF (s ²)	0.13 (0.05–0.28)	0.08 (0.03–0.24)*	0.06 (0.03–0.19)**	<.001
LF (s ²)	0.11 (0.05–0.18)	0.08 (0.05–0.13)	0.08 (0.05–0.21)	NS
HFnu (%)	64 (40–73)	50 (37–65)**	43 (29–49)**,***	<.0001
LFnu (%)	36 (27–60)	50 (35–63)**	57 (51–71)***,****	<.0001
BIS	40 (36–45)	44 (40–52)	50 (43–58)***,****	<.0001

Source: Jeanne, M., Logier, R., De Jonckheere, J., Tavernier, B., *Auton. Neurosci.*, 147, 91–96, 2009a. With permission.

Note: ANOVA + Fisher's PLSD post-hoc test.

* p < .05 versus NoStim; ** p < .01 versus NoStim; *** p < .05 versus EarlyLightAnalg.

**** p < 0.01 versus EarlyLightAnalg

Values are median (25%–75% interquartile range).

B. HRV measurements during EarlyLightAnalg and LightAnalg periods

Nineteen patients presented at least one episode of hemodynamic reactivity while thirty did not. Additional opioid administration was needed at least once for 19 patients, and a total of 51 sequences (1–4 per patient) of EarlyLightAnalg and LightAnalg MWs were recorded (Figure 13.2). In accordance with our definition of hemodynamic reactivity, the measurements during various periods of reactivity showed significantly increased HR and SBP. We also found that during the LightAnalg MW, there was an overall reduction in total power (HF + LF) and HF power without any changes in the LF power. The HFnu decreased significantly, which was interpreted as a decreased parasympathetic activity during these periods of hemodynamic reactivity. Moreover, HRV measurements at EarlyLightAnalg showed that changes in HF and HFnu powers occurred earlier than changes in HR (Table 13.3, from Jeanne et al. [2009a]). The LFnu increased in the same proportion as the HFnu decreased by a simple “mirror” effect. Given that the parasympathetic activity is the only influence on the HF spectral power, these results suggest that there is an early decrease in the parasympathetic activity before an increase in sympathetic modulation of the sinus node becomes apparent, which accounts then for the increased HR and SBP.

The fact that hypnosis was maintained at a constant level during anesthesia probably played an important role in the early decrease of HFnu before hemodynamic reactivity occurred: the well-described attenuation of ANS activity induced by propofol anesthesia could dampen ANS reactions to nociceptive stimulations when used at high doses, which would make hemodynamic reactivity less probable than with lower doses of propofol. Other factors that may have contributed to the reproducibility of HFnu decrease were the constant respiratory rate and the tidal volume, as their influence on HRV analysis has been shown to play a central role in the HF spectral power (Poyhonen et al., 2004) (see Section 13.2.5).

13.3.4 Area Measurements of the RR Series

The results obtained using the power spectral analysis of HRV during general anesthesia lead us to believe that HRV analysis, and more specifically its HF component, is related to

the analgesia–nociception balance in propofol–opioid anesthetized patients, provided that hypnosis and ventilation are maintained at a constant level or rate. Our results provide a basis for the development of an index that may help determine the adequacy of analgesia during general anesthesia. Since RSA is related to the parasympathetic tone and the HF spectral power, we developed an algorithm designed to quantify the magnitude of the respiratory pattern (i.e., the RSA) of selected RR series via an area measurement (Jeanne et al., 2009b; Logier et al., 2010).

13.3.4.1 An Algorithm for Quantifying RSA

The mean of the RR intervals is subtracted and the RR series is resampled at 8 Hz. The normalized RR series is obtained using the vectorial norm S of the mean-centered RR series:

$$S = \sqrt{\sum_{i=1}^N (\text{RR}_i)^2}.$$

The RR series, considered a vector, is divided by S , thus leading to the normalized RR series, which is then band pass filtered between 0.15 and 0.50 Hz using the “Daubechies 4” wavelet transform, which yields an RR_{HF} series, containing only the RSA content.

When parasympathetic tone is present, each respiratory cycle influences the RR_{HF} series, causing a brief decrease in the heart period (Figure 13.3, upper panel). In the case of parasympathetic withdrawal, the influence of respiratory cycles is diminished, leading to a decrease in the area generated by ventilation in the RR_{HF} series (Figure 13.3, lower panel).

The area generated by ventilation is measured as shown in Figure 13.3: local minima and maxima are detected, thus defining the lower and the upper “envelopes.” The area between them is measured as four subareas (A1, A2, A3 and A4) in each of the four 16 s subwindows.

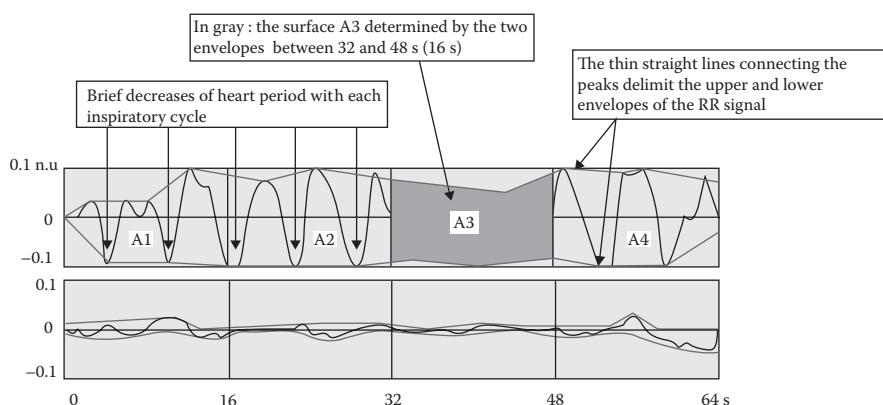


FIGURE 13.3

RR_{HF} series in two different states of analgesia–nociception balance during general anesthesia. A1, A2, A3 and A4 are the four areas generated by ventilation in the RR_{HF} series. *Upper*: Adequate analgesia. *Lower*: Decreased A1, A2, A3 and A4 surfaces in case of light analgesia leading to hemodynamic reactivity.

AUCmin (minimal area under curve) and EnvTot (total envelope surface) are defined as follows:

AUCmin is the smallest of A1, A2, A3 and A4.

EnvTot is the sum of A1, A2, A3 and A4.

In adult patients under general anesthesia, we observed that the amplitude of the normalized RR_{HF} series never exceeded 0.2 normalized units (nu). Assuming this to be true for all such patients gives a maximum possible area of the RR_{HF} series of $0.2 \text{ nu} \times 64 \text{ (s)} = 12.8 \text{ (s)}$. One can then quantify the size of the ventilation-generated area as a percentage:

$$100 \times \text{EnvTot}/12.8 \quad (13.1)$$

13.3.5 Simulated RR Series

We used computer-generated RR series to simulate the effect of varied respiratory rates and patterns on spectral and graphical measurements. The HRV power spectral analysis obtained from the wavelet transform was used as a gold standard.

Using the ECG recorded from a patient during surgery under general anesthesia with controlled ventilation, we reproduced one typical ventilatory pattern (Figure 13.4, upper and middle panels) in order to generate several RR series simulating the respiratory rates of 8, 10, 12 and 15 cycles/min (Figure 13.4, lower panel) and three ventilatory pattern amplitudes ($\times 1$: original amplitude; $\times 2$: double; $\times 3$: triple).

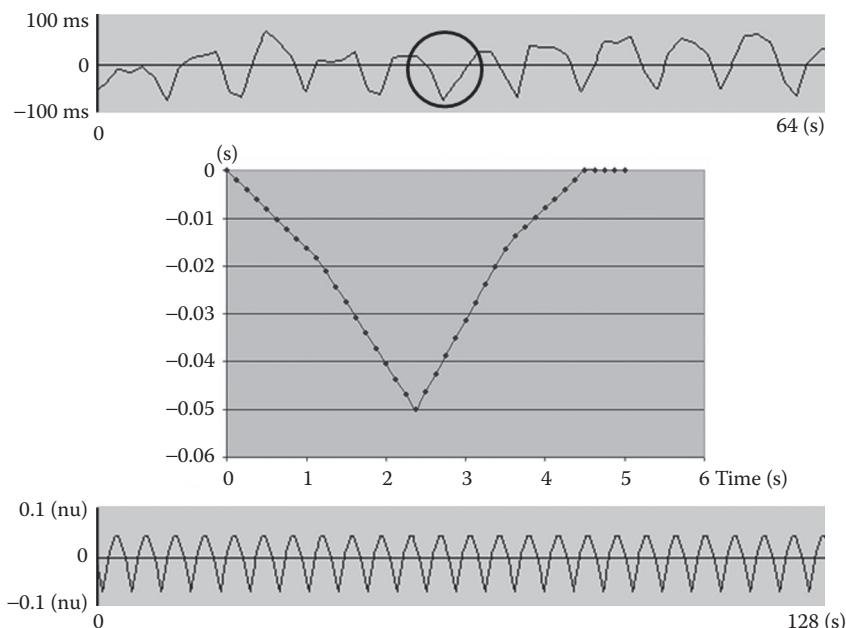
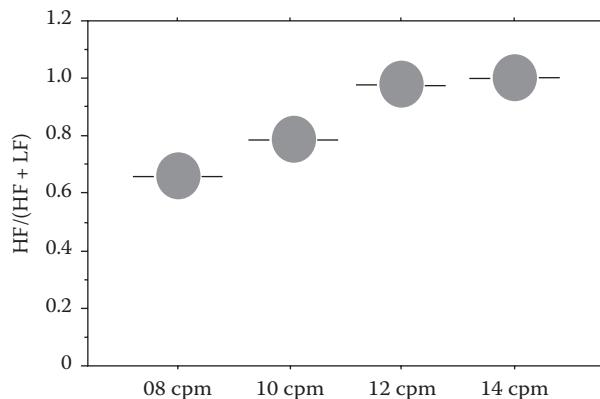


FIGURE 13.4

Upper: Real case RR series during general anesthesia—respiratory pattern is clearly visible. *Middle:* The extraction of one respiratory panel. *Lower:* An example of a simulated RR series by reproducing the same respiratory pattern for a pre-defined respiratory rate; in this case, 12 cycles/min. (From Jeanne, M., Logier, R., De Jonckheere, J. and Tavernier, B., *Conf. Proc. IEEE Eng. Med. Biol. Soc.* 2009, 1840–1843 © 2009b IEEE.)

**FIGURE 13.5**

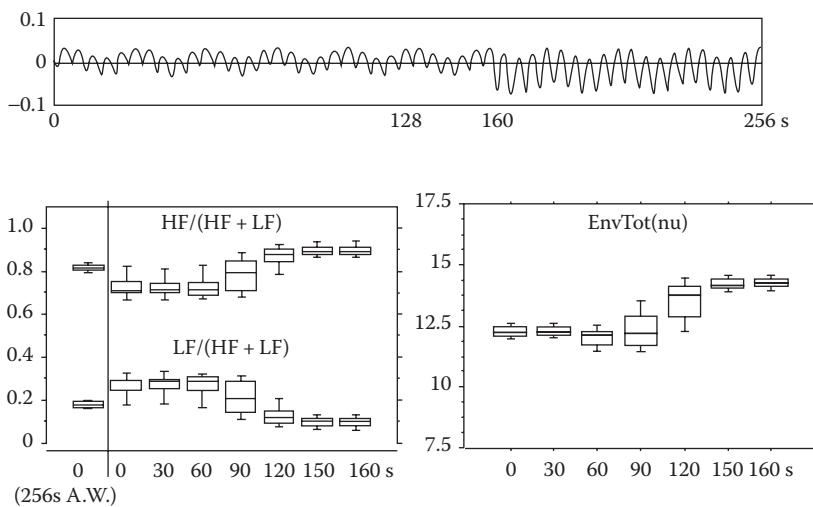
HF/(HF + LF) results in a simulated RR series with respiratory rates of 8, 10, 12 and 15 cycles/min. (From Jeanne, M., Logier, R., De Jonckheere, J. and Tavernier, B., *Conf. Proc. IEEE Eng. Med. Biol. Soc.* 2009, 1840–1843 © 2009b IEEE.)

The absolute (HF, LF) and relative (HFnu, LFnu) spectral powers and the graphic measurements (EnvTot, EnvTot[nu]) were measured over 316 s, using a 256 s analyzing window with a 2 s step. The HF power was decreased, and LF power was not null when the respiratory rate was set at 8 or 10 cycles/min (corresponding to the frequencies of 0.13 and 0.17 Hz, respectively), as compared with rates higher than 10 cycles/min (Figure 13.5), although no LF component was added to these simulated RR series. This indicates that wavelet spectral HF measurements are underevaluated when the respiratory rate is less than 12 cycles/min. By contrast, the EnvTot measurements, absolute and normalized, were not altered by changes in the respiratory rate.

Finally, in order to evaluate the impact of window length (60 vs. 256 s) on the ability of spectral and graphical measurements to detect an abrupt change in the ventilatory pattern amplitude, we designed a 320 s simulated RR series (Figure 13.6, upper panel) where the respiratory pattern amplitude doubled after 160 s. As shown in Figure 13.6 (lower panel), the analyzing window of 60 s allowed quasi-instantaneous detection of the HRV change via HF or EnvTot (either absolute or normalized), whereas a conventional 256 s window provided only a global measurement of power spectra and graphical measurements and showed almost no change in its parameters.

13.3.6 Clinical Validation of Graphical Measurements

Graphical measurements were made on the ECG recordings and during the pre-defined MWs for spectral measurements in 19 of 49 patients described in Section 13.3.3, which displayed hemodynamic reactivity and provided EarlyLightAnalg and LightAnalg sequences (see Section 13.3.3). An additional MW was analyzed in the 5 min following opioid administration, called “DpngAnalg” for “deepening analgesia.” An ANOVA followed by Fisher’s PLSD post-hoc test was used, with the statistical significance set at $p < .05$. The results presented in Table 13.4 show that the graphical measurements EnvTot(nu) and AUCmin(nu) followed the same variations as the normalized HF power. There was a statistically significant decrease from noStim to EarlyLightAnalg, followed by a further decrease to LightAnalg. After additional opioid administration (DpngAnalg), the graphical measurements EnvTot(nu) and AUCmin(nu) increased significantly when compared to LightAnalg, while hemodynamic

**FIGURE 13.6**

Upper: A simulated RR series using a respiratory rate of 12 cycles/min and an LF content at 0.04 Hz. The magnitude of the respiratory pattern is doubled after 160 s, while the LF is unchanged. *Lower:* HFnu, LFnu and EnvTot(nu) at 0, 30, 60, 90, 120, 150 and 160 s. Analyzing window (A.W.) of 64 s for all measures except the first left one, measured over 256 s (reference). Box plots: median and interquartiles; whiskers: 10th and 90th percentiles.

reactivity (HR and SBP) decreased. Interestingly, HF/(HF + LF) did not change significantly after opioid administration.

These results strongly suggest that the behavior of EnvTot(nu) is similar to that of AUCmin(nu), with a higher sensitivity to opioid addition than the ratio of the power in HF band. Figure 13.7 shows each recording before and after hemodynamic reactivity.

The close relationship between graphical measurements and spectral measurements clearly appears as a strong correlation between EnvTot(nu) and HF/(HF + LF) ($r^2 = 0.86$; Figure 13.8). Furthermore, EnvTot(nu) is also strongly correlated with AUCmin(nu) ($r^2 = 0.87$). Multiple regression findings show that EnvTot(nu) can be predicted by AUCmin(nu) with the following formula:

$$\text{EnvTot(nu)} = 5.1 \times \text{AUCmin(nu)} + 1.2 \quad (13.2)$$

TABLE 13.4

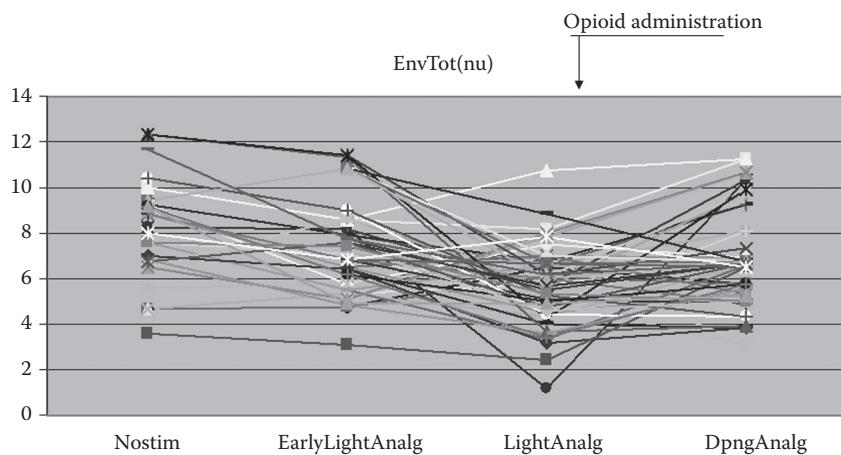
Hemodynamic, BIS and HRV Measurements in 19/49 Patients Presenting with "EarlyLightAnalg-LightAnalg-DpngAnalg" Sequences

	NoStim	EarlyLightAnalg	LightAnalg	DpngAnalg
HR	65 (58–70)	67 (57–74)	71 (65–75)***	67 (59–70)
BIS	40 (36–45)	44 (40–52)	50 (43–58)***	44 (40–51)*
HF/(HF+LF)	64 (40–73)	50 (37–65)*	43 (29–49)****	43 (33–54)***
EnvTot(nu)	8.23 (6.73–9.41)	6.98 (5.71–8.57)*	5.72 (4.54–6.69)***	6.60 (5.30–8.08)**
AUCmin(nu)	1.09 (0.96–1.59)	1.09 (0.84–1.31)*	0.85 (0.68–0.98)***	1.02 (0.80–1.28)**

Notes: Measures presented as median (25%–75% quartiles). HR, heart rate; SBP, systolic blood pressure; BIS, bispectral index; HF, normalized spectral content; EnvTot(nu); AUCmin(nu).

ANOVA followed by Fisher's PLSD post-hoc test.

* $p < .05$ versus NoStim; ** $p < .01$ versus NoStim; *** $p < .05$ versus EarlyLightAnalg; **** $p < .01$ versus EarlyLightAnalg.

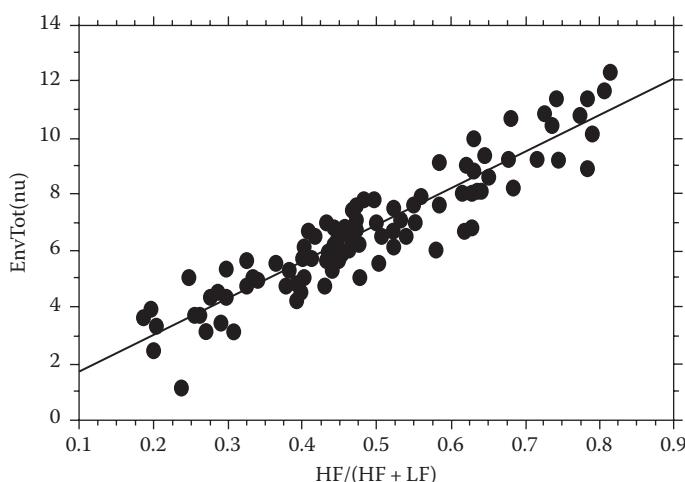
**FIGURE 13.7**

Individual sequences ($n = 51$) of EnvTot(nu) (y-axis) during anesthesia at specific MWs before and after the hemodynamic reactivity: EarlyLightAnalg, LightAnalg and DpngAnalg.

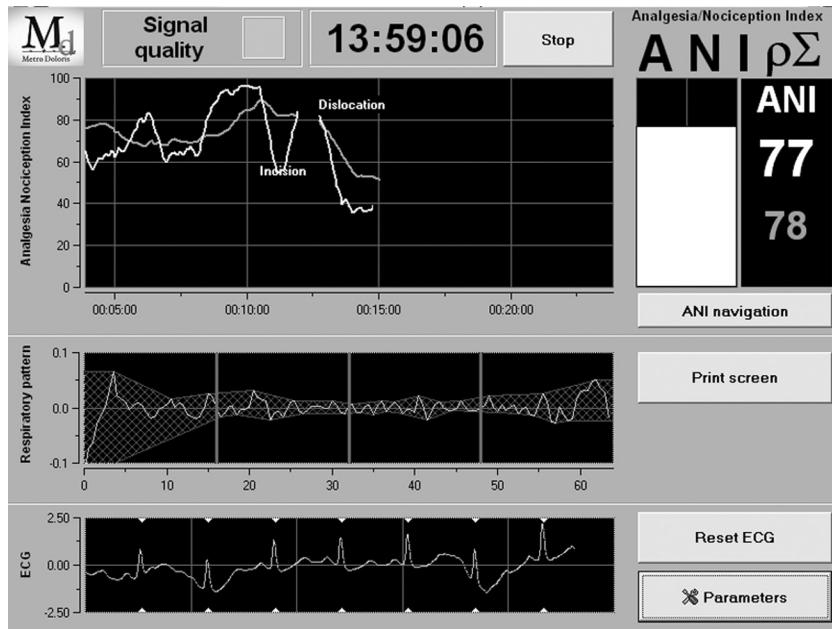
These findings have led our group to conclude that one can develop a monitor to assess the balance between analgesia and nociception in real time using only the ECG signal (Figure 13.9). The analgesia nociception index (ANI) is measured according to the formulas given in Equations 13.1 and 13.2 as follows:

$$\text{ANI} = 100 \times [5.1 \times \text{AUCmin(nu)} + 1.2] / 12.8. \quad (13.3)$$

The ANI measure is averaged over 120 and 240 s and displayed in the trend window where events can also be displayed. We believe that the ANI monitor is useful for

**FIGURE 13.8**

A bivariate plot between EnvTot(nu) and HF/(HF + LF). (From Jeanne, M., Logier, R., De Jonckheere, J. and Tavernier, B., *Conf. Proc. IEEE Eng. Med. Biol. Soc.* 2009, 1840–1843 © 2009b IEEE.)

**FIGURE 13.9**

A display screen of the ANI monitor (MetroDoloris, Lille, France).

anticipating hemodynamic reactivity during general anesthesia (Logier et al., 2010). Its potential benefit for patients is currently being investigated in several clinical trials at our University Hospital and other medical centers.

13.4 Discussion and Suggestions for Future Research

13.4.1 Discussion

During anesthesia and surgery, significant changes in ANS tone lead to variations in HR and blood pressure, which anesthesiologists use as markers to control the levels of hypnosis and analgesia. A change in body temperature and blood loss are also important events that require monitoring and have ANS effects. Numerous authors have tried to find a relationship between HRV-derived parameters and the depth of anesthesia, with varying degrees of success. It is acknowledged that effects of hypnotic and analgesic drugs used for anesthesia are complex and multifactorial. It is recommended that the ventilatory rate be strictly regulated during such studies (Brown et al., 1993; Koh et al., 1998). The value of using the LF:HF ratio as a measure of the sympathovagal balance has come under criticism (Eckberg, 1997). The physiological mechanisms that modulate the RR interval signal have two major components: (i) the reflex loop between the pulmonary cyclic expansion and the sinus node via the brainstem and (ii) other external influences impinging directly on the sinus node and thus its cyclic pacemaking. In particular, when testing HRV reactions to anticholinergic drugs (e.g., atropine), one should keep in mind that the direct action of the

drug on the sinus node may impede its very capability to provide an adequate measure of the ANS reaction to the drug.

There are multiple questions arising from a new HRV index. Given the ANI is a new and original computational technique, the extrapolation of past knowledge is necessarily limited. A whole range of questions need to be addressed with the new technique. The advantage of ANI over HFnu is due to its independence from respiratory rate and its pattern, but the very limited insight into the ANI index in itself needs to be kept in mind when designing new clinical studies: its content is that of the normalized HF spectral (HFnu) power. When investigating situations and medications where the ANS is likely to vary than just the HFnu, additional means of measuring HRV should be considered.

13.4.2 Limitations of Using HRV during General Anesthesia

Non-sinus rhythm and ectopic beats in the ECG records during a study are major limitations in a long list of adverse conditions that arise during general anesthesia. Other limitations arise out of pathological situations of the ANS and pharmacological conditions. In particular, HRV analysis works best under stable conditions of HR and blood pressure.

13.4.3 Suggestions for Future Research

Future research on HRV analysis has large potential, especially for the management of anesthesia/analgesia. The validation of ANS monitoring needs to be performed for a large number of patients where a potential benefit is expected, to prevent unnecessary pain and hemodynamic events during anesthesia. In particular, ANS monitoring using HRV also needs to be validated in all chronic conditions affecting ANS reactions, such as diabetes mellitus, chronic alcohol consumption, use of β -blockers, etc. We need to know if HRV can help determine the analgesia–nociception balance during anesthesia and whether thresholds for adequate analgesia are changed in such subgroups of patients.

13.5 Conclusion

Since both hypnotic and analgesic drugs interfere with the functioning of ANS, anesthesiologists have long been looking for indirect signs of its reactions during anesthesia and surgery. The emergence of new ANS monitoring devices in the last decade, such as skin conductance, pupil dilation monitoring and HRV monitoring, will probably turn anesthesia practice toward more personalized analgesia to help avoid both overdosing and underdosing of analgesia. These new monitoring devices still need to be validated in a variety of surgical procedures in order to ascertain their benefit to patients. In addition, the potential applications of HRV monitoring are currently being investigated, which include both acute and chronic pain management and comfort assessment of patients who cannot communicate. It is our strong belief that using a monitor based on HRV, where only indirect signs were previously available, will lead to better clinical practice.

13.6 Appendix

13.6.1 Definitions

- *Autonomous nervous system (ANS)*: the part of the nervous system that unconsciously controls homeostasis.
 - *Heart rate variability (HRV)*: expresses as a whole the multiple influences that are exerted on the heart rate. The definition supposes that the heart rate microvariations along a mean heart rate are analyzed. It is also used as a general descriptor of heart rate and heart period variability.
 - *Heart period variability analysis*: an analysis of the microvariations in the heart period occurring around a mean heart period calculated over the analysis window.
 - *Respiratory sinus arrhythmia (RSA)*: the specific influence of ventilation on the heart rate; it has been related to the parasympathetic tone.
 - *Heart period*: the time (measured in seconds or milliseconds) between two heartbeats.
-

Abbreviation

ANI	Analgesia nociception index
MW	Measuring window

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14

Heart Rate Variability in Functional Neurosurgery

Jonathan A. Hyam, Erlick A.C. Pereira and Alexander L. Green

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14.1 Introduction

Functional neurosurgery treats neurological disorders by changing the activity of neural circuitry. Deep brain stimulation (DBS) is a form of electrical neuromodulation that involves chronic implantation of an electrode within various sites of the human brain. By 2006, more than 40,000 stimulators were implanted worldwide (Benabid et al., 2006). The most common indication is the treatment of symptoms of movement disorders, but conditions such as depression, obsessive-compulsive disorder and chronic neuropathic pain are other frequent targets. The last of these, chronic pain, is a huge burden to society and to those individuals affected. It results from a wide variety of conditions, such as trauma, cancer, stroke and failed surgery (Ashburn and Staats, 1999), with a suspected prevalence of over 20% (Gureje et al., 1998). DBS for chronic pain has been shown to influence not only pain pathways, but also the autonomic nervous system with which it is intimately associated. In this chapter, we describe the application of heart rate variability (HRV) in the intra-operative and post-operative assessments of functional neurosurgery procedures, in particular, DBS for chronic neuropathic pain, and novel applications of DBS.

14.2 DBS for Chronic Pain

DBS involves chronic implantation of a macroelectrode within the deep nuclei or, occasionally, the cortex of the brain, in patients suffering from a wide range of neurological and

medical conditions. The electrode is implanted in the operating theater via a small craniostomy, a hole fashioned in the skull, often while the patient is awake. The targeting is extremely refined and is based on pre-operative brain magnetic resonance imaging fused with a computerized tomogram undertaken while the patient wears a dedicated localizing frame with metal struts as spatial landmarks. Based on these images, coordinates of the target can be calculated, and using a fixed "stereotactic" frame that directs instruments to accurately reach the target in three-dimensional space, the electrode is passed to the desired deep brain site. Further feedback on the accuracy of targeting is provided by a variety of modalities, such as microelectrode recordings or radio-frequency impedance monitoring. Arguably, the most important feedback is the intra-operative symptom or sign improvement reported by the patient. A description of the magnitude and distribution of analgesia during pain surgery are vital prior to the completion of electrode implantation. The stimulator hardware itself is very similar to the cardiac pacemaker in that there is a pulse generator/power supply that is implanted subcutaneously, most commonly in the infraclavicular fossa, and a subcutaneous extension lead linking it to the intracranial electrode.

The most popular application of DBS is for the relief of the symptoms of Parkinson's disease, namely, tremor, rigidity, bradykinesia and gait disturbance, as well as for the dyskinesias that arise as side effects of the pharmacological therapy for Parkinson's disease. In other movement disorders, such as essential or secondary tremor and dystonia, DBS can make startling improvements in symptoms and quality of life. The last decade has shown that surgical therapies for psychiatric diseases (Kringelbach and Aziz, 2009; Pereira et al., 2007), such as depression and obsessive-compulsive disorder, can offer promising results, while in epilepsy, a 50% reduction was achieved in seizure incidence in patients already on maximal medical therapy, which was maintained over 2 years after surgery (Fisher et al., 2010).

The application of DBS for chronic neuropathic pain predated these other indications by a decade. Reynolds (1969) first reported the remarkable phenomenon that analgesia could be evoked by the stimulation of the midbrain in conscious rats. The ability to directly modulate the performance of pain inhibitory pathways then led to human therapies for chronic, debilitating pain. Promising results were reported in pain relief by the original pioneers (Hosobuchi et al., 1977; Richardson and Akil, 1977; Young and Brechner, 1986), although the side effect profile limited the popularity of the procedure (Nashold et al., 1969; Kumar et al., 1997). With state-of-the-art advancements in neuroanesthesia, neuroimaging and stereotactic methods, DBS for pain has seen a re-emergence over the last decade.

The experience at our institution is reported in an article describing a series of 47 consecutive chronic neuropathic pain patients who underwent DBS (Owen et al., 2007). The etiologies of the pain included stroke (18), phantom limb/brachial plexus injury (12) and others such as anesthesia dolorosa, spinal cord injury and post-herpetic neuralgia. The overall result at a mean follow-up of 4 years was a 52% ($SD \pm 27\%$) reduction in pain. Pain relief of more than 50% was obtained in 50% of the patients, including a 60%–79% improvement in 13% and an 80%–100% improvement in 19%. However, a poor result with pain relief of less than 40% was seen in 38% of the patients. DBS for pain has a low complication rate, but risks include intracranial hemorrhage, infection and brain injury. Furthermore, it is an expensive therapy because of both initial hardware cost (electrode and pulse generator) and the subsequent need for follow-up and battery replacement surgeries.

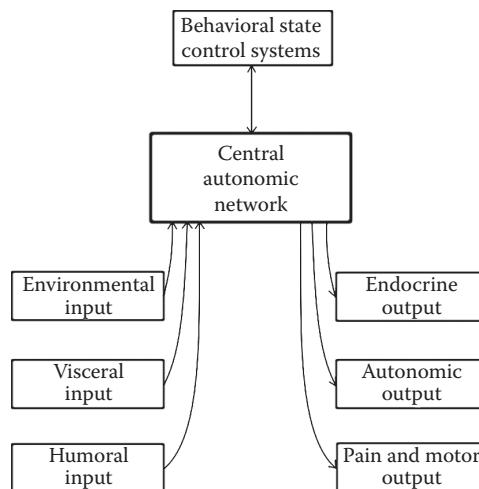
Discrimination between patients who are or are not likely to derive the maximal benefit from this surgery is therefore crucial and depends on successful identification of indices and predictors of eventual outcome, namely, pain relief. For example, the etiology of the pain itself appears to be an important predictor of the outcome. Post-stroke pain in this series had an outcome inferior to the group average, with only 44% receiving more than 50% pain relief. By contrast, over 60% of the phantom limb/brachial plexus injury patients received more than 50% pain relief, including 40% who received over 60% relief.

Nevertheless, even more accurate and precise predictors of optimal surgical results are needed to increase the degree to which patients who receive some benefit will be useful and to avoid exposing those patients who will receive no benefit due to unnecessary surgery. The intertwined physiological and anatomical relationships between pain and autonomic activity provide a surrogate set of parameters that can indicate how DBS interferes with pain pathways and, therefore, whether a benefit is to be expected for a particular patient. HRV is a recognized non-invasive index of autonomic nervous system activity and can reflect the shifting balance between sympathetic and parasympathetic drives. It can also provide information on anatomical, physiological and clinical effects of DBS for chronic neuropathic pain. This is so because a major subcortical DBS target is the periaqueductal gray matter (PAG) of the midbrain, which is integral to both pain and the autonomic pathways.

14.3 Higher Neural Control of the Autonomic Nervous System

Autonomic function is orchestrated by what has been termed the “central autonomic network” (CAN), which is contained within the neuraxis. The CAN receives ascending peripheral autonomic afferent information not only in the form of autonomic visceral inputs, but also in the form of humoral and environmental information. These inputs are processed either simply within a reflex arc, or they contribute to multiple integrated functions that can influence multiple organ systems (Loewy and Spyer, 1990). The efferent output from the CAN also takes the form of multiple modalities, consisting of not only the autonomic efferents but also endocrine, motor and pain pathway outputs. The CAN also has reciprocal connections to reticular and forebrain monoamines and to cholinergic attentional, motivational, emotional and sleep–wake cycle pathways (Benarroch, 1997). In this way, the CAN is capable of orchestrating moment-to-moment maintenance of autonomic, endocrine, motor and pain (Lovick, 1993) parameters in response to internal and external factors, as summarized in Figure 14.1 (Benarroch, 1997).

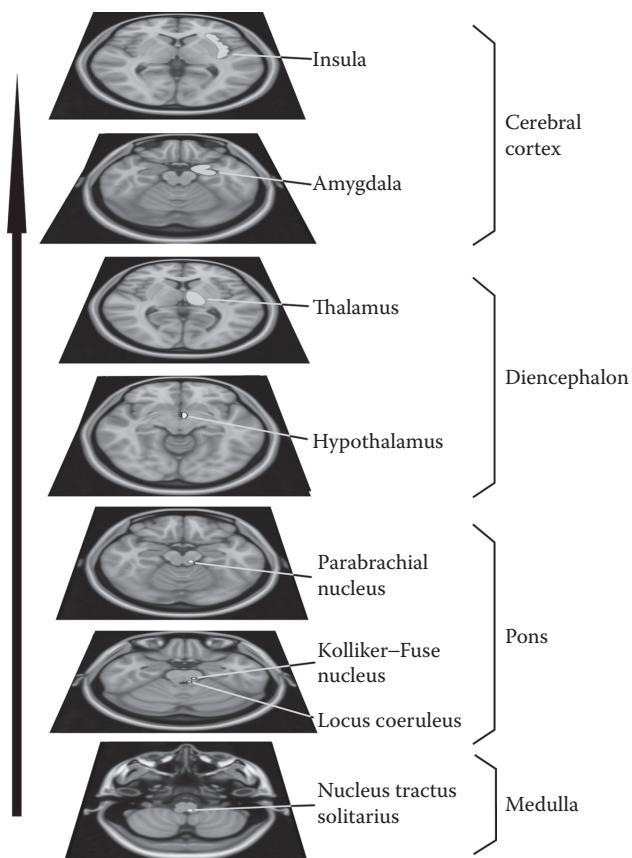
The CAN is chiefly composed of brainstem and forebrain structures. The CAN structures within the medulla oblongata include the nucleus tractus solitarius (NTS), area postrema, the nucleus ambiguus (NA), dorsal motor nucleus of the vagus nerve (DMNX) and the rostral ventrolateral medulla (RVLM); within the pons are the locus coeruleus (LC), Kölliker–Fuse nucleus, A5-cell group and parabrachial nucleus; within the midbrain, the PAG; within the diencephalon are periventricular gray matter (which we shall consider as one with the PAG), thalamus and the paraventricular nucleus and lateral area of the hypothalamus; and sites within the cortex include the amygdala of the limbic system and the insula (alternatively referred to as the visceral primary sensorimotor

**FIGURE 14.1**

A schematic representing the inputs and outputs of the central autonomic network. (Adapted from Benarroch, E.E., *Central Autonomic Network: Functional Organization and Clinical Correlations*, Futura, New York, 1997.)

cortex [Cechetto and Chen, 1990; Craig, 2002]) (Benarroch, 1997; Loewy and Spyer, 1990; Nadapow et al., 2008). Autonomic visceral afferents from the thoracolumbar (sympathetic) and craniosacral (parasympathetic) levels ascend to the NTS, which is the principle site of termination of the afferents from cardiovascular receptors. Afferents from arterial baroreceptors in the aortic arch and the carotid sinus, the cardiac baroreceptors in the walls of the cardiac ventricles and the atria and the arterial chemoreceptors from the aortic and the carotid bodies (Dampney, 1994) reach the NTS as part of the glossopharyngeal and vagus nerves. The NTS is also the site of termination of visceral and somatic second-order neurons (Dampney, 1994) with plasma electrolyte and humoral and cerebrospinal fluid chemical information arriving from the area postrema (Loewy and Spyer, 1990). The latter is a circumventricular organ on the floor of the fourth ventricle without a blood–brain barrier and is increasingly recognized to be important in cardiovascular regulation as well as emesis (Dampney, 1994). The NTS then relays this information rostrally to multiple sites within the CAN, as shown in Figure 14.2.

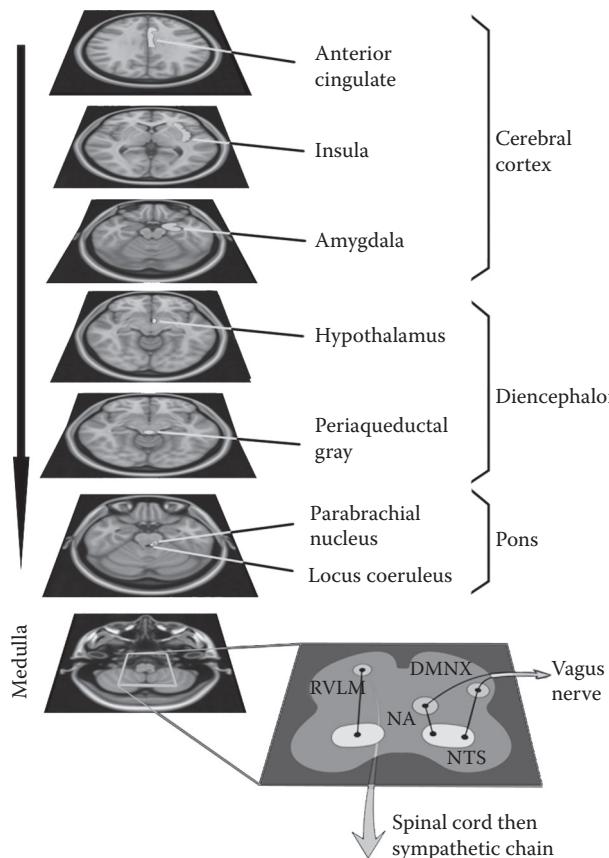
There are multiple and complex reciprocal connections between these higher neural sites and a number of other critical sites involved in formulating the efferent outflow of the CAN (Figure 14.3). These include the anterior cingulate gyrus, amygdala and insula within the cerebral cortex, the hypothalamus and PAG within the diencephalon and the LC and parabrachial nucleus of the pons (PBN) before the final pathways of the CAN within the medulla and intermediolateral spinal cord. The NTS is the main receiving site not only for afferent information but also for efferents. The NTS forms a crucial junction point at which the selection of sympathetic or parasympathetic drives is mediated. First, it projects to the RVLM, which then activates the sympathetic outflow from preganglionic neurons of the spinal cord and sympathetic chain. Second, it projects to the NA and the DMNX, which are the main medullary sites mediating parasympathetic outflow and contain parasympathetic preganglionic neurons prior to their exit from the brainstem (see Figure 14.3). In this way, the CAN orchestrates the balance between sympathetic and parasympathetic drives and is crucial to the level of the end-organ parameters, including heart rate.

**FIGURE 14.2**

A schematic showing the ascending afferent circuitry of the central autonomic network. Complex reciprocal interactions exist between the individual nuclei and cortices. The brain slices were created using the Montreal Neurological Institute (MNI) standard and structural brain template of 152 averaged brains, using the fMRI Software Library. (Adapted from Smith, S.M., Jenkinson, M., Woolrich, M.W., et al., *NeuroImage*, 23, 208–219, 2004; Woolrich, M.W., Jbabdi, S., Patenaude, B., Chappell, M., Makni, S., Behrens, T., Beckmann, C., Jenkinson, M. and Smith, S.M., *NeuroImage*, 45, S173–S186, 2009. With permission.)

Arterial baroreceptors in the carotid sinus and the aortic arch fire in response to arterial wall stretch, and this information is continuously projected to the NTS via the glossopharyngeal and vagus nerves, respectively (Wieling and Karemaker, 1999). The default sympathetic resting activity provides chronotropic, inotropic and vasoconstrictive tendencies in the cardiovascular system. As stretch is detected in baroreceptors, the NTS inhibits the RVLM while exciting the NA and DMNX, producing a reduction in sympathetic tone and an increase in vagal activity. The end result is a reduction in heart rate via the sinoatrial node, in addition to negative inotropic and vasodilatory effects.

This medullary circuitry is therefore integral to the baroreceptor reflex and to the beat-to-beat dynamics, which confer the continual alteration of the sympathetic:parasympathetic balance in response to changing cardiorespiratory factors. Accordingly, the baroreceptor reflex can consequently be influenced by the activity of the higher CAN centers, so neuro-modulation of component parts of the CAN may alter autonomic function throughout the body with an accompanying variation in HRV.

**FIGURE 14.3**

A schematic showing the descending efferent circuitry of the central autonomic network. Complex reciprocal interactions exist between the individual nuclei and cortices. (Adapted from Benarroch, E.E., *Central Autonomic Network: Functional Organization and Clinical Correlations*, Futura, New York, 1997; Schmidt, R.F., Thews, G., *Human Physiology*, Springer-Verlag, New York, 1983.) The brain slices were created using the Montreal Neurological Institute (MNI) standard and structural brain template of 152 averaged brains, using the fMRI Software Library. (Adapted from Smith, S.M., Jenkinson, M., Woolrich, M.W., et al., *NeuroImage*, 23, 208–219, 2004; Woolrich, M.W., Jbabdi, S., Patenaude, B., Chappell, M., Makni, S., Behrens, T., Beckmann, C., Jenkinson, M., and Smith, S.M., *NeuroImage*, 45, S173–S186, 2009. With permission.)

14.4 DBS and Its Effects on the Autonomic Nervous System

For some time, electrical stimulation of the brain has been known to influence cardiorespiratory factors. In 1949, Pool and Ransohoff (1949) demonstrated during psychosurgery that direct electrical stimulation of the anterior cingulate cortex in humans caused changes in heart rate, blood pressure and respiratory rate. Stimulation of the anterior cingulate cortex has also been shown to cause a voltage-dependent increase in skin conductance activity, an index of autonomic arousal (Gentil et al., 2009).

The PAG of the midbrain, another component of the CAN, has been more extensively investigated and is an important target for DBS for pain syndromes. In 1935, Kabat showed that PAG stimulation changed cardiovascular parameters in cats. Similar responses have

been demonstrated in human patients undergoing neurosurgery for chronic pain syndromes. The PAG is divided into four longitudinal columns (Carrive et al., 1989; Carrive and Bandler, 1991a,b) with differing physiological roles and is instrumental to the “defense” reaction, an essential mechanism promoting survival in the wild (Reis et al., 1967). In rats, if it is possible to escape the threat, the “flight or fight” reaction manifests as an increase in heart rate and blood pressure, non-opioid-mediated analgesia, emotions such as fear (Carrive and Bandler, 1991a; McGaraughty et al., 2004) and other autonomically mediated responses, including pupillary and skeletal muscle flow changes, micturition and vocalization (Bittencourt et al., 2004). Conversely, if it is not possible to escape and remaining undetected is safer, the ensuing “passive” or “coping” reaction manifests as decreased heart rate and blood pressure, opioid-mediated analgesia and freezing behavior, as well as fear (Finnegan et al., 2005; Johnson et al., 2004). Stimulation of the ventrolateral columns in animals produces bradycardia, hypotension and freezing behavior, whereas stimulation of the dorsolateral and dorsomedial columns produces increased heart rate and blood pressure (Abrahams et al., 1960; Carrive and Bandler, 1991a; Duggan and Morton, 1983; Lovick, 1985, 1992). Green et al. (2005) demonstrated the same phenomena in humans with deep brain stimulators *in situ* for chronic pain syndromes. Electrical stimulation of the dorsal PAG caused an increase in systolic blood pressure of approximately 16 mmHg, while stimulation of the ventral PAG caused a decrease of approximately 14 mmHg in patients seated at rest. Intra-operative stimulation of the PAG caused systolic blood pressure changes, which correlated with changes in the low-frequency (LF) and high-frequency (HF) HRV components, as well as in the low frequency:high frequency (LF:HF) ratio, although only the first reached statistical significance, whereby the LF change explained 70% of the blood pressure variance (Green et al., 2010). Stimulation of the PAG was also found to prevent the postural drop in blood pressure that occurs on standing from sitting (Green et al., 2006). This was seen not only in patients with mild orthostatic intolerance, but also in patients with clinical orthostatic hypotension. The LF component of HRV increased compared to the off-stimulation state and the baroreceptor sensitivity also increased.

14.5 Relationship between Pain and the Autonomic Nervous System

The autonomic nervous system and pain pathways are inextricably linked, but the relationship is complex and not yet perfectly defined. In 1884, William James (1884) argued that pain sensations are at least due in part to autonomic reactions changing local blood flow and blood pressure. Indeed, certain pain syndromes are intimately associated with aberrations in local or systemic autonomic indices. In the case of acute pain, an associated increase in blood pressure is well recognized and is believed to be mediated by a combination of elevated arousal and sympathetic drive (Maixner et al., 1990; Nordin and Fagius, 1995). In chronic pain, the relationship between two systems is far more complex and difficult to elucidate. In pain-free patients, there is an inverse relationship between pain sensitivity and blood pressure at rest. For example, the feeling of pain in hypertensives is less intense than in non-hypertensives (Bradley et al., 2002; Ghione, 1996; Ghione et al., 1988; Sheps et al., 1992). This phenomenon was shown in rats to be mediated by stimulation of baroreceptors, leading Dworkin et al. (1979) to propose that hypertension itself was an adaptive behavior to minimize the effects of stress. The relationship is reversed in chronic pain patients in whom there is a positive correlation between blood pressure

and pain sensitivity (Bragdon et al., 2002; Maixner et al., 1997; Bruehl et al., 2002). Further evidence of the intimate relationship between pain and autonomic function is seen in complex regional pain syndrome, also known as Sudeck's atrophy, causalgia or reflex sympathetic dystrophy. Within the bodily territory where the pain manifests, there is an aberrant autonomic function, including vasomotor and trophic skin changes and sweat secretion. Interruption of sympathetic pathways to the painful body area by pharmacological blockade or surgical transection in certain cases provides relief of not only the pain but also the aberrant autonomic features. Such aberrant autonomic features are also seen in other forms of chronic pain, such as exaggerated peripheral blood flow in painful diabetic neuropathy (Archer et al., 1984).

Pain is also linked to the autonomic responses of emotion. Affective states are proposed to be related to physiological arousal (Hagmann et al., 2003). An affective state such as pain promotes arousal and can thus manifest as autonomic changes. The polyvagal theory (Porges, 1997) suggests that the vagal system rapidly allows mammals to inhibit such autonomic arousal to produce a state of calmness. Indeed, in subjects with less emotional pain valence and higher pain thresholds after exposure to an identical noxious stimulus, there is a reduced LF component of HRV (Appelhans and Luecken, 2006).

Certain parts of the CAN are known to play a vital role in the modulation of multiple body systems including pain, as shown in Figure 14.1. Anatomically, there is an overlap in intracranial areas that are important in both pain processing and autonomic function, namely, the NTS, PAG and LC (Ghone, 1996). The role of the PAG within the pain pathways appears to be crucial to its integration with other associated responses. It is composed of multiple descending control systems with modulatory effects on nociceptive transmission, both inhibitory and excitatory, acting on the spinal and trigeminal dorsal horns (Gebhart, 2004). The control system originating in the PAG orchestrates a dynamic balance between facilitation and inhibition of nociception, which is tipped back and forth depending on the circumstances that the organism finds itself in, and is crucial for facilitating successful survival behaviors. The PAG is ideally located to detect changes outside the central nervous system and initiate appropriate behavioral and autonomic responses to counteract and limit the disruptive effects of pain by virtue of the multiple inputs it receives from organs throughout the body via the vagus nerve (Lovick, 2010; Viltart et al., 2006). Classically, after tissue injury, there are a series of adaptive physiological and behavioral changes in response to the stress or threat of the situation. There is an initial inhibition of pain pathways with an elevation of pain thresholds to avoid hampering of emergency motor and cognitive activities to evade the imminent danger, followed by a facilitation of the nociceptive pathways to motivate protective behaviors promoting healing. A descending inhibition of the pain pathways then occurs if the pain persists beyond the initial healing period, to allow a return to behaviors necessary for long-term survival (Lovick, 1993, 2010; Millan, 2002).

The degree of chronic neuropathic pain relief achieved by DBS of the PAG has been shown to be positively correlated with the change in blood pressure when the stimulator is switched to on from off (Green et al., 2006). Patients who experienced the greatest relief from their chronic pain during stimulation were also those whose blood pressure declined most when the stimulator was switched on. A reduction in local blood flow is associated with pain relief. However, it is not clear whether this is a parallel phenomenon or whether the reduction in blood flow is analgesic in itself. Tanaka et al. (2004) demonstrated a reduction in local cutaneous blood flow occurring in association with spinal cord stimulation, a recognized treatment for chronic pain. However, Green et al. (2006) found only a weak correlation between pain relief and reduction in pulse pressure, a validated marker of vaso-dilation (Laskey et al., 1990). Rather, pain relief was strongly and inversely correlated with

the rate of change of systolic blood pressure, a good index of cardiac contractility (Brinton et al., 1997). Therefore, blood pressure change with pain relief was more likely to be due to changes in cardiac performance, suggesting that the change in peripheral blood flow itself may not be the analgesic factor. During the autonomic challenge of standing from sitting, patients with PAG stimulation produced an increase in both pulse pressure and rate of change of systolic blood pressure, suggesting that stimulation can still exert peripheral as well as central effects (Green et al., 2006). Therefore, this suggests that the analgesic results of DBS are not achieved chiefly through changes in local cutaneous blood flow, but are associated with central cardiovascular effects.

14.6 HRV as a Predictor of Outcome after DBS for Pain

The analgesic effects of DBS have been shown to be associated with alterations in various indices of autonomic activity. One index is the power of the Meyer wave present at 0.1 Hz in the autoregressive power spectrum of blood pressure, which is a non-invasive, albeit approximate, index of the sympathetic activity (Pagani et al., 1997). In 16 patients receiving PAG stimulation, the power at this frequency increased when blood pressure increased and, in the cases experiencing pain relief, the power at this frequency decreased with blood pressure (Green et al., 2006). Therefore, this sympathetic index decreased with analgesic effect of PAG stimulation.

HRV has been shown to change according to the analgesic efficacy of PAG stimulation for pain. Pereira et al. (2010a) studied 16 patients with chronic pain who had undergone PAG DBS. Heart rate and the analgesic effect of stimulation on a 10-point visual analogue scale (VAS) were recorded while the stimulation was on and off, and HRV was derived. Stimulation reduced VAS by 84% from a mean of 7.52/10 down to 4.34/10. The LF:HF ratio was significantly reduced in patients undergoing stimulation via electrodes in a more ventral part of the PAG (shown on the post-operative imaging in Figure 14.4), a site recognized in animals to have a depressive effect on autonomic variables. This reflected an increase in the HF HRV power and a reduction in the LF power (see Figure 14.5). The improvement in

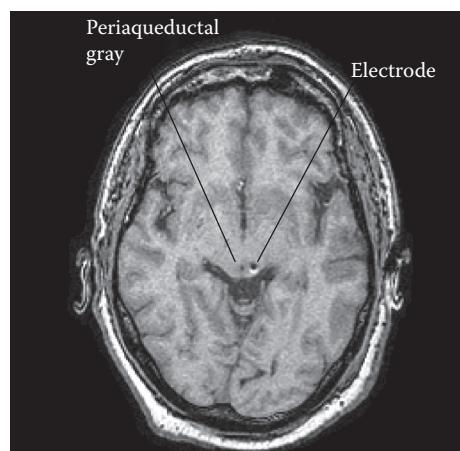
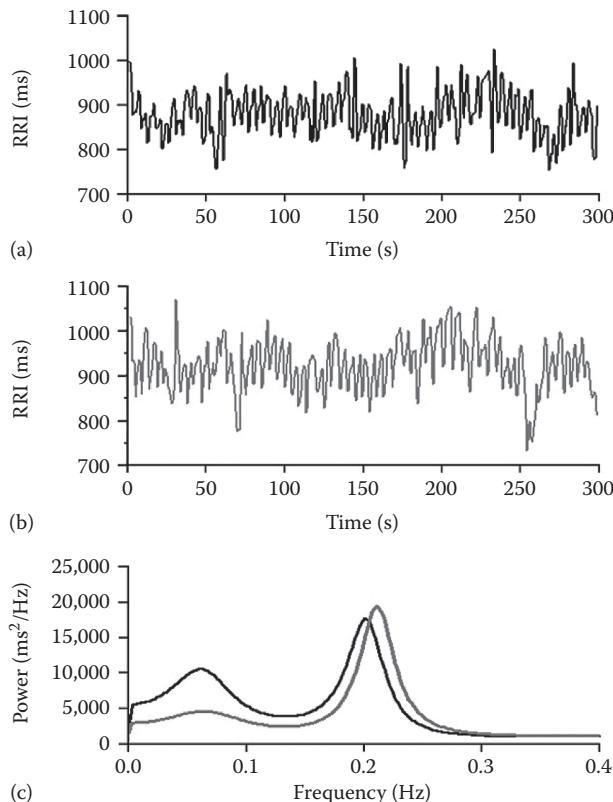


FIGURE 14.4

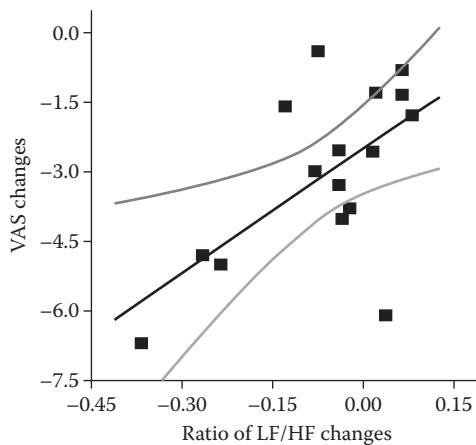
The location of the ventral periaqueductal gray electrode on axial post-operative magnetic resonance imaging.

**FIGURE 14.5**

(a) RR intervals with no stimulation; (b) RR interval with ventral periaqueductal gray stimulation; (c) the heart rate variability spectrum showing a reduction in the low-frequency power and an increase in the high-frequency power with ventral periaqueductal gray stimulation (gray line) compared to no stimulation (black line). (Adapted from Pereira, E.A.C., Lu, G., Wang, S., Schweder, P.M., Hyam, J.A., Stein, J.F., Paterson, D.J., Aziz, T.Z. and Green, A.L., *Exp. Neurol.*, 223, 574–581, 2010a. With permission.)

pain within the VAS correlated with the change in power in the HF HRV component and LF:HF ratio (see Figure 14.6). Therefore, we believe that changes in the components of HRV can be used to predict optimal electrode positioning for PAG stimulation.

There are various stages at which HRV could be recorded and used to predict whether a patient will receive an analgesic benefit from PAG stimulation. During the intra-operative stages, arguably the most useful index of successful targeting is a clinical improvement in the patient's pain severity and distribution. However, in some patients, it takes days to months to fine-tune stimulation parameters to maximize analgesia. Still other patients are unable to tolerate the full procedure without sedation, excluding analgesia as an intra-operative marker for correct electrode placement, although this is a rare occurrence. Using HRV as a surrogate index instead of the reported pain improvement is, therefore, of immense help in determining whether the electrode siting is optimal or can be improved. Intra-operatively, once the electrode is at the target, as determined by imaging and the stereotactic frame, stimulation can be switched on and off at various electrical levels and HRV can be recorded. The increase in the HF component or the LF:HF ratio can be used as an objective measure of proximity to the optimal electrode site. Alternatively, an evaluation may be undertaken while these patients are assessed

**FIGURE 14.6**

A scatterplot showing the positive linear relationship between VAS score changes and LF:HF ratio changes. (Adapted from Pereira, E.A.C., Lu, G., Wang, S., Schweder, P.M., Hyam, J.A., Stein, J.F., Paterson, D.J., Aziz, T.Z. and Green, A.L., *Exp. Neurol.*, 223, 574–581, 2010a. With permission.)

for efficacy in the hospital over the ensuing days. It is usual that only the electrodes are implanted at a first surgery. The leads are left externalized for 1 week to allow an evaluation of efficacy and only then are they internalized along with implantation of the pulse generator. Sometimes, even after this period, it is unclear whether the stimulation is significantly beneficial to an individual patient, for several reasons. First, the perfect stimulation parameters may still not have been found; second, the electrode may be in a suboptimal position; or third, it may be that the stimulation of any area in this patient will not produce an analgesic benefit. In the first scenario, the second surgery should go ahead as the patient will eventually benefit from DBS. In the second scenario, the electrode will need repositioning and, subsequently, either another stimulation trial or a commitment to full hardware implantation at the same time. In the third scenario, the electrodes should be removed and the surgeon should not proceed with the implantation. Distinguishing between the three scenarios is difficult and can be subjective. Measuring HRV with the stimulation on and off will be instructive and provides an important objective index to help base the surgical decision. If the power of the HF component increases and LF:HF ratio decreases, as seen by Pereira et al. (2010), then it is likely that the electrode is influencing the autonomic nervous system as expected and is therefore correctly positioned to influence the pain pathways. If so, then completing the surgical implantation with internalization of electrodes and insertion of the pulse generator is appropriate as the patient is expected to receive benefit from the surgery. In this manner, HRV measurement in pain surgery is useful in determining whether a patient should or should not receive electrode implantation.

14.7 Future Potential of HRV in Autonomic Neurosurgery

The future application of HRV measurement in functional neurosurgery may include an evaluation during surgery for dysautonomias. Building on the discoveries of Green et al.

(2005, 2006, 2010) that DBS can influence blood pressure, heart rate and HRV, applications of DBS to either reduce or help maintain blood pressure is a possibility.

Hypertension in carefully selected cases has previously been treated by neurosurgery, namely, microvascular decompression of the rostroventral medulla (Frank et al., 2009). PAG stimulation in a hypertensive patient with neuropathic pain was seen to reduce systolic blood pressure by 25 mmHg at surgery, a reduction that was maintained during chronic stimulation when followed up 1 year later. Ambulatory monitoring demonstrated a mean reduction of 12.6 mmHg in systolic blood pressure and 11.0 mmHg in diastolic blood pressure (Pereira et al., 2010). Should DBS for hypertension become established, an intra-operative evaluation of HRV will be a vital index to assess the success of electrode implantation and choice of stimulation parameters. A reduction in the LF component (which at least, in part, reflects the sympathetic drive) and the LF:HF ratio and/or an increase in the HF component would be indicative of a desired autonomic response.

Conversely, postural hypotension can be severely debilitating and restrict the quality of life, with extreme cases requiring sympathetically active medications and invasive treatments with recognized adverse effects on end organs, such as noradrenaline pumps. DBS for postural hypotension is, therefore, another potential application of functional neurosurgery, building on Green and colleagues' findings of abolished postural blood pressure drop on standing, in a patient with clinical postural hypotension (2006). HRV measurements would also be instructive intra-operatively or afterward in tailoring and evaluating therapy. Either the stimulation could be set to provide a sympathomimetic effect with increased LF and LF:HF ratio and/or a reduced HF component intra-operatively, or the patient can be tested post-operatively during postural challenges such as head-up tilt, to achieve a transient sympathomimetic effect.

14.8 Conclusions

Functional neurosurgery using DBS is a branch of medicine that affects the entire body. HRV measurement has been shown to correlate with the degree of chronic neuropathic pain relief and provides an important objective index on which to base neurosurgical decisions in pain surgery. Future therapies for cardiovascular disorders may also benefit from HRV measurement to fine-tune the therapy to each individual patient. Therefore, elements and techniques in cardiovascular physiology and cardiology can contribute enormously to the optimal, contemporary and future management of this patient group.

Abbreviations

CAN	Central autonomic network
DBS	Deep brain stimulation
DMNX	Dorsal motor nucleus of the vagus nerve
LC	Locus coeruleus
NA	Nucleus ambiguus
NTS	Nucleus tractus solitarius

PAG	Periaqueductal gray matter
PBN	Parabrachial nucleus of the pons
RVLM	Rostral ventrolateral medulla

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15

Bariatric Surgery and Its Effects on Heart Rate Variability

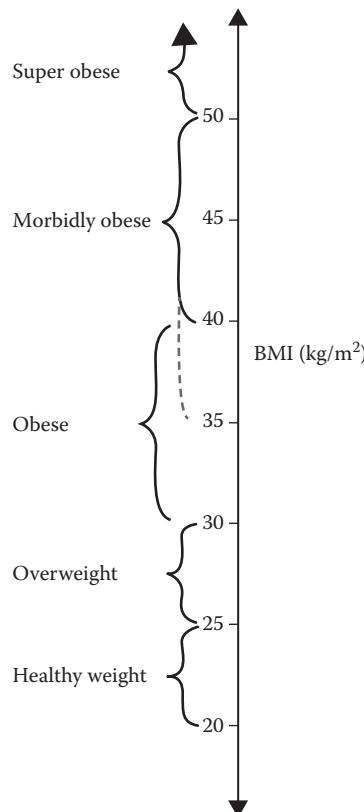
Anton F. Lodder, Markad V. Kamath, David Armstrong and Adrian R.M. Upton

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15.1 Introduction

Obesity, ranging from “overweight” to “super obese” (Figure 15.1), is a highly prevalent condition that is fast-approaching epidemic proportions in the developed world. The World Health Organization (2010) reported that approximately 1.6 billion adults worldwide were overweight in 2005, with at least 400 million adults being obese (having a body mass index [BMI] greater than 30 kg/m^2). According to the International Association for the Study of Obesity (2010), 22.9% of men and 23.2% of women in Canada were obese (2004 estimates) and 32.2% of men and 35.5% of women in the United States were obese (2007 estimates). Similarly, 25% of adults in the United Kingdom were obese (2008 estimates) (Organization for Economic Co-operation and Development, 2010). A recent study estimated the medical cost of obesity in Canada to be 4.1% of all medical expenditures (Anis et al., 2010). Another study estimated the medical costs of obesity worldwide to be 0.7%–2.8% of the global expenditure on health care and also estimated the lifetime medical cost for an obese individual to be 30% higher than for someone at a healthy weight (BMI less than 25 kg/m^2) (Withrow and Alter, 2011). In recent years, bariatric surgery has gained clinical acceptance for the induction of weight loss in individuals who are morbidly obese or super obese. This chapter examines four major bariatric procedures currently used to treat obesity and summarizes the studies that have examined heart rate variability (HRV) and autonomic nervous system (ANS) function before and after these surgeries.

**FIGURE 15.1**

The definition of the levels of obesity according to the BMI. The dotted line indicates patients who are between 35 and $40 \text{ kg}/\text{m}^2$ but have significant morbidities associated with obesity and are considered morbidly obese. Bariatric surgery has been recommended for patients who are morbidly obese. (Based on Hamoui, N., Anthone, G.J., Kaufman, H.S. and Crookes, P.F., *Obes. Surg.*, 16, 1445–1449, 2006; Fontana, M.A. and Wohlgemuth, S.D., *Gastroenterol. Clin. North Am.*, 39, 125–133, 2010; Ren, C.J., Patterson, E. and Gagner, M., *Obes. Surg.*, 10, 514–523, 2000.)

15.2 Effects of Obesity on Overall Health and the Autonomic Nervous System

Obesity has numerous negative effects on overall health, decreasing both quality of life (Fontaine and Barofsky, 2001) and life expectancy (Peeters et al., 2003). Morbidities associated with obesity include cardiovascular conditions such as stroke (Rexrode et al., 1997; Uchiyama et al., 2010), myocardial infarction, arrhythmias (Uchiyama et al., 2010; Anand et al., 2008), hypertension (Chockalingam, 2010; Reisin and Jack, 2009), coronary artery disease (Benderly et al., 2010; Willett et al., 1995; Rimm et al., 1995), congestive heart failure (Hubert et al., 1983; Alpert, 2001), cardiomyopathy, increased left ventricular wall stress, left ventricular hypertrophy, diastolic dysfunction (Alpert, 2001; Wong and Marwick, 2007; Celik et al., 2010) and sudden cardiac death (Chugh et al., 2008). Other major comorbidities include type 2 diabetes (Manson et al., 1992), hyperlipidemia

(Rabkin et al., 1997), cancer (Folsom et al., 1989; Lee and Paffenbarger, 1992; Sellers et al., 1992), sleep apnea (Sunita and Kumar, 2010) and musculoskeletal complications (Chan and Chen, 2009; Anandacoomarasamy et al., 2009).

Several of these obesity-related conditions are also associated with ANS dysfunction, evident as changes in HRV. Sleep apnea, as well as most cerebrovascular accidents, myocardial infarction, hypertension, coronary artery disease and congestive heart failure, are linked to reduced HRV (Burns et al., 2005; Grassi et al., 2001, 2010; Kotsis et al., 2010; Lambert et al., 2010; Skrapari et al., 2007; Kleiger et al., 1987; Dekker et al., 2000; Naver et al., 1996). Sudden cardiac death has been predicted by reduced HRV and is believed to be triggered by autonomic abnormalities, among other causes (La Rovere et al., 2003; Barron and Lesh, 1996; Billman, 2009). Furthermore, it has been observed that increased weight alone, independent of obesity-related conditions, is associated with decreased HRV and parasympathetic withdrawal (Gao et al., 1996; Emdin et al., 2001; Snitker et al., 2000) and that the level of sympathetic dominance may increase with the degree of obesity (Alvarez et al., 2002). In healthy individuals, a weight gain of just 10% leads to a sympathetic activation and a reduction in the parasympathetic control; conversely, a weight loss of only 10% leads to a sympathetic suppression and an increase in the parasympathetic modulation of the sinus node (Arone et al., 1995). Obesity is correlated with increased insulin levels due partly to high energy and glucose intake and partly to insulin resistance (Laitinen et al., 1999; Emdin et al., 2001; Anderson et al., 1992); insulin resistance and hyperinsulinemia have, in turn, been linked to sympathetic overdrive and withdrawal of vagal input with respect to cardiac regulation (Van De Borne et al., 1999; Laitinen et al., 1999; Isomaa et al., 2001).

15.3 Surgical Intervention for Obesity as a Potential Therapy

Treating obesity is an important step in preventing or reducing comorbidities and in improving the quality of life of obese patients; weight-loss treatments have also been shown to exert a beneficial effect on HRV indices of ANS function. Bariatric surgery and accompanying weight loss result in a restoration of HRV and vagal tone, coupled with a reduction in comorbidities (Karason et al., 1999; Gao et al., 1996; Emdin et al., 2001; Snitker et al., 2000). Studies have also found weight loss by dietary means to be associated with an increased HRV in the absence of surgical intervention (Emdin et al., 2001). Correlations have been observed between increasing body fat and decreasing HRV (Peterson et al., 1988; Alvarez et al., 2002). Scherrer et al. (1994) demonstrated a direct correlation between BMI and sympathetic nervous activity, as measured by muscle sympathetic nerve activity (MSNA), for healthy subjects who had BMI of between 15 and 45 kg/m². Alvarez et al. (2002) found that subcutaneous abdominal fat and abdominal visceral fat were correlated with a decreased MSNA as well, with visceral fat having a greater effect than subcutaneous fat.

Many factors influence a person's likelihood of becoming obese. Genetic factors may affect the regulation of hunger, energy intake, metabolic rate, ability to process energy (Wilding, 2001) and susceptibility to weight gain in response to over feeding (Bouchard et al., 1990). In addition, social factors and lifestyle choices contribute to manifestations of the obese state (Wilding, 2001). Obesity occurs when the energy intake is higher than the energy utilization in the body, a state brought about by a combination of overconsumption

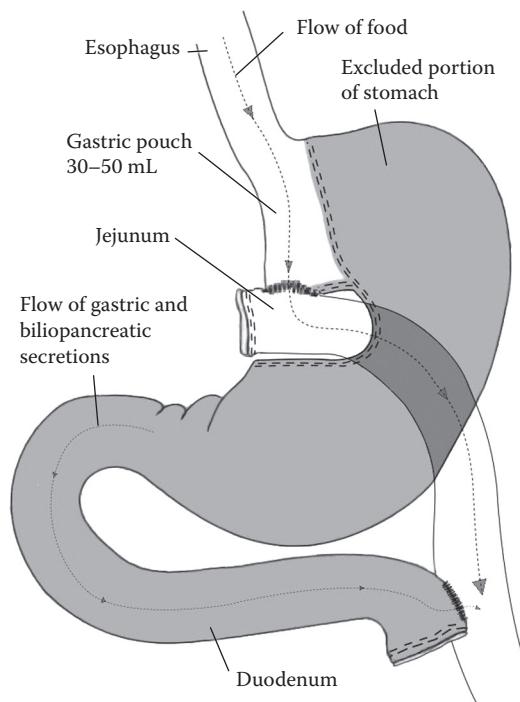
of food, consumption of energy-dense food and lack of physical activity. These mechanisms involve lifestyle choices, such as the type and quantity of food that people eat, as well as the amount of physical activity that they engage in. Thus, the rise in obesity in recent years can be correlated with social changes such as decreased participation in active leisure activities, decline in jobs requiring manual labor, an increase in the use of cars, the increasing popularity of television and video games and the popularity of energy-dense foods that tend to affect the satiety mechanisms differently (Wilding, 2001). Emotional and psychological factors can influence a person's energy intake as well; the term "comfort food" highlights the influence that food consumption has on an individual's mental and emotional states, irrespective of his/her physical need for nourishment (Mela, 2005). Generally, foods that are seen as "rewarding" are high-energy foods such as ice creams, cookies, cakes, soft drinks and candies; thus, one may feel better after eating such foods, even if one knows that poor eating patterns can cause weight gain and negatively affect one's body image and self-image.

Diet regulation and regular exercise are the primary strategies in managing obesity, as they are the most accessible methods of treatment (Strychar, 2006; Poirier et al., 2003). Unfortunately, these methods generally lead to only modest weight loss and this is sustained only to the extent that the lifestyle changes can be maintained. Therefore, it is common for weight to be regained in the long term (Miller, 1999). For more serious conditions, such as morbid obesity (BMI greater than 40 kg/m²), modest reductions of 5%–10% may not be enough to bring the weight to a healthy level. Furthermore, obese patients may not be able to tolerate exercise or may be at risk for serious musculoskeletal damage due to exercise. Under these circumstances, a "bariatric" procedure may be considered to decrease the energy intake or absorption, thereby facilitating weight loss. A variety of bariatric procedures have been developed and these may be characterized as "restrictive" (reducing the intake of food), "malabsorptive" (reducing the absorption of digested food) or a combination of the two.

Currently, there are four major bariatric surgeries, namely, gastric bypass, gastric banding, biliopancreatic diversion (BPD) and sleeve gastrectomy (SG) (see Figures 15.2 through 15.5) (Brolin, 2002; Ren et al., 2000).

Other techniques, such as intragastric balloons, have also been used as restrictive procedures. Deep brain stimulation has also been suggested for drastic weight loss, as it is thought to alter the mechanisms that control hunger and reward sensations in response to eating, thus interacting with the more emotionally subjective mechanisms controlling energy intake (Pisapia et al., 2010; Halpern et al., 2008; Mantione et al., 2010). It has also been shown that the vagus nerve stimulation can alter the brain's perception of fullness, helping patients to stop eating (George et al., 2002). Because these techniques are new, mechanisms by which they work are not yet understood and their efficacy has not been documented, bariatric surgery remains the predominant surgical weight loss intervention. It should be noted that, while bariatric surgery is extremely effective in causing drastic weight loss and permanent reduction in energy intake, the weight loss may be reversed in the long term if dietary adjustments are not made to maintain a reduced energy intake.

While it is known that obesity modifies the ANS, and vice versa, little is known about the mechanisms and interactions that change the state of the ANS in obesity. The physiological changes brought about by bariatric surgery are not well understood, especially with respect to how they affect the functioning of the ANS. The central question is whether or not ANS function improves after bariatric surgery. If it does, it still remains to be seen whether or not the cardiac risk profile is altered. Beyond cardiac conditions, will

**FIGURE 15.2**

Roux-en-Y gastric bypass. The proximal end of the jejunum is attached to a gastric pouch formed by stapling off most of the stomach, and the distal end of the duodenum is attached to the jejunum further down, allowing the flow of the biliopancreatic secretions and the gastric secretions from the excluded portion of the stomach.

bariatric surgery modify signalling via the ANS to other organs? Will it affect metabolic syndrome (diabetes) or other comorbidities? Although current studies have identified a correlation between bariatric surgery and HRV increases (see Table 15.1), a crucial question is whether or not the increase in HRV after bariatric surgery is due to weight loss and its physiological effects or whether it is a direct result of the surgery itself and/or the associated anatomical and physiological changes.

Research in exploring bariatric surgery and its effects on the ANS has the potential to explain the mechanisms of obesity and how they interact with the ANS in the propagation of obesity-related conditions. It also provides a window for exploring the coupling of these obesity mechanisms with other body systems, such as the cardiorespiratory organs (Novak et al., 1993). How do obesity and the compromised energy management mechanisms translate to altered autonomic regulation of heart rate? Understanding the mechanisms of obesity and its effects on HRV dynamics may allow application of HRV analysis techniques in the evaluation of obese patients, since HRV can often provide the earliest indications of susceptibility to many cardiac conditions. Furthermore, an understanding of the effects of anatomical and physiological changes brought about by bariatric surgery on autonomic function may give an insight into the use of HRV-based evaluation for post-bariatric patients, identifying a baseline for evaluating the risk of cardiac and other complications in these patients.

TABLE 15.1

Summary of Research on the Effects of Bariatric Surgery on the ANS as Studied by Various Heart Rate Variability Parameters

Study	Patient Population	Procedures	Surgical Effect	ANS Parameters	Effects Observed
Perugini et al. (2010)	30	l-RYGB	R, M	HRV index SDNN SDNN index SDANN rMSSD Heart rate	Excess body weight reduced by 13% at 2 weeks and 45% at 6 months HRV measures increased by 9% at 2 weeks and 31% at 6 months Reduced insulin resistance
Alam et al. (2009a)	13 8 obese 5 non-obese	l-RYGB (5 obese) Open BPD (3 obese) l-fundoplication (5 non-obese)	R, M M, R	RMSSD SDNN VLF, LF, HF LFn, HFn SampEn Hurst exponent FWHM HWHM+ HWHM-	Multifractal parameters FWHM, HWHM+/- were much higher in the non-obese surgical group No HRV parameter separated the bariatric surgical group LF and HF are altered by anesthesia
Alam et al. (2009b)	11 obese	LGB (6 obese) BPD (5 obese)	R M, R	rMSSD SDNN SampEn QT SampEn RR DFA QTVI Heart rate	BPD/DS excess body weight reduced by 19.8% at 1 month, 36.4% at 6 months and 48.6% at 12 months LGB excess body weight reduced by 23.0% at 1 month, 46.3% at 6 months and 53.8% at 12 months Increased HRV measures Reduced medication for diabetes in LGB group Cessation of medication for diabetes in BPD/DS group
Bobbioni-Harsch et al. (2009)	12 obese	RYGB	R, M	SDNN rMSSD HRV index TINN pNN50	Excess body weight reduced by 23% at 6 months and 48% at 12 months Energy intake reduced by 48% at 3 months and 26% at 12 months; shows regression HRV measures increased by 58% at 3 months and 42% at 12 months; shows regression

Nault et al. (2007)	10 obese 7 control	BPD-DS	M, R	SDNN SDANN rMSSD pNN50 LF HF LF/HF Evaluated during both daytime and nighttime	Body weight decreased by 28.3% at 6.8 ± 1.8 months in patients HRV time domain measures increased by 266% during daytime and 85% during nighttime at 6.8 ± 1.8 months HRV frequency domain measures increased by 38.9% LF/HF not significantly altered
Machado et al. (2009)	71	RYGB	R, M	Mean RR SDNN pNN50 rMSSD	Mean weight decreased by 25.5% at 6 months HRV measures increased by 22.2% at 6 months Age and gender related to weight loss and HRV increases
Karason et al. (1999)	84 28 obese gastroplasty 24 obese Dietary treatment 28 lean	Gastroplasty	R	Mean RR SDNN SDANN SDNN index HF LF	Mean weight decreased by 27.6% at 1 year HRV measures increased by 13.5% at 1 year Significant increase in SDNN index and HF at 1 year Restored circadian rhythms

Gastroplasty is an older technique where gastric pouch is stapled off similar to RYGB and food empties into the remainder of the stomach via a controlled outlet. l: laparoscopic; R: restrictive; M: malabsorptive; FWHM: full width of the spectral curve at half the maximum amplitude; HWHM: the half width at half the maximum amplitude for h values less than the modal h value; HWHM+/-: the half width at half the maximum amplitude for h values greater than the modal h value (FWHM and HWHM+/- are multifractal properties); BPD: biliopancreatic diversion portion of the BPD/DS procedure; QTIVI: QT variability index; HRV index: HRV triangular index; TINN: triangular interpolation of NN intervals histogram; HFn: HF normalized by the sum of LF and HF; LFn: LF normalized by the sum of LF and HF; SampEn: sample entropy, an estimate of entropy by evaluating predictability of data; SampEn QT: sample entropy of a time series of QT-interval lengths for successive P-QRS-T complexes; SampEn RR: sample entropy of a time series of RR intervals; VLF: very-low-frequency HRV content, below 0.04 Hz.

15.4 Bariatric Surgical Techniques

Bariatric surgical procedures are designed with the goal of creating either a restrictive effect or a malabsorptive effect on the gastrointestinal tract, or a combination of the two. The restrictive procedures reduce the capacity of the stomach, while malabsorptive procedures reduce the functional length of the intestine by removing or bypassing a segment of small bowel. The standard criterion used for evaluating the success of a bariatric surgical procedure is the percentage of the excess weight lost by a patient 1 year after surgery. The excess weight is the difference between a patient's weight and his/her ideal weight. The generally accepted success criterion for bariatric surgery is a loss of 45% of the excess weight after 1 year (Pisapia et al., 2010). Although the loss of the excess body weight may be a good indicator of the success of the surgery, the true success of the procedure involved also needs to take into account the risk of surgical mortality, side effects in the uptake of nutrients and long-term regaining of weight (Flum and Dellinger, 2004). The success rates and surgical mortality rates for the various procedures are given in Table 15.2.

15.4.1 Roux-en-Y Gastric Bypass

The Roux-en-Y gastric bypass (RYGB) procedure is considered by many to be the gold standard of weight-loss surgeries and is the most popular of bariatric procedures in the United States (Livingston, 2004; Santry et al., 2005). This technique is performed by stapling off the major portion of the stomach, leaving a 30–50 mL pouch at the proximal end, just below the lower esophageal sphincter (Figure 15.2)—by contrast, the normal stomach can accommodate 1–3 L of food. The distal end of this pouch is attached directly to the jejunum so that the food bypasses the entire duodenum. The bypassed duodenum is also connected

TABLE 15.2

Summary of Bariatric Surgical Techniques

Procedure	Method	Effect	Surgical Mortality	Reduction in Excess Weight
Biliopancreatic diversion with duodenal switch (BPD/DS)	Staple stomach into a tube, bypass most of small intestine including pancreatic input	Malabsorptive, restrictive	1.1% (<i>n</i> = 3030) (Buchwald et al., 2004)	75%–80% (Scopinaro et al., 2002; Brolin, 2002)
Roux-en-Y gastric bypass (RYGB)	Remove most of stomach, bypass part of the digestive tract	Restrictive, malabsorptive	0.5% (<i>n</i> = 5644) (Buchwald et al., 2004)	65% (Fontana and Wohlgemuth, 2010)
Sleeve gastrectomy (SG)	Staple stomach into a tube	Restrictive	0.57% (<i>n</i> = 699) (Gumbs et al., 2007)	55%–66% (Cottam et al., 2006; Himpens et al., 2006)
Laparoscopic gastric banding (LGB)	Put an adjustable band around the proximal end of the stomach	Restrictive	0.1% (<i>n</i> = 2297) (Buchwald et al., 2004)	47%–60% (Himpens et al., 2006; Fielding and Ren, 2005; Belachew et al., 1998)

to the jejunum to allow the gastric and pancreaticobiliary secretions to mix with the food. The RYGB surgery is primarily restrictive but includes a malabsorptive component since it prevents much of the digestive processing of the food in the stomach and impairs the mixing of food with pancreaticobiliary secretions that facilitate digestion and absorption. The RYGB has been reported to cause a 50% reduction in the excess weight after 6 months and 75% after 18 months, although 10% of this weight may be regained after 4–5 years (Fontana and Wohlgemuth, 2010). There is a risk of nutritional deficiencies, depending on the patient's lifestyle adjustments to the procedure (Tucker et al., 2007) and the degree of malabsorption induced by the procedure.

15.4.2 Biliopancreatic Diversion

BPD with duodenal switching (BPD/DS) is one of the most effective bariatric procedures (Figure 15.3). The procedure involves stapling to exclude greater curvature of the stomach, turning the stomach into a 200–500 mL tube. The portion of the small bowel between the biliopancreatic duct and the distal end of the jejunum (the biliopancreatic limb) is bypassed. The distal end of the jejunum is joined to the ileum 100 cm before the ileocecal junction. The food from the stomach passes into the proximal duodenum, which is connected directly to the ileum, forming the alimentary limb. This procedure shortens the functional length of the small bowel and diverts biliopancreatic input,

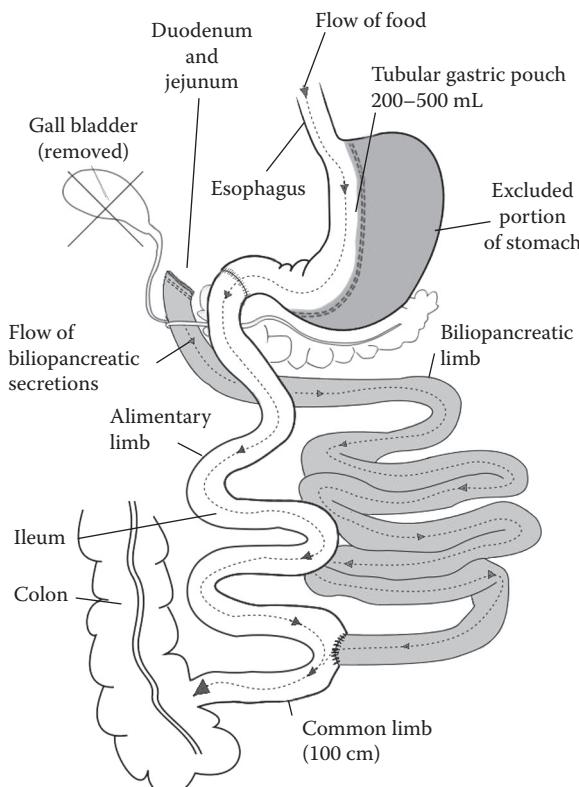


FIGURE 15.3

An illustration of the biliopancreatic diversion with duodenal switching. This procedure results in three different structures in the small intestine: the alimentary limb, the biliopancreatic limb and the common limb.

creating a significant malabsorptive effect (Marceau et al., 1998). Furthermore, the procedure has some restrictive properties because it reduces the size and distensibility of the gastric reservoir (Moy et al., 2008). This surgery has the greatest associated weight loss, approaching a 75% excess weight reduction in the long term without major nutritional complications (Scopinaro et al., 2002; Fontana and Wohlgemuth, 2010; Marceau et al., 1998), and it has the advantage of not severely restricting eating habits (Marceau et al., 1998). A BPD results in a higher weight loss than a gastric bypass and is more durable because it does not depend as much on the patient's dietary habits after surgery. However, this procedure also has a high operative mortality rate of 1.1% (Buchwald et al., 2004) due in part to its technical complexity and in part to its greater use in super-obese patients (BMI greater than 50 kg/m^2), who have a higher risk of operative mortality (Fontana and Wohlgemuth, 2010). The complications of the BPD/DS surgery include wound infection, leakage, pulmonary embolism and pancreatitis, occurring in up to 23% of patients (Marceau et al., 1998; Kim et al., 2003; Parikh et al., 2006).

15.4.3 Sleeve Gastrectomy

SG is, in effect, the restrictive component of the BPD/DS procedure described earlier (Figure 15.4). It involves stapling off the greater curvature of the stomach to create a tube based around the lesser curvature, reducing the gastric reservoir to between 100 and 150 mL. This procedure is used especially for those, such as super-obese patients, who are at high risk from conventional bariatric surgery. SG can often provide preliminary

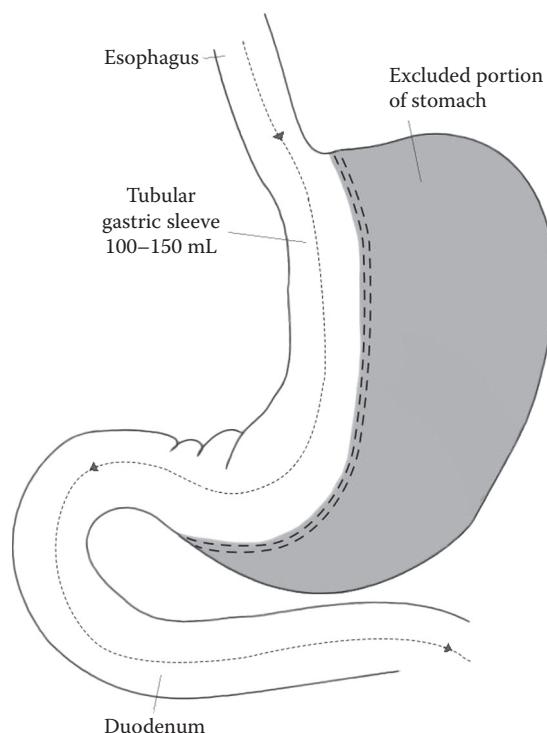


FIGURE 15.4

Illustration of sleeve gastrectomy.

weight loss and can be augmented by RYGB or BPD/DS later, when the patient is less at risk (Fontana and Wohlgemuth, 2010). It is also supported as a stand-alone treatment because of the ease of performing the procedure and the low complication rate. SG is reported to reduce the excess weight by 59% (Lee et al., 2007); however, patients with a higher BMI may remain well above their ideal weight and need further treatment.

15.4.4 Laparoscopic Gastric Banding

Laparoscopic gastric banding (LGB) is designed to restrict the amount of food that can be consumed; it is generally preferred to RYGB, in Europe and Australia (Buchwald and Williams, 2003). The technique illustrated in Figure 15.5 generally involves implanting a saline-filled band that encircles the proximal end of the stomach, creating a small gastric pouch (20–30 mL) at the proximal end of the stomach (Kuzmak, 1991). This procedure gives the patient a sensation of fullness after consuming only a small amount of food. The band allows a slow outflow of the food into the distal stomach for digestion and uptake of nutrients. This technique has the lowest short-term complication rate but demonstrates more long-term negative effects, with 12% late complications such as gastric prolapse, erosion or infection. The mortality rate is the lowest among common bariatric surgical procedures (Buchwald and Williams, 2003). Long-term complications are more common for LGB than for RYGB, coupled with higher rates of repeat or revision surgical procedures (Tice et al., 2008). LGB is considered the least effective of bariatric surgeries, with 50%–60%

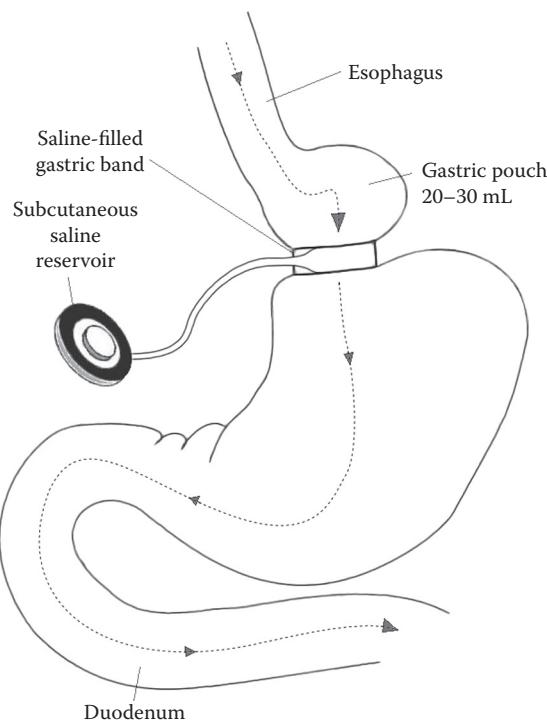


FIGURE 15.5

Laparoscopic gastric banding. Gastric banding reduces the amount of food that the patient can eat before feeling full, while allowing the food to pass slowly to the remaining portion of the stomach for digestion. The subcutaneous saline reservoir allows for a laparoscopic adjustment of the tightness of the band.

excess weight loss (Belachew et al., 1998). The advantages of this technique include reversibility and the possibility of applying laparoscopic techniques to the initial surgery and adjustments.

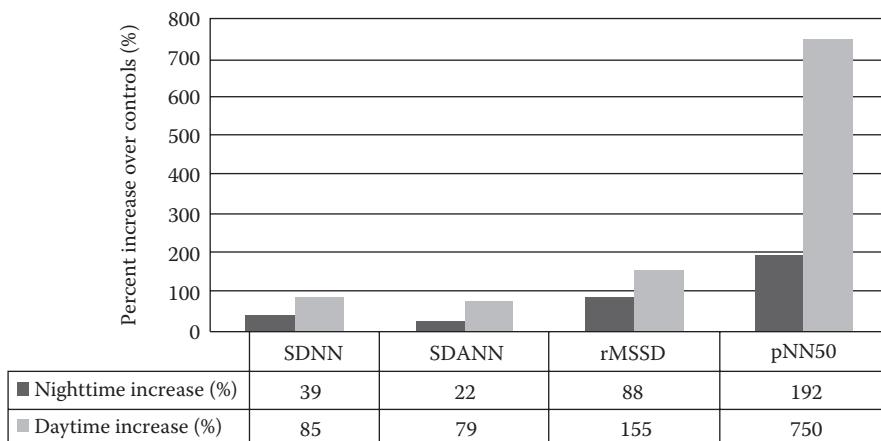
All of the bariatric techniques, described here, lead to weight loss and improvement in the morbid conditions associated with obesity. Buchwald et al. (2004) found that diabetes resolved in 70%–82% of the patients after surgery, while 78%–93% of patients experienced an improvement in their condition. The resolution of diabetes was most common after BPD/DS (98.9% resolution), compared with RYGB (71.6%), SG (70%, includes improvement) (Hamoui et al., 2006) and LGB (47.9%). In hyperlipidemia, 99% of the patients undergoing BPD/DS experienced resolution compared to 96.9% of the RYGB patients. Hypertension resolved in 61.7% of patients and improved in 78.5% of bariatric surgery patients, with no procedure demonstrating a clear advantage. SG has been shown separately to cause an improvement or a resolution of hypertension in 32% of the patients, well under the average for hypertension in bariatric surgery. A cessation of obstructive sleep apnea has been observed in 85% of the patients. Overall, BPD/DS shows the best rate of improvement and resolution of the comorbidities, while LGB has, by far, the least observed benefit.

15.5 Effects of Bariatric Surgery on HRV

Because bariatric surgery is highly specialized in nature, it is performed only in few centers, and even fewer centers study the effects of the bariatric procedures on autonomic function. We review these reports.

Karason et al. (1999) conducted one of the earliest investigations. They compared obese patients who underwent either gastroplasty ($n = 28$) or dietary treatment ($n = 24$) with matched non-obese controls ($n = 28$). All the patients underwent 24 h Holter recordings pre-operatively and 1 year post-operatively. After 1 year, patients who were treated with bariatric surgery had a significantly reduced body weight, heart rate, BMI, blood pressure and levels of norepinephrine excretion compared to the dietary treatment patients. They found that the standard deviation of the mean of consecutive 5 min segments of normal-to-normal RR intervals (SDANN) and the standard deviation of normal-to-normal RR intervals (SDNN) increased by 5% and 24%, respectively, in patients who underwent bariatric surgery. In the frequency domain, both low-frequency (LF) and high-frequency (HF) amplitudes increased by 21% in the weight-loss group. These changes suggest an overall improvement in the HRV, but extra gains in HF power and the short-term variability suggest a change in autonomic balance, consistent with a restoration from autonomic imbalance brought about by obesity. Karason et al. (1999) also reported that changes in the spectral power due to surgery were visible only during daytime hours.

Nault et al. (2007) presented a study involving 17 morbidly obese patients, 10 of whom underwent BPD/DS (mean BMI of $52.3 \pm 7.6 \text{ kg/m}^2$) and 7 matched controls (mean BMI of $54.3 \pm 10.9 \text{ kg/m}^2$, NS) who did not. They recorded the ECG pre-operatively and once post-operatively between 6 and 12 months (mean 6.8 ± 1.8 months). The BPD/DS resulted in an average weight reduction of 28.3%, accompanied by a decrease in the mean and minimal heart rates. Patients also demonstrated reductions in low-density lipoprotein (LDL) cholesterol (37%), apolipoprotein B (32%), triglycerides (35%), blood glucose (25%)

**FIGURE 15.6**

The percentage increase in the measures of the HRV for patients after bariatric surgery compared to obese controls. The HRV increases were more pronounced during daytime measurements as opposed to nighttime measurements. (Based on results from Nault, I., Nadreau, E., Paquet, C., Brassard, P., Marceau, P., Marceau, S., Biron, S., Hould, F., Lebel, S. and Richard, D., *Metab. Clin. Exp.*, 56, 1425–1430, 2007.)

and insulin (71%). Significant increases in the time domain HRV parameters SDNN, SDANN, the root-mean-squared value of differences between successive RR intervals (RMSSD) and the percentage differences between normal-to-normal RR intervals greater than 50 ms (pNN50) were observed, with greater increases during daytime compared to nighttime, as shown in Figure 15.6. A frequency domain analysis revealed increases in overall power but no shift in LF/HF balance. Echocardiographic signs indicating cardiac remodeling suggested a potential resolution of hypertrophy and heart failure in these patients. Overall, the study population showed normalized levels of fasting glucose and a decrease in fasting insulin. The authors suggested that functional changes involved in the BPD surgery may lead to an unique physiologic and metabolic process, affecting the autonomic tone.

Perugini et al. (2010) studied 30 patients who were to undergo RYGB surgery. All patients underwent 24 h Holter recordings pre-operatively and at 2 weeks and 6 months post-operatively. They documented a significant weight loss, with the BMI dropping from 46 ± 6 to $35 \pm 5 \text{ kg/m}^2$ at 6 months and the excess body weight dropping from 151 ± 39 to $83 \pm 37 \text{ kg}$. Patients also demonstrated reduced triglycerides and cholesterol:high-density lipoprotein ratio, with an increase in high-density lipoproteins. Following the procedure, all patients also exhibited a significant improvement in HRV measures (increased HRV index, SDNN, the mean of the standard deviation of consecutive 5 min segments of normal-to-normal RR intervals [SDNN index], SDANN and RMSSD and a decreased average heart rate) along with decreased measures of insulin resistance and increased measures of Glucose Disposition Index (HOMA-DI). They observed that HRV was more significantly related to insulin resistance than to the degree of obesity, with obesity correlating weakly with insulin resistance but not with HRV at all. It is suggested that sympathetic dominance in obesity may be driven by insulin.

The results of Perugini et al. (2010) contrasted with those of a smaller study by Bobbioni-Harsch et al. (2009), who investigated the effect of post-bariatric surgical weight reduction through RYGB, on cardiac autonomic neural regulation and insulin resistance in 12 obese

women. They performed 24 h Holter ECG monitoring, a 120 min euglycemic/hyperinsulinemic clamp, a measurement of the plasma glucose/free fatty acid/insulin leptin/adiponectin and a measurement of the body composition via body impedance analysis. These tests were performed pre-operatively and at 3 and 12 months post-operatively. In these subjects, the BMI went from 44.6 ± 1.1 kg/m² pre-operatively to 37.1 ± 1.2 kg/m² at 3 months and 29.7 ± 1.7 kg/m² at 12 months. The excess body weight fell from 59.7 ± 2.6 kg pre-operatively to 46.2 ± 2.4 kg at 3 months and 31.0 ± 3.5 kg at 12 months. The plasma insulin levels decreased concurrently, from 0.97 ± 0.13 ng/mL pre-operatively to 0.47 ± 0.04 ng/mL at 3 months and 0.31 ± 0.03 ng/mL at 12 months, significantly lower than the control group ($p = .002$). At the same time, the glucose uptake was increased from 4.3 ± 0.5 mg/kg lean-body-mass/min pre-operatively to 4.9 ± 0.5 mg/kg lean-body-mass/min at 3 months and 7.0 ± 0.5 mg/kg lean-body-mass/min at 12 months. The authors interpreted the decrease in the plasma insulin and increase in the glucose uptake to indicate a decreased insulin resistance. They found that the majority of HRV indices that they measured (HRV index, SDNN, pNN50 and RMSSD) increased after 3 months but showed a slight regression in 12 months post-surgically. For example, the SDNN of the patient group was 116 ± 7 ms pre-op, 161 ± 10 at 3 months, $p = .008$ versus pre-op, and 146 ± 15 at 12 months, $p = .03$ versus pre-op and $p = .02$ versus 3 months. Concomitantly, the energy intake was halved after 3 months and rose again by one-third at 12 months. In addition, the plasma leptin decreased after surgery, the plasma adiponectin and the free fatty acids increased after surgery, and the glucose uptake increased over the course of follow-up. They postulate that leptin, adiponectin and free fatty acid concentrations also contribute to autonomic changes in the weight loss. The study demonstrates that cardiac autonomic improvement may be reversible and also illustrates the dynamic progression of the weight loss and the physiological change after the bariatric surgery. The authors also noted that, unlike HRV parameters, which were reduced slightly at 12 months, the glucose uptake continued to increase. The authors suggested that a change in the energy uptake and the changing body weight were responsible for 20% and 16% of the cardiac autonomic improvement, respectively. Bobbioni-Harsch et al. (2009) concluded that marked improvements in the metabolic and cardiac functions induced by the weight loss occurred concomitantly and that there was no significant relationship between the insulin resistance and the HRV.

Neither Perugini et al. (2010) nor Bobbioni-Harsch et al. (2009) accounted for the effects of β -blockers, angiotensin-converting enzyme inhibitors and statins in their studies, which may have had an effect on their results. Furthermore, the two studies used different measures of insulin resistance; Perugini et al. used the homeostatic model of assessment-insulin resistance (HOMA-IR) test to quantify glucose uptake corresponding to the insulin sensitivity, while Bobbioni-Hirsch et al. used the hyperinsulinemic euglycemic clamp procedure. Although Perugini et al. (2010) did not observe a correlation between body fat and HRV, other studies have observed such a correlation (Peterson et al., 1988; Alvarez et al., 2002; Scherrer et al., 1994; Emdin et al., 2001). Finally, both studies made only two follow-up measurements: Perugini et al. (2010) recorded data at 2 weeks and 6 months post-operatively, while Bobbioni-Harsch et al. (2009) recorded data at 3 and 12 months post-operatively. Larger sample sizes with an increased frequency of recording the physiological variables (e.g., once every month up to 12 months) are needed to resolve differences in these observations.

Machado et al. (2009) studied 71 obese patients (mean BMI of 43 kg/m²) who were selected for RYGB and analyzed effects of age and gender. The 24 h Holter recordings were obtained before and 6 months after surgery. Patients demonstrated an overall weight

loss of 25.5%, with men losing more weight than women. In addition, they observed that younger patients lost more weight than older patients and had a greater decrease in their BMI and waist circumference. There was a significant increase in SDNN, pNN50 and rMSSD 6 months after surgery. While SDNN was similar in both genders before surgery, there was a greater increase in SDNN for men than for women after surgery and weight loss. This may be because men tend to demonstrate a higher sympathetic drive than women (Dart et al., 2002). Increases in the pNN50 and rMSSD after the weight change diminished with age, although the values of the pNN50 and rMSSD prior to surgery already diminished with age.

Alam et al. (2009b) studied 11 morbidly obese patients (BMI: $48.2 \pm 6.9 \text{ kg/m}^2$) before and after they underwent BPD/DS (5 patients) or LGB (6 patients). They recorded ECG during supine, sitting and mild exercise pre-operatively and at 1, 6 and 12 months post-operatively. On average, there was a decrease in excess weight of $19.8\% \pm 7.5$ for BPD/DS versus $23\% \pm 8.2$ for LGB after 1 month, $36.4\% \pm 13.5$ versus $46.3\% \pm 14.6$ after 6 months and $48.6\% \pm 21.0$ versus $53.8\% \pm 15.5$ after 12 months. Both LGB and BPD/DS were followed by improvements in diabetic patients with respect to lowered dosage or discontinuation of their anti-diabetic medications. Both procedures resulted in similar increases in HRV, as measured by sample entropy, detrended fluctuation analysis (DFA), SDNN and rMSSDN, but they did not differ significantly with respect to the changes in cardiac autonomic parameters, suggesting that weight loss was the common denominator in improvement of comorbidities and HRV parameters for both patient groups. Larger sample sizes are needed to gain further insights into the effects of each type of surgery on the ANS.

Alam et al. studied HRV during bariatric surgery itself to determine whether restoration of autonomic function following procedures was due to direct effects of surgery rather than to subsequent effects of weight loss. In that study, ECG was recorded throughout the duration of surgery (Alam et al., 2009a). They compared laparoscopic RYGB with open BPD/DS and included a control group of non-obese patients undergoing laparoscopic-fundoplication surgery for gastroesophageal reflux disease (GERD). They found that during surgery, LF power increased while HF power decreased as a result of anesthesia, but there was no difference between RYGB and BPD/DS groups during this period. The key parameter, the multifractal dynamics of the HRV signal during the surgery, did not significantly discriminate between the RYGB and BPD/DS groups, but was significantly different from the non-obese patients undergoing laparoscopic surgery. A multifractal analysis, specifically the global Hurst dimension, also demonstrated a sensitivity to the temporal progression of the surgical procedure itself. They concluded that the ANS function was restored by weight loss, rather than the surgery. One limitation of this study was that the non-obese control group was treated for GERD, a condition that may have a different mechanism of ANS dysfunction (Dobrek et al., 2004).

15.6 Discussion

Several studies have explored the response of HRV and improved health to various types of bariatric surgery, and modes of improvement are consistent across different procedures. The HRV generally improves, often with a marked vagal recovery, after a

significant weight change is observed. An improvement or a resolution of the comorbidities, such as cardiovascular disease, hypertension, diabetes, insulin resistance and other metabolic abnormalities, was reported in all studies, pointing to similar mechanisms of pathology and recovery being affected by several different surgical procedures that involve varying degrees of invasiveness and functional change (restrictive vs. malabsorptive). LGB, a simple, reversible, restrictive procedure, brings about improvements or recovery of the HRV similar to BPD/DS, an invasive, open, malabsorptive procedure that produces profound changes in the anatomy and physiology of the gastrointestinal tract.

While weight loss and the accompanying autonomic restitution have been documented following bariatric surgery, there is little information comparing the recovery in comorbidities, cardiac risk and metabolic mechanisms involved, due to a specific type of surgical procedure. Any differences in the effects of different weight-loss treatments could shed light on differences due to surgical intervention, separate from the weight loss itself.

In healthy individuals, a diet-induced weight gain of 10% leads to a sympathetic activation and a reduced parasympathetic control and, conversely, a diet-induced weight loss of 10% leads to a sympathetic suppression and a parasympathetic activation (Poirier et al., 2003; Arone et al., 1995). These observations suggest that ANS has negative feedback mechanisms that respond to changes in weight, following either a weight loss or a weight gain above a person's optimal weight. Characterizing the transition between the body's reaction to weight gain and persistent pathological functions in ANS and metabolism could provide an insight into mechanisms of morbidities related to obesity.

15.7 Summary

The recovery of autonomic function after significant weight loss, such as that induced by bariatric surgical procedures, is multifactorial in nature. Obesity has a negative effect on breathing (Burwell et al., 1956), which consequently reduces the HRV. A combination of an augmented cardiac risk profile, a metabolic reaction due to weight gain, a metabolic dysfunction and possibly other mechanisms may all contribute to sympathetic activation, vagal withdrawal and overall depression of the HRV as a result of the obesity.

The direct effects of the anatomical change, along with effects of removing the stress on a patient's physiology brought about by obesity, may all play a role in improving the HRV and autonomic function after bariatric surgery. There is a need to explore and validate mechanisms that bring about restitution of HRV after drastic weight loss, such as that due to bariatric surgery, for understanding the physiology of obesity and autonomic function. While it is clear that HRV measures of ANS function improve after bariatric surgery, it is not yet clear if this process is a reversal of reduced HRV brought on by obesity, or a response to anatomical and physiological changes that accompany the bariatric surgery. Such knowledge may contribute to an understanding of interactions of the ANS with obesity mechanisms, resulting in obesity-related pathological conditions. Furthermore, an understanding of the dynamics of HRV in obesity and after bariatric surgery opens doors for using HRV as a tool for an assessment of the cardiac risk in these patients.

Abbreviations

BMI	Body mass index
BPD	Biliopancreatic diversion
BPD/DS	Biliopancreatic diversion with duodenal switching
DFA	Detrended fluctuation analysis
GERD	Gastroesophageal reflux disease
HF	High frequency
HOMA-DI	Homeostatic model of assessment-disposition index
HOMA-IR	Homeostatic model of assessment-insulin resistance
LDL	Low-density lipoprotein
LF	Low frequency
LGB	Laparoscopic gastric banding
MSNA	Muscle sympathetic nerve activity
pNN50	Percentage differences between normal-to-normal RR intervals greater than 50 ms
RMSSD	Root-mean-squared value of differences between successive RR intervals
RYGB	Roux-en-Y gastric bypass
SDANN	Standard deviation of the mean of consecutive 5 min segments of normal-to-normal RR intervals
SDNN	Standard deviation of normal-to-normal RR intervals
SDNN index	Mean of the standard deviation of consecutive 5 min segments of normal-to-normal RR intervals
SG	Sleeve gastrectomy

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Section IV

Clinical Applications of Heart Rate Variability—Chronic Disorders

16

Heart Rate Variability in Congestive Heart Failure

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16.1 Cardiac Autonomic Derangements in Heart Failure

The incidence and progression of heart failure are associated with an increasing severity of autonomic derangements, specifically a compensatory increase in activity of the sympathetic nervous system and a decrease in activity of the parasympathetic nervous system (Floras, 2009; Binkley et al., 1991). In this simplistic model, left ventricular (LV) systolic dysfunction elicits an increase in sympathetic outflow directed at the entire vascular system. From this perspective, increasing sympathetic activity is mediated by reflexes associated with arterial baroreceptors, which respond to decreased systolic and pulse pressures and decreased functioning of cardiopulmonary baroreceptors due to prior myocardial infarction (MI), receptor down-regulation or ventricular dilatation. If this simplistic description were sufficient, more severe heart failure should always be associated with a decrease in both global measures of heart rate variability (HRV) and in those that specifically reflect parasympathetic activity. In reality, abnormalities in HRV among patients with heart failure have heterogeneous characteristics despite similar degrees of cardiac dysfunction, indicating that changes in the autonomic function of such patients are complex.

In his excellent review of the topic, Floras (2009) presents a far more nuanced picture of autonomic changes in heart failure. In this review, he makes the following important

points: (1) Changes in sympathetic activation, both time course and magnitude, are not a sole function of ventricular systolic function but rather are target-organ specific and (2) human heart failure is characterized by a rapidly responsive regulation of muscle sympathetic nerve activity (MSNA) by the arterial baroreflex, a reduction in cardiopulmonary reflex modulation of MSNA, a sympathoexcitatory cardiac reflex due to increased cardiopulmonary filling pressure and by variation between patients in other non-baroreflex-mediated sympathoexcitatory mechanisms, which might include comorbid sleep apnea, myocardial ischemia, obesity and sympathetic reflexes from exercising muscles. Other factors that can modify the relationship between heart failure and autonomic function include: age, possibly gender, diabetes, ischemic versus non-ischemic etiology, diastolic function and, of course, concomitant medical therapy. A detailed discussion of this complex phenomenon is beyond the scope of this review, but this perspective points to the exciting possibility that a detailed analysis of different aspects of HRV, coupled with a clearer picture of the exact nature of individual physiological changes associated with heart failure, could point to a way to obtain far more meaningful information from HRV and the progression of HRV.

Further, as will be seen in this chapter, the ability to compare findings of different studies is limited by differences in the length of ECG records used for HRV measurement as well as in the HRV measures selected. More subtle are differences that arise from precision of ECG scanning software used, or the care with which interbeat intervals are characterized (cleaned up). It is worth mentioning here, that among heart failure patients there is a tendency for disorganization in HR due to a high degree of sinus arrhythmia that does not track respiration, a phenomenon which we have termed erratic rhythm (Stein et al., 2005a,b). This phenomenon is not limited to heart failure patients and strongly affects the magnitude of HRV variables that represent beat-to-beat changes in HRV including rMSSD, pNN50, high-frequency (HF) power, normalized low-frequency (LF) and HF powers and the LF/HF ratio, making them look “better” than they really are. Graphical analyses of HR patterns, including tachograms of instantaneous HR, power spectral plots and Poincaré plots are useful in identifying erratic rhythm and should be considered whenever any analysis involving beat-to-beat HRV in heart failure patients is considered. Fortunately, novel HRV measures such as the short-term fractal scaling exponent do represent changes brought about by increased erratic rhythm, and that may help explain why they are better at predicting outcomes than many traditional HRV measures (Stein et al., 2005a,b).

16.2 Predictors of Incident Heart Failure

One population at high risk of incident heart failure is the group with acute MI (AMI). Perkiomäki et al. (2010) recently compared the ability of brain natriuretic peptide (BNP), HRV and baroreflex sensitivity (BRS) assessed by the phenylephrine method to predict acute heart failure hospitalizations in 569 patients initially hospitalized for AMI who were followed for up to 8 years. Of these, 79 patients reached the study endpoint. After adjustment for covariates, increased BNP, decreased values for short-term fractal scaling exponent and decreased HR turbulence slope (TS), all identified patients at increased risk of heart failure hospitalization after their MI. To our knowledge this is the only study to have tested the ability of abnormal HRV to identify post-MI patients at risk for congestive heart failure (CHF) hospitalization.

16.3 Association of HRV with Heart Failure Severity

Various clinical measures are used to quantify heart failure severity, including: New York Heart Association (NYHA) Class I–IV, left ventricular ejection fraction (LVEF), echocardiographic measures of ventricular function, pulmonary capillary wedge pressure and markers of diastolic function. The relationship of these markers with HRV has been explored in several studies. Lucrezio et al. (2000) collected 5 min ECG recordings in 75 ambulatory CHF patients being evaluated for transplant. No correlation was found between NYHA functional class and HRV (although it must be recognized that most patients were class III or IV), but significant relationships were found between HRV (especially decreased LF power) and other hemodynamic parameters including LVEF. Also, interestingly, decreased HRV (specifically LF power) was highly related to *right ventricular* dysfunction. In another study, Soejima et al. (2000) evaluated 24 h HRV as a marker for severity of heart failure in 90 patients (51 ischemic, 39 with idiopathic dilated cardiomyopathy [DCM]) with LV dysfunction defined as LVEF <40%. Severity of heart failure was also assessed by LVEF, LV end-systolic diameter and left atrial diameter. Normal controls ($n = 52$, aged >50) were selected from a prior study. None of the measures of heart failure severity correlated with NYHA. HF power declined in heart failure patients but reached its nadir in NYHA class II patients, whereas LF power continued to decline with increasing NYHA class. Normal versus abnormal HRV was determined by the lower limit of LF or HF among normal controls. With the exception of NYHA class IV patients (100% abnormal), subjects with HRV within normal limits could be found in each functional class, although the proportion with normal HRV declined to 58% in class III. An interesting corollary to these observations was an investigation of differences between patients with LVEF $\leq 40\%$ who did or did not have symptomatic heart failure (Kocaman et al., 2010). They reported that although BNP and NT-pro-BNP levels were significantly higher in symptomatic patients, only markedly decreased HRV in these patients independently predicted whether patients were symptomatic.

It is well known that diabetes is associated with decreased HRV, and is prevalent in patients with heart failure (Burger and Aronson, 2001). Aronson and Burger (2001) compared HRV among diabetic and non-diabetic patients with heart failure and concluded that diabetes had no additional effect on HRV among heart failure patients. HRV was extremely depressed in this study, however, and all patients were in NYHA functional class III and IV. This question was revisited by Stein et al. (2010). They analyzed the effect of diabetes on HRV in NYHA class II and III heart failure patients via a *post hoc* analysis of pre-treatment HRV in 80 diabetic and 74 non-diabetic systolic heart failure patients entered into a heart failure drug evaluation study. Results indicated that diabetes was associated with further decreases in age-adjusted HRV among NYHA class II patients, but had little further impact on the more depressed HRV of class III patients.

Finally, systolic dysfunction might not be the only factor influencing HRV, because patients with systolic dysfunction also have varying degrees of diastolic dysfunction, and some patients present primarily diastolic impairment. Arora et al. (2004) reported in a study involving 19 patients with diastolic heart failure, 9 patients with systolic heart failure and 9 healthy volunteers, that time and frequency domain HRV was reduced in both heart failure groups compared to healthy controls, and that patients with diastolic heart failure had higher HRV than those with systolic heart failure. Reduced HRV in patients with restrictive filling was also reported by Poulsen et al. (2001) who studied 64 consecutive patients with first AMI. Furthermore, the presence of a restrictive filling pattern and

reduced ejection fraction (EF) were independent predictors of cardiac death and readmission to the hospital with heart failure. Stein et al. (2007) explored the impact of concomitant and more severe diastolic dysfunction, categorized as impaired relaxation time versus a restrictive filling pattern on HRV in the same cohort as that analyzed by Stein et al. (2010). Consistent with other reports, the presence of a restrictive pattern was associated with further reductions in HRV, even after adjustment for clinical covariates including NYHA.

16.4 Effect of Interventions on HRV in Heart Failure

16.4.1 Cardiac Resynchronization Therapy

Cardiac resynchronization therapy (CRT) is delivered via a small implantable device (called a CRT or biventricular pacing device), which is prescribed to heart failure patients who, in general, meet the following criteria: NYHA III/IV with QRS duration ≥ 120 ms and LVEF $\leq 35\%$. By sensing the patient's natural sinus rhythm, the device delivers pacing pulses to both left and right ventricles to resynchronize the dyssynchronized contractions (between left and right) of the ventricles in order to improve cardiac hemodynamic function and heart failure symptoms. The CRT device is a proven therapy that significantly reduces morbidity and mortality among select CHF patients (Feldman et al., 2005). That is, CRT works well for many patients, but studies have also demonstrated that CRT therapy has a non-responder (lack of therapeutic efficacy) rate ranging from 18% to 52% (Auricchio et al., 2011). To our knowledge, there are no tests that can help predict beforehand which patients will respond and which patients will not respond to CRT but, as described in the next section, patients who are responders are more likely to show improvements in HRV.

In a 3-month follow-up study (Livanis et al., 2003) on 13 CRT patients, HRV (mean 24 h RR, SDNN, SDNN-I, rMSSD, total, ultralow-frequency [ULF] and very-low-frequency [VLF] power) measured via 24 h Holters, improved significantly after 3 months of CRT therapy. Improvements were also seen in NYHA functional class, quality of life, 6 min walk distance and exercise duration. Cha et al. (2008) conducted a study of 16 consecutive CRT recipients compared with 10 controls. Twenty-four hour ambulatory ECG-based HRV (measured by SDNN) increased significantly (from 82 ± 30 ms to 111 ± 32 ms) after 6 months of CRT. There were also improvements in NYHA class and LVEF while at the same time cardiac sympathetic activity measured by iodine-123-metiodobenzylguanidine (I-MIBG123) decreased significantly, also indicating improvement in cardiac autonomic control.

In another test of the effect of CRT on HRV, Adamson (2003) randomized 25 patients who were on CRT therapy to CRT-ON and 25 to CRT-OFF. HRV, measured as the standard deviation (SD) of the atrial cycles sensed by the CRT device, was monitored. After 2 months, HRV was higher in the CRT-ON group than in the CRT-OFF group, despite a similar mean atrial cycle length between these two groups (844 ± 129 vs. 851 ± 110 ms). However, changes in plasma catecholamines from baseline to follow-up were not different between these two groups. Hence, these authors conclude the "improvement in ventricular performance by CRT shifts cardiac autonomic balance toward a favorable profile that is less dependent on sympathetic activation." However, it must be noted that SDANN is primarily a marker of circadian rhythm. Thus, if patients feel better and are more active, this is likely to be reflected in SDANN.

Finally, Gademan et al. (2008) studied 32 CRT patients to determine the acute effect of CRT on arterial baroreflex function the day after they received device implantation. HRV (SDNN during 10 min of supine paced breathing) and non-invasive BRS were measured during a randomized order of CRT on/off for each patient. CRT ON resulted in a significant immediate increase in SDNN (18.5–24.0 ms) and a significant BRS increase as well, with the latter correlating significantly ($r = 0.44$) with the change in LVEF.

Today, many CRT devices offer HR and HRV-based diagnostic features, such as HRV Footprint/Heart Rate trend/HRV Trend (Boston Scientific) or Heart Rate Trend or HRV Trend (Medtronic), in order to capture baseline HRV and trends in the HRV status of heart failure patients. These HRV features are mostly time domain indices based on SD over a window of approximately 5 min. Unlike HRV calculated from a single 24 h Holter ECG, CRT device-based HRV enables follow-up in a large number of patients at multiple follow-up time points.

Using this technology, Gilliam et al. (2007) conducted an analysis based on 1421 patients in the Heart Failure HRV registry for patients who received CRT devices capable of HRV measurement. Measures included HRV footprint, SDANN, mean, minimum and maximum of HR at four visits over a year (2 weeks, 3 months, 6 months and 12 months after implantation). Significant ($p < .001$) improvements were found in SDANN and HRV footprint, along with significant improvements in clinical status such as quality of life, activity and NYHA. The greatest change was observed between the 2-week and 3-month visits.

In another 12-month follow-up study on 509 consecutive CRT patients, device-computed HRV (SDANN) increased after 4 weeks of CRT (from 69 ± 22 to 82 ± 27 ms, $p < .001$) with a further increase observed after 6 months (Landolina et al., 2008). In a randomized 12-month follow-up study (Piepoli et al., 2008), both control ($n = 45$) and CRT groups ($n = 44$) underwent cardiopulmonary exercise testing, 2D-Echo, HRV measurements, carotid baroreflex and BNP assessments at baseline, 6-month and 12-month follow-up. It was observed that both cardiac indices and BNP concentration improved after 6 months and such improvement persisted at 12-month follow-up. CRT “responders” as defined by changes in LVEF and LV diameters, had greater improvements in the above assessments. Less depressed functional status at baseline was the strongest predictor of being a responder to CRT therapy.

Although it is a proven therapy for CHF patients with qualified indications, CRT (device + surgery) is associated with a high non-responder rate as well as potential patient complications due to the invasiveness of the therapy. Even though considerable evidence exists for restoration of HRV along with overall improvement in heart failure status by CRT, whether HRV can add to functional status parameters in predicting who will respond to therapy is still an open question. Further discussion of the relationship of HRV measured by implantable devices and outcomes will be found in Section 16.5.4.

16.4.2 Pharmacological Interventions

The effect of pharmacological interventions on HRV in heart failure patients has been examined in numerous studies, although many of them involve relatively small numbers of patients. This topic has recently been reviewed by Desai et al. (2011). Use of ACE inhibitors (ACE-I) has been clearly associated with symptomatic improvement and better survival in heart failure, but whether this is mediated by changes in the autonomic nervous system is not completely clear. The effect of different ACE-I on HRV in heart failure yielded inconsistent results. No effect on HRV was found in association with treatment with Lisinopril in a study of 16 patients with mild-to-moderate heart failure (Inkoko et al.,

2001), but Zhang et al. (1995) reported a positive effect of treatment with Enalapril in 12 similar patients. Two early studies, one using Zofenopril ($n = 13$) (Binkley et al., 1993) and the other using Captopril ($n = 32$) (Flapan et al., 1992), reported an increased in parasympathetically mediated HRV in heart failure, but Kamen et al. (1997) suggested that this effect was dose-dependent with increased parasympathetic control of HR only with low doses of Captopril. However, their sample size consisted of only nine patients.

Angiotensin receptor blockers (ARBs) are also common therapy in heart failure patients. De Tommasi et al. (2003) compared HRV effects of Valsartan (an ARB) and Lisinopril (an ACE-I) in 80 mild-to-moderate heart failure patients randomized to one or the other therapy over 16 weeks. No difference was observed between therapies in the effect on HRV, but plasma norepinephrine (NE) levels showed greater reductions with Valsartan. Vaile et al. (2001) failed to find any effects of the acute and chronic administration of another ARB, candesartan, on the HRV in 21 patients, despite its beneficial effects on baroreceptor sensitivity.

β -Blockers and Carvedilol (a combined α - β blocker) have had considerable success in improving both EF and survival in heart failure patients. Since these drugs act directly on the autonomic nervous system, it is not surprising that they have uniformly been associated with improved HRV in most heart failure patients. Lin et al. (1999) studied the effect of β -blocker therapy with Atenolol before and after 1, 3, 6 and 9 months in 15 patients with advanced heart failure. Although 2 patients died within a month, the 13 survivors showed marked improvements in cardiac function and increased HRV after at least 3 months of therapy. In another study of Atenolol treatment in 10 patients with advanced heart failure, Lin et al. (2004) reported that 3 months of treatment also improved heart rate turbulence (HRT) slope and that this improvement was strongly correlated with improvements of vagally modulated HRV indices. Aronson et al. (2001) tested the effect of β -blocker therapy on HRV in 199 patients with decompensated heart failure. Of these patients, 46 received a β -Blocker (Carvedilol, Atenolol, Metoprolol or Labetalol depending on what was prescribed by their physician). Patients on a β -blocker, despite being more likely to have coronary artery disease, had significantly higher HRV than those who were not, suggesting the potential benefit of β -blockers even during this time of high stress.

Multiple studies with small-sample sizes have reported a generally beneficial effect of Carvedilol therapy on HRV in heart failure patients. In perhaps the largest such study, Nessler et al. (2007) followed 86 patients in class II or III heart failure over a year of treatment. Patients were already receiving an ACE-I and diuretics. The focus of the study was on risk factors for sudden cardiac death, including HRV. After 1 year of treatment, the number of risk factors per patient including HR >75 bpm or SDNN <100 ms declined significantly (from 50 to 16 for HR and from 19 to 9 for SDNN). Akdeniz et al. (2006) studied the effects of Carvedilol therapy in heart failure from the perspective of ventricular repolarization characteristics. They studied 31 patients over 6 months. Unlike Nessler et al. (2007), they found little change in HRV, although SDANN did increase, but they reported a significant improvement in various QT-based ventricular repolarization parameters. Mortara et al. (2000) performed a case-control study to investigate the effect of 6 months of Carvedilol on HRV and BRS in 19 consecutive patients in stable class II or III heart failure. Controls were matched based on age and heart failure characteristics from an existing database. In addition to symptomatic improvement, which was found in all studies, significant decreases in HR and improvements in SDNN and rMSSD and improvements in BRS were reported while no change was seen in controls. Also, during 19 months of follow-up, fewer Carvedilol-treated patients than controls reached an endpoint of death or transplantation (31% vs. 58%). Bullinga et al. (2005) performed a randomized study of 4 months of Carvedilol ($n = 17$) versus placebo ($n = 12$) in symptomatic heart failure patients. The group

treated with Carvedilol had significant increases in total power, VLF power, HF power, SDNN, rMSSD and pNN50, and those changes corresponded with improved hemodynamics. Finally, Ridha et al. (2002) included the short-term fractal scaling exponent (DFA1), one of the strongest predictors of mortality among cardiac patients (Stein et al., 2005b), as well as other HRV measures in a study of 15 heart failure patients (class II–III) treated for 12 weeks with Carvedilol. The average HR decreased significantly while parameters such as LF and HF as well as rMSSD and pNN50 increased. DFA1 increased significantly especially for those with the most depressed values of the parameter. Also, the change in DFA1 correlated strongly ($r = 0.63$) with the change in LVEF.

Spironolactone, an aldosterone blocker has also been shown to improve symptoms and survival in heart failure as well. Korkmaz et al. (2000) studied the effects of Spironolactone on a group of 126 patients with heart failure and angiographically documented coronary artery disease. HRV was measured on three occasions, at baseline, and at 1 and 12 months of therapy. After 1 month of therapy, the triangular index of HRV and pNN50 increased significantly and this effect persisted for 12 months. Changes in echocardiographic parameters and symptomatic improvement were noted. However, changes in normalized LF or HF power were not seen. Shehab et al. (2008) investigated the effect of Spironolactone versus the ARB Losartan versus both on HRV in eight patients with class III–IV heart failure. They reported that each treatment resulted in increased HRV (triangular index, SDANN, rMSSD), with no differences between treatments. However, there does not seem to have been a washout period between treatments, so these results have to be interpreted with caution.

16.4.3 Exercise Training

It was once believed that patients who developed heart failure needed to rest in order to avoid putting additional stress on their already compromised cardiovascular systems. This advice has been proven to be incorrect, and now, exercise is recognized as an important component of managing patients with heart failure. In addition, several studies with relatively small enrollments of class II–III heart failure patients have suggested that the benefit of exercise in heart failure is mediated by favorable changes in autonomic function. In the first of these studies, Kiilavuori et al. (1995) randomized 8 heart failure patients to a training group and 12 to a usual care control group. The training consisted of 3 months of exercise on a bicycle ergometer (30 min, 3×/week, 50%–60% of VO_2 peak). A significant “training effect” was seen for exercise duration with a trend to increased VO_2 peak and these were unchanged among controls. Daytime HF power increased in the training group and the LF/HF ratio decreased as well. The LF/HF ratio also decreased in the control group.

Malfatto et al. (2002) studied the effect of 3 months of low-intensity rehabilitation compared with conventional therapy in only 45 patients (30 receiving rehabilitation, 15 not) and further studied the effect of an additional 6 months of at home exercise in 11 of those in the rehabilitation group. LF/HF was tested during supine rest with free breathing, supine rest with paced breathing, and during standing. After 3 months, resting HRV was unchanged, but LF/HF during paced breathing and during standing increased significantly, as did VO_2 peak. This favorable trend was more pronounced after 6 months of exercise at home, while no changes were seen in those randomized to conventional care.

Selig et al. (2004) randomized 19 heart failure patients to 3 months of resistance training using hydraulic ergometers. There were 20 patients in the control group. Both strength and endurance increased in the exercise group but were unchanged in the control group. VO_2 peak increased in the exercise group and actually decreased in the control group.

The LF/HF ratio decreased in the exercise group and was unchanged in the control group suggesting improved autonomic balance and supporting the beneficial effect of this form of exercise training in heart failure patients.

Recently, Piotrowicz et al. (2009) studied the effect of 8 weeks of physical therapy on HRV, HRT and HR recovery after exercise in 41 patients with heart failure. All patients demonstrated improved physical fitness. Training was associated with a significant increase in SDNN, HF power and a decrease in the LF/HF ratio, but there was no change in HRT or HR recovery.

16.5 HRV and Risk Stratification in Heart Failure

16.5.1 HRV and Outcomes in Heart Failure of Mixed Origins

Although there is limited evidence that HRV may be higher in patients with DCM compared to patients with ischemic cardiomyopathy, many studies of HRV and outcomes have included heart failure patients of both etiologies. Most studies have focused on stable patients, usually in NYHA class II–III heart failure. However, patients in acute heart failure have been studied. Other investigators have focused on heart failure after AMI; still others on patients with advanced heart failure (class III–IV) and at least one included patients described as having mild-to-moderate heart failure. Usually, HRV has contributed risk stratification as an independent variable, but results have not been consistent as to the specific HRV measure that best predicts outcomes. This could be due to differences in the study design and algorithms used to compute HRV measures or the specific etiology or degree of heart failure. In general, as can be seen from the studies cited below, traditional time and frequency domain HRV have had a strong association with mortality due to pump (i.e., mechanical) failure and a less clear, but sometimes significant, association with sudden death (typically due to arrhythmia).

Ponikowski et al. (1997) explored the prognostic value of HRV in NYHA class II–IV patients of whom 24 had heart failure due to idiopathic DCM and 78 had heart failure due to ischemic disease. During a mean follow-up of 584 days, 19 patients died. SDNN <100 ms identified patients more likely to die. Also, the combination of decreased SDNN and VO₂ peak <10 mL/kg/min identified a subgroup with a 1-year survival of 68% compared to 94% for the remaining patients.

Guzzetti et al. (2000) examined the prognostic power of both spectral and non-linear HRV measures from 24 h Holters in 30 stable heart failure patients followed for 2 years. In a model that also included HR and SDNN, they found that decreased values for normalized LF power were an independent predictor of mortality. Bonaduce et al. (1999) also examined the predictive value of HRV to beyond that of clinical data and measures of LV dysfunction in 97 patients with moderate heart failure (LVEF ≤40%) of mixed origin. Mean follow-up was for 39 months during which period 32 patients died. Decreased LF/HF ratio and decreased pNN50 entered the model which also included age and LV end-diastolic volume.

The UK-Heart study (Nolan et al., 1998) focused on the prognostic significance of HRV in 431 outpatients with NYHA class I–III CHF and showed that reduced SDNN predicted mortality better than any conventional or clinical measure. Annual mortality rates for the study population were 5.5% for SDNN >100 ms, 12.7% for SDNN = 50 to 100 ms and 51.4% for SDNN <50 ms. Increased mortality was mainly due to progressive heart failure rather

than sudden death among the CHF patients with reduced SDNN. LaRovere et al. (2003) examined the hypothesis that HRV measured from short-term laboratory recordings during both spontaneous and controlled breathing can predict sudden (presumably arrhythmic) death in 202 consecutive heart failure patients with moderate-to-severe disease (mean LVEF 24%). From these data, they created a risk model which they then validated against 242 subsequent patients. Sudden death was predicted by a model that included decreased LF power during controlled breathing, increased LV end-diastolic diameter and an increased number of ventricular premature beats (VPCs) on 24 h Holter recordings, suggesting that this model might be applied to risk stratification for requiring implantable cardiac defibrillator (ICD) implantation.

In another study, Guzzetti et al. (2005) examined the usefulness of HRV from 24 h Holters to predict whether patients would die suddenly or from pump failure. They tested their hypothesis on 330 consecutive patients in sinus rhythm. They were able to develop two simple multivariate models to identify those at risk for one or the other outcome. Decreased nighttime VLF power, combined with high pulmonary wedge pressure and LVEF $\leq 24\%$ identified those at high risk of progressive pump failure, while decreased LF power and increased LV end-systolic diameter were associated with sudden death.

Poinkowski et al. (1996) examined whether HRV could predict either ventricular tachycardia (VT) or death in 50 patients with advanced heart failure (mean LVEF 19%) of mixed origin during a mean follow-up of 2 years. Half of the patients went on to have at least one episode of VT, but there were no clinical differences between those who did or did not have this outcome. However, those with VT had decreased HRV. Decreased values of HF power were the only independent predictor of this outcome. The 12 patients who died during follow-up did have lower LVEFs. Upon multivariate analysis, either decreased SDNN or SDANN (which are highly correlated) was the best predictor of mortality.

HRV has been studied in stable patients with advanced heart failure. Binder et al. (1992) examined time and frequency domain HRV as a predictor of mortality in patients awaiting cardiac transplantation. SDANN < 55 ms was found to have the greatest sensitivity (90%) and specificity (91%) for increased risk of death. Furthermore, HRV was better than any other clinical risk factor.

Lucrezio et al. (2000) tested the ability of frequency domain HRV from 5 min recording to predict outcome in 75 advanced heart failure patients referred for transplant evaluations. Patients were followed for a median of 11.4 months. Decreased LF/HF ratio was an independent predictor of cardiac events. Decreased HRV, and especially LF power was also highly related to right ventricular dysfunction.

The predictive value of HRV has also been tested on hospital admission for heart failure exacerbation, that is admission for symptomatic worsening of heart failure. Aronson et al. (2004) obtained 24 h HRV during admission for 199 patients with a previous diagnosis of NYHA class III or IV heart failure. During a mean follow-up of 312 days, 40 patients died. Being in the lowest tertile of measures primarily reflecting circadian rhythm, namely, SDNN, SDANN and their frequency domain equivalents total and ULF power, identified those who were at high risk of death. The independence of these predictors was confirmed by a multivariate model.

Hadase et al. (2004) studied a similar population, although HRV was measured after pulmonary congestion had improved. In their study, 54 consecutive patients were recruited, of whom 7 died, 18 experienced cardiovascular events and 11 were re-hospitalized with worsening heart failure, within a mean 20 month follow-up. In a multivariate model, cardiac events were most strongly predicted by LF power, total power, diabetes, BNP and NYHA functional class, and decreased VLF power was also an independent predictor.

Finally, Smilde et al. (2009) tested the usefulness of HRV to risk stratify patients with mild heart failure. They studied 90 patients, 80% in NYHA class II and 20% in NYHA class III, who had been enrolled in the Dutch Ibopamine Multicenter Trial. During follow-up, digoxin, ACE inhibitor and β -blocker treatment were initiated in this unusual population. During 13 years of follow-up, 47 patients died, 39 of cardiovascular causes of which 28 were sudden. Independent risk factors for cardiac and sudden death were LVEF $\leq 30\%$ and VPCs $>20/h$. However, decreased total power was also an independent predictor of cardiovascular but not sudden death.

16.5.2 HRV and Outcomes in Ischemic Heart Failure

Blichik et al. (2002) retrospectively examined Holter data from 127 patients in the Veterans Affairs' Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure to determine if SDNN would be useful as a predictor of mortality and sudden death. They found that SDNN <65.3 ms (lowest quartile) was the only independent predictor of survival in a multivariate model, and that patients in this high-risk group also had an increased risk of sudden death.

16.5.3 HRV and Outcomes in DCM Patients

In one of the earlier trials of HRV and mortality in DCM, Yi et al. (1997) analyzed HRV in 64 patients and 19 relatives with LV enlargement and compared it with HRV in 33 healthy controls. HRV was reduced in patients and was similar in both relatives of the patients and in controls. After a mean 24 months of follow-up, those with lower HRV (SDNN <50 ms) were found to develop progressive heart failure, whereas those with higher HRV remained clinically stable. Stepwise multiple regression analysis confirmed that SDNN <50 ms was an independent predictor of heart failure progression. At about the same time, Fauchier et al. (1997) compared 24 h HRV in 93 patients with idiopathic DCM and 63 control subjects. Even patients who never had heart failure had lower HRV than controls. During a mean follow-up of 49.5 months, patients with decreased SDNN had an increased risk of death or cardiac transplantation, which remained significant upon multivariate analysis.

In the DEFINITE (Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation) trial, SDNN was evaluated by tertiles (Rashba et al., 2006). There were no deaths during a 3-year follow-up among those with SDNN >113 ms (highest tertile). Among those with SDNN 81–113 ms, 7% of the patients died and among those with SDNN <81 ms, 10% of the patients died. Among excluded patients (atrial fibrillation or $>25\%$ ectopic beats) 17% patients died.

16.5.4 HRV and Risk Stratification in ICD and CRT Patients

Implantation of ICD and CRT devices enables long-term tracking of SDNN or SDANN of atrial rhythm as an indirect assessment of autonomic function. Adamson et al. (2004) studied CRT device-measured HRV (the SD of 5 min median atrial–atrial intervals or SDAAM) from 370 patients who received CRT implantation. They found that SDAAM <50 ms was associated with an increased mortality risk and was persistently lower among patients who required hospitalization or died. Automated detection of decreases in SDAAM had a 70% sensitivity in identifying cardiovascular hospitalization, with 2.4 false-positives per patient-year during follow-up.

Among 509 patients who received a CRT device for primary or secondary prevention of sudden death or who received a CRT pacemaker, the use of CRT was associated with a significant increase in SDANN as monitored by the device (Landolina et al., 2008). However, SDANN \leq 65 ms at baseline or SDANN \leq 76 ms 4 weeks after implantation were the strongest predictors of need for transplant or mortality, and there was a significant negative correlation between the reduction in LV end-systolic volume with CRT and SDANN at baseline and at week 4. Thus, HRV measured after implantation might identify CRT patients who are less likely to benefit and who remain at higher risk for adverse events.

Piccirillo et al. (2006) had similar findings in a study of 16 patients. In that study the key HRV parameter used was LF power. They found that a low LF power (defined as \leq 13 ms²) at baseline predicted an increased risk of ventricular arrhythmias during a 1-year follow-up. CRT improved HRV, including LF power as well as systolic blood pressure variability. This study concluded that low baseline LF power may predict an increased risk of malignant ventricular arrhythmias in patients with severe CHF treated with ICD or ICD+CRT.

Molon et al. (2010) measured traditional time domain HRV (mean NN, SDANN) and novel non-linear indices for HR complexity at baseline and 1-year later in 60 CRT recipients. Poor baseline autonomic function, as measured by low HRV and especially by reduced values of complexity-related indices, was associated with adverse clinical outcomes at 1 year following implantation among these patients.

However, the DINAMIT study showed that in patients with recent MI, LVEF \leq 35% and signs of impaired cardiac autonomic modulation (SDNN \leq 70 ms and mean RR \leq 750 ms), there was no difference in overall mortality among those who randomly received an ICD (7.5%) versus controls (6.9%), although arrhythmic death per se was significantly lower in the ICD group (1.5%) than in the control group (3.5%). This led to the speculation that in this population, the ICD resulted in a change in the mode of death but not in overall survival.

Grimm et al. (2003a) studied 70 patients with idiopathic DCM who received ICD implantation due to low LVEF. Mean follow-up was 43 months. SDNN (90 ± 25 ms) in patients who received at least one ICD shock for sustained VT or ventricular fibrillation (VF) was not different from SDNN (94 ± 33 ms) in those who did not, supporting the possibility that at least SDNN is not useful for identifying heart failure patients at increased risk of sudden death.

The mixed results of using HRV for ICD risk stratification may have resulted from heterogeneous patient populations in terms of the etiology of the heart failure and different HRV measures used in various studies. Decreased SDNN, which is strongly associated with overall mortality in the heart failure population primarily reflects a lack of circadian rhythm, and is usually seen as a failure of HR to decrease during the night, and is itself a marker for a specific and severe type of autonomic dysfunction. On the other hand, despite the variety of specific HRV measures, CRT studies do consistently demonstrate increased HRV in the presence of improved cardiac function.

16.6 Novel HRV Measures in Heart Failure

Calculation of traditional frequency domain HRV requires certain mathematical conditions (often ignored), for example signal stationarity and a minimum duration for analysis. Various novel methods to extract further information from HR patterns are under active

development and will be reviewed in this section. One of the most successful is HRT, an alternative, but simple and novel approach to characterizing autonomic function that does not require the same assumptions as traditional frequency domain HRV does. Calculation of HRT generally requires the presence of at least 5 VPCs with at least 2 normal beats before and at least 15 normal beats afterwards (Bauer et al., 2008). HRT quantifies the autonomic response to the circulatory disturbance induced by a VPC and the subsequent return to equilibrium via two metrics: turbulence onset (TO) and TS. TO describes the acceleration of HR (if any) immediately after the VPC (presumably capturing acute vagal withdrawal) and TS represents the magnitude of the oscillation of HR afterwards (believed to represents baroreflex function). In general, TO <0% and TS >2.5 ms/RR are considered lower risk, based on post-MI studies, but higher cut-off points for TS values have been found in other populations (Stein et al., 2008).

HRT was originally applied to risk stratification after MI. Schmidt et al. (1999) first assessed HRT as a predictor of mortality in a study that enrolled 100 AMI patients as the training group, and then analyzed data from two existing studies of AMI patients—MPIP ($n = 715$) and EMIAT ($n = 743$) as the validation group. HRT parameters were obtained from 24 h Holter ECG. Results showed that a combination of abnormal TO and TS was the most powerful risk stratifier for mortality compared with other predictors like low LVEF or high mean HR.

The EPHESUS study enrolled high-risk patients who developed heart failure after an AMI and also post-AMI patients with diabetes and LV dysfunction (Pitt et al., 2001). Patients ($n = 481$) were randomized to Eplerenone or placebo on top of standard therapy and had a 24 h Holter recording before randomization. Over a mean 1-year follow-up, 49 patients died of cardiovascular causes. HRT was the only HRV variable that predicted outcome. In the final multivariate model which also included LVEF $\leq 30\%$, the combination of abnormal TS and TO was associated with a relative risk of 3.6 for cardiovascular death. Notably the optimal cutpoint for TS in this study was 3.0 ms/beat rather than 2.5 (Stein et al., 2009).

In another large, prospective study, Cygankiewicz et al. (2006) assessed HRT as a marker of heart failure advancement and progression. In this study 487 heart failure patients, mostly in NYHA class II, were prospectively enrolled with standard tests performed. Patients in NYHA III had significantly lower TS and greater TO than in NYHA II. HRT parameters correlated significantly with LVEF, LV diameter, as well as with N-terminal-pro-BNP levels. Multivariate analyses showed that abnormal HRT parameters were independent predictors of heart failure severity and associated LV dysfunction indicated by NYHA class III and LVEF $<40\%$.

The association of HRT with outcome was also tested in another prospective study ($n = 553$) of heart failure patients (Moore et al., 2006). HRT was calculated from 24 h Holters at baseline, and patients were followed for 5 years. Abnormal HRT, serum sodium and serum creatinine were independent predictors of death due to decompensated heart failure. The combination of these three variables was able to identify patients at increased risk of dying from decompensated HF, suggesting that these measures might help tailor therapy in this high-risk group.

Sredniawa et al. (2010) also evaluated HRT collected from 24 h Holter recordings for risk stratification among 110 stable CHF patients (NYHA II–IV, LVEF = 30% \pm 10%) followed for an average of 5.8 years. The endpoint was heart transplantation or all-cause mortality. TO, TS or the combination of both, were abnormal in 35%, 50% and 25% of all patients respectively and 31% patients reached an endpoint. There was a 5-year cardiovascular event-free rate of 33% among patients for whom both HRT parameters were abnormal,

while it was 83% among those who had at least one HRT parameter preserved. Although results showed that abnormal HRV measured as SDNN <70 ms was the most powerful predictor of outcome and decreased LVEF was the second most powerful predictor, abnormal TS + TO and also abnormal TO by itself were also independent predictors, suggesting that HRT has a role in risk prediction in CHF.

Cygankiewicz et al. (2008) studied the ability of HRT to predict mortality in 651 CHF patients with NYHA II–III, a cohort with 50% ischemic etiology. Abnormal TS was found to be independently associated with all-cause mortality, sudden death and death due to heart failure progression in a follow-up with a median of 44 months. When the prognostic value of TS for predicting total mortality was explored in various groups dichotomized by age, gender, NYHA class, LVEF and CHF etiology, there was no difference between groups. However, abnormal TS was found to be predictive for total mortality only in patients with QRS >120 ms.

HRT also had predictive value for survival when applied to DCM patients. In a follow-up (41 ± 23 months) study on 242 DCM patients from the Marburg Cardiomyopathy Database (Grimm et al., 2003b), HRT measurements, along with LVEF, LV size and NYHA class III were significantly associated with total mortality or the need for heart transplantation. An abnormal TO identified surviving patients who required heart transplantation, as did LV size and being in NYHA class III. Although abnormal TO, or abnormal TO combined with abnormal TS, were associated with a higher incidence of major arrhythmic events on univariate analysis, only LVEF was a significant independent arrhythmia risk predictor.

A similar lack of association between HRT and incident VT was reported by Koyama et al. (2002) who enrolled 50 heart failure patients (LVEF <50% and/or LV end-diastolic dimension >55 mm; 34 DCM and 16 ischemic) and a control group of 21 patients without known heart disease. Although TS and TO were identical between CHF patients with VT and without VT, both were significantly different ($p < .05$ and $p < .01$, respectively) in heart failure versus control patients.

The CARISMA and REFINE (Huikuri et al., 2009, 2010) studies included post-AMI patients with depressed LV function after AMI (LVEF <40%) and showed that HRV/HRT measured late (i.e., 6 weeks), but not early after AMI, predicted fatal or near fatal arrhythmic events in these patients.

Fractal analysis of HR dynamics has been another promising method to quantify complexity of HR and identify higher-risk heart failure patients. Mäkikallio et al. (1999) studied short-term fractal properties (exponent α -1 [DFA1] and exponent β [power law slope]) along with traditional HRV indices in 159 patients with depressed LV function (LVEF <35%) after an AMI. Reduced scaling exponent α (<0.85) was the best univariate predictor of mortality (relative risk 3.17, 95% confidence interval 1.96–5.15, $p < .0001$), with positive and negative predictive accuracies of 65% and 86%, respectively. In the multi-variable Cox proportional hazards analysis, mortality was independently predicted by the reduced exponent α ($p < .001$) after adjustment for several clinical variables and LV function.

Salo et al. (2009) studied the short-term scaling exponent [α (1) or DFA1] and frequency domain measures of HR at the baseline and 5-month follow-up among patients with DCM ($n = 16$), and found that α (1) correlated significantly with LV myocardial efficiency at baseline. They also found improvements in α (1) among a majority of patients after medical intervention. They did not find significant effects on any other indices as a result of the intervention. Hence they concluded that α (1) is an important prognostic marker in heart failure and is related to LV myocardial efficiency.

The DIAMOND-CHF (Danish Investigations of Arrhythmia and Mortality ON Dofetilide) study, which enrolled patients admitted to the coronary care unit with new or worsening heart failure, found that only reduced DFA1 was independently associated with mortality in a population that was followed for a mean of 1.8 years and had a 42% mortality (Mäkikallio et al., 2001). Furthermore, the prognostic value of HRV in this population was stronger in class II than in class III and IV patients.

The Poincaré plot of RR intervals is another non-traditional HRV measure which reflects the non-linear complexity of the HR signal. The Poincaré plot is a graph of each successive RR (or NN) interval versus the next. The Poincaré plot can be analyzed in two ways, either qualitatively by characterizing the plot or quantitatively by calculating the properties of the plot. The simplest and oldest method involves fitting an ellipse to the plot itself and then quantifying the two axes of the ellipse (called SD1 and SD2). SD1, usually the short axis, reflects beat-by-beat changes in HR and correlates almost perfectly with rMSSD. SD2, usually the long axis, reflects the range of HRs and longer-term trends. The plot can be constructed from the entire 24 h beat file or from hourly subsets of the data. The ratio of these measures (SD1/SD2) reflects the organization of the plot, with lower values associated with comet-shaped or torpedo-shaped plots and higher values reflected in more abnormal plots.

Woo et al. (1992) performed a qualitative analysis of Poincaré plots from 24 h recordings to compare HR patterns between healthy subjects ($n = 24$) and heart failure patients ($n = 24$). They found that while healthy patients presented a comet-shaped Poincaré plot, none of the heart failure patients had such a pattern but rather had one of three distinctive patterns (a torpedo-shape, a fan-shape, or a complex pattern with clusters.) Woo et al. (1994) also demonstrated that heart failure patients presenting with more complex Poincaré plots had higher serum NE levels and more severe hemodynamic decompensation, despite having similar LVEF, HR and HRV. Kamen et al. (1995) applied qualitative Poincaré plot methodology to the resting HR data (20–40 min) of a group of 23 CHF patients with a control group of age-matched subjects ($n = 20$). Their results demonstrated a significant difference ($p < .0001$) in the Poincaré plot pattern types by NYHA class.

Entropy-based methods provide another way to quantify HRV complexity. Truebner et al. (2006) found that compression entropy using beat-to-beat intervals from 24 h Holter ECG, enhanced risk stratification for cardiac death ($p = .005$) and sudden death ($p = .02$) among 300 CHF patients with ischemic heart failure etiology.

Maestri et al. (2007) applied 20 different non-linear HRV indices (symbolic dynamics, entropy, fractal-multifractality, predictability, and Poincaré plot methods, etc.) to 24 h Holter recordings from 200 stable CHF patients, in order to assess the prognostic value of a comprehensive set of non-linear HRV measures. Their results demonstrated that there were correlations >0.80 between several non-linear variables and provided evidence that, despite some redundancies in informative content of non-linear indices and differences in their prognostic power, quantification of non-linear properties of HRV provides independent information in risk stratification of heart failure patients.

16.7 Summary and Conclusions

We emphasize that the measurement of HRV in heart failure patients supports its usefulness in this population. Time domain measurements like SDNN and SDANN that capture

circadian rhythms, when decreased, are clearly associated with higher risk in many studies. However, there have been recent findings which suggest that SDNN has lost its predictive power in post-MI patients, likely due to drastic reductions in the proportion of very sick patients (to <10%) who would be identified by low values for SDNN, thanks to improved modern therapies (Jokinen et al., 2003; Erdogan et al., 2008). In general, low values for SDNN and SDANN reflect either very low levels of daytime activity or a failure of the HR to decrease at night. The prognostic value of other time domain HRV measures like rMSSD and pNN50 depend on accurate Holter scanning and on a clear distinction between normal sinus and erratic rhythm.

In the frequency domain, measurements of total and ULF power correspond to SDNN and SDANN in the time domain, although sometimes 5 min averaged total power is reported as total power due to a misunderstanding of the Holter scanner HRV software output. However, decreased values for LF power have been associated with higher risk in heart failure patients, and there is evidence that loss of LF power may reflect decreased sympathetic control of HR due to central saturation. Thus, a recent study (Kubo et al., 2011) reporting that treatment with β -blockers restored both LF power and MSNA in the LF band suggests an important mechanism by which decreased LF is associated with higher risk in CHF, and by which β -blocker therapy improves survival. Decreased normalized LF power has also been associated with adverse outcomes in heart failure. However, an important caveat must be added. In general, normalized LF power correlates very closely with the detrended fractal scaling exponent (DFA1). Lower values for DFA1 (i.e., <0.80–0.85) are associated with a higher risk of mortality in patients with heart failure and also with the presence of an erratic rhythm. Because the denominator of normalized LF power includes HF power and erratic rhythm exaggerates HF power (beat-to-beat variability), lower values for normalized LF power might be due to decreased LF power, but could also be due to a relatively increased HF power. Either of these might be associated with higher risk for mortality in heart failure, but the interpretation would be dependent on the patient population being studied.

Finally, there is considerable promise in the newer HRV measures. HRT, especially because it reflects the ability of the autonomic nervous system to adapt to perturbations in cardiac output, has been very successful in identifying heart failure patients with higher risk. There are multiple newer measures and combinations of measures that may prove to be even more closely associated with function and outcomes in these patients (Voss et al., 1998).

In conclusion, there are a large number of existing studies involving Holter recordings of patients with various degrees and types of heart failure and undergoing various types of therapies. At the same time, no *one* HRV measure or group of measures has proven itself to have the greatest value for risk stratification. Thus, the question of which measures are optimal in which patients under which circumstances has not been clearly answered. Although, as has been found in the field of risk stratification post-MI, historic trends in treatment may diminish the usefulness of some of the older datasets, sharing of these resources and testing the efficacy of existing and novel algorithms on these data sets can help optimize the utility of HRV for risk stratification in patients with heart failure. Moreover, as described at the beginning of this chapter, it is possible that specific HRV changes may be associated with individual changes in autonomic function and that tracking changes in specific HRV measures in individual patients, rather than grouping all heart failure patients together, might provide insights into the underlying pathophysiological processes.

Abbreviations

ARB	Angiotensin receptor blocker
BNP	Brain natriuretic peptide
BRS	Baroreflex sensitivity
CHF	Congestive heart failure
CRT	Cardiac resynchronization therapy
DCM	Dilated cardiomyopathy
ECG	Electrocardiogram
EF	Ejection fraction
HF	High frequency
HR	Heart rate
HRT	Heart rate turbulence
HRV	Heart rate variability
ICD	Implantable cardiac defibrillator
LF	Low frequency
LV	Left ventricular
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
MSNA	Muscle sympathetic nerve activity
NE	Norepinephrine
NYHA	New York heart association
pNN50	Percentage differences between normal-to-normal RR intervals greater than 50 ms
rMSSD	Square root of the mean squared standard differences of successive normal-normal RR intervals
SDANN	Standard deviation of sequential 5 min intervals
SDNN	Standard deviation of normal-to-normal intervals
TO	Turbulence onset (heart rate turbulence parameter)
TS	Turbulence slope (heart rate turbulence parameter)
ULF	Ultralow frequency
VLF	Very low frequency
VPC	Ventricular premature beat
VF	Ventricular fibrillation
VT	Ventricular tachycardia

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17

Heart Rate Variability Analysis in Ischemic Cardiomyopathy and Aortic Stenosis Patients

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17.1 Introduction

17.1.1 Ischemic Cardiomyopathy

Cardiomyopathies are an important and heterogeneous group of diseases of the myocardium, which are associated with mechanical and/or electrical dysfunctions that usually exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes that are frequently genetic. Dilated cardiomyopathy (DCM) is a common and largely irreversible form of heart muscle disease that is characterized by ventricular chamber enlargement, systolic dysfunction and normal left ventricular wall thickness. DCM leads to progressive heart failure, a decline in left ventricular contractile function, ventricular and supraventricular arrhythmias, conduction system abnormalities, thromboembolism and sudden or heart failure-related death (Maron et al., 2006). Ischemic cardiomyopathy is the most common cause of DCM and congestive heart failure (Cirillo et al., 2008; Maron et al., 2006). Ischemic cardiomyopathy is a type of cardiomyopathy that is due to ischemic myocardial damage, that is, damage caused by insufficient coronary arterial flow, usually as a result of atherosclerotic coronary artery disease (CAD). Ischemic cardiomyopathy is the initiating cause of approximately 70% of all cases of heart failure (Dickstein et al., 2008). In particular, the presence of CAD may accelerate the progression of heart failure, explaining the higher mortality among ischemic heart failure (IHF) patients compared to non-ischemic heart failure patients (Gheorghiade et al., 2006).

Ischemia can produce a rapid and massive increase in the concentration of endogenous catecholamines such as norepinephrine, epinephrine, endothelin and dopamine in the myocardial interstitial fluid, with a deleterious effect on the cardiac myocytes (Tomai et al., 1999; Gheorghiade et al., 2006), culminating in myocardial apoptosis, fibrosis and susceptibility to ventricular arrhythmias. Substantial changes in gene expression are required to bring about the profound changes within the ischemic and non-ischemic myocardia (Sharma et al., 2005; Severino et al., 2007). These findings suggest that development of ischemic cardiomyopathy is a continuous process (Frangogiannis et al., 2007): at an early stage, brief episodes of ischemia may induce an inflammatory response that activates fibrogenic pathways; a prolonged activation of ischemia-induced inflammation may trigger inhibitory mechanisms while inducing the synthesis of genes associated with fibrosis (Frangogiannis, 2004).

Risk factors for ischemic cardiomyopathy are the same as those associated with CAD and can be classified as non-modifiable or modifiable (Goldstein et al., 2006; Goldhaber, 2010). The non-modifiable risk factors include the following: (i) age: the cumulative effects of aging on the cardiovascular system increase the risk of CAD (Wolf et al., 1992; Brown et al., 1996); (ii) gender: CAD is more prevalent in men than in women (Brown et al., 1996); and (iii) genetic factors: both paternal and maternal histories of CAD have been associated with an increased risk of ischemia (Welin et al., 1987; Kiely et al., 1993). The modifiable risk factors include the following: (i) hypertension: higher the blood pressure, greater the CAD risk (Lewington et al., 1993); (ii) cigarette smoking: smoking is believed to play a significant role in the evolution of cardiomyopathy and its negative effect is specified by both nicotine and carbon oxide generated during smoking (Kirvalidze et al., 2009); (iii) diabetes: the susceptibility to atherosclerosis, hypertension, obesity and abnormal blood lipids is increased (American Heart Association, 2004); and (iv) dyslipidemia: higher levels of total cholesterol increase the ischemia rates (Kagan et al., 1980; Iso et al., 1989).

CAD includes acute myocardial infarction, ischemic coronary heart disease, angina pectoris and atherosclerotic cardiovascular disease. In 2006, it had a prevalence of 7.9% in adults ≥ 20 years of age (17.6 million patients in the United States). In the same year, mortality from CAD was 425,400 patients of all ages. Ischemic cardiomyopathy may manifest clinically most often in middle-aged to elderly men (Cirillo et al., 2008) and also in young children (Maron et al., 2006).

In 2010, the estimated direct and indirect costs associated with this disorder amounted to \$177.1 billion (American Heart Association, 2010). In 2006, \$11.7 billion was paid to Medicare beneficiaries for in-hospital costs where CAD was the principal diagnosis (\$14,009 per discharge for acute myocardial infarction, \$12,977 per discharge for coronary atherosclerosis and \$10,630 per discharge for other ischemic heart diseases) (Dracup et al., 2008; Centers for Medicare, 2008).

There are several types of treatment for CAD and heart failure: pharmacological treatment, cardiac transplantation, electrophysiological devices and surgery (revascularization, mitral valve repair and surgical ventricular restoration) (Bax, 2005).

- *Pharmacological treatment:* In recent years, large-scale clinical trials have documented the benefits of pharmacological therapies in the post-myocardial infarction period aimed at limiting left ventricular remodeling, recurrent ischemia and progressive CAD. In particular, angiotensin-converting enzyme inhibitors, β -blockers and aldosterone antagonists can ameliorate the progressive deterioration of the remaining viable myocardium after an acute myocardial infarction (Gheorghiade et al., 2006).
- *Cardiac transplantation:* Heart transplantation remains the last, but ideal, treatment option for patients with end-stage cardiac disease. Such diseases include ischemic cardiomyopathy, non-ischemic cardiomyopathy and other conditions such as arrhythmogenic right ventricular dysplasia, cardiac sarcoidosis and cardiac amyloidosis (Luk et al., 2009). A heart transplantation has an excellent long-term prognosis, with an approximate survival rate of 90% during the first year and 75% over the initial 7-year period after transplantation (Kirklin et al., 2004). However, the limited number of donor hearts fails to meet the enormous demand, and therefore, it is not a realistic option in clinical cardiology (Bax, 2005).
- *Electrophysiological devices:* The benefit of implantable cardioverter-defibrillators on mortality has been similar in patients with IHF and non-IHF (Cleland et al., 2005). The implantation of a cardioverter-defibrillator in patients with a prior myocardial infarction and advanced left ventricular dysfunction improves survival. On the other hand, electrical conduction defects in heart failure are translated into abnormal myocardial metabolism and redirection of regional coronary perfusion (Auricchio and Abraham, 2004), which could be deleterious in patients with underlying CAD. Thus, restoring the electrical synchrony could potentially be a major goal in the treatment of heart failure patients with CAD. Cardiac resynchronization therapy is a relatively new therapeutic option for patients with severe heart failure, DCM and a wide QRS complex (>120 ms). However, 30% of such patients do not respond, and it has been postulated that left ventricular dyssynchrony is mandatory for clinical benefit (Bax, 2005).

- *Surgical approaches:* Surgical treatment for heart failure caused by CAD includes revascularization, mitral valve repair and surgical ventricular restoration. In patients with ischemic cardiomyopathy, coronary artery bypass grafting offers an important therapeutic option, but it is still associated with a high perioperative mortality (Boehm et al., 2010). Uncertainty still exists about the role and benefits of revascularization in patients with CAD and heart failure (Gheorghiade et al., 2006). Restoration of left ventricular size and shape is an effective surgical procedure in patients with DCM (Isomura et al., 2006). Left ventricular reconstruction is performed to improve the morphologic structure and function of the heart in patients with heart failure (O'Neill et al., 2006). The optimization of surgical repair is mandatory, because ischemic cardiomyopathy is a worldwide disease responsible for many cardiac deaths and because of its (potential) use as an alternative to heart transplantation in selected patients (Cirillo et al., 2008).

The sympathetic nervous system activation is a well-established characteristic of chronic heart failure attributed to the loss of inhibitory modulation by high-pressure arterial or low-pressure cardiopulmonary baroreceptor reflexes (Notarius et al., 2007). Myocardial ischemia may stimulate cardiac sympathetic excitatory afferents even when the reduction in myocardial blood flow is above the anginal threshold (Malliani and Montano, 2002). Such stimulation should elicit greater sympathoexcitation in patients with ischemic cardiomyopathy than in those without ischemic cardiomyopathy (Graham et al., 2002; Malliani and Montano, 2004). Myocardial injury leads to an impaired contractile state of the cardiac pump, resulting in systolic functional failure and hence cardiac output reduction. This condition produces cessation of stimulation of aortic and carotid baroreceptors, inhibitors of the sympathetic nervous system. The sympathetic hyperactivity induces tachycardia as a mechanism to compensate for the decreased cardiac output, which is potentially harmful because of its higher energy costs and hemodynamic alterations related to ventricular filling (De la Serna, 2003). However, there are important limitations to the use of heart rate variability (HRV) as an index of sympathetic outflow in chronic heart failure. Indeed, there is an absence rather than an enhancement of spectral power in the low-frequency (LF) range that is very closely associated with resting muscle sympathetic nerve activity in patients with moderate and severe chronic heart failure (Notarius et al., 2007).

An analysis of HRV has been used to assess the autonomic function and/or to quantify risk in a wide variety of both cardiac and non-cardiac disorders. Methods for quantifying HRV are categorized as time domain, spectral or frequency domain, geometric and non-linear. The baroreflex sensitivity and heart rate turbulence can also be considered measures of HRV (Kleiger et al., 2005). While time domain measures aid in assessing the magnitude of temporal variations in autonomically modulated cardiac rhythm, frequency domain analysis provides the spectral composition of these variations. The changes in LF spectral power (LF: 0.04–0.15 Hz) are regarded as a marker that reflects a combination of sympathetic and vagal autonomic nervous system outflow variations, while the changes in high-frequency spectral power (HF: 0.15–0.40 Hz) reflect the vagal modulation of cardiac activity. The LF/HF power ratio is used to assess the sympathovagal balance (Task Force, 1996). Nowadays, practically all 24 h Holter electrocardiogram (ECG) recording systems have their own software modules for the computation of long-term and short-term HRV parameters in both time and frequency domains (Cerutti et al., 2006), in addition to beat recognition algorithms. Additionally, given the intrinsic non-linear nature of cardiac regulatory mechanisms, a detailed description and classification of dynamical changes

of HRV is not feasible if only linear methods of analysis are employed (Bezerianos et al., 1999; Wessel et al., 2000). The non-linear interaction between various regulatory systems of the heart rate gives rise to clinically useful concepts of variability and regularity; therefore, an application of signal processing techniques based on non-linear dynamics provides supplementary information about various physiological systems involved in cardiovascular pathology (Moraru et al., 2005a). Indeed, these techniques examine the hypothesis that the complexity of HRV decreases with disease. However, a major challenge is to demonstrate the utility and clinical implications of specific measures of HRV in diagnosis and monitoring, so that such measures become part of routine patient care (Cerutti et al., 2006).

17.1.2 Ischemic Process Generated by PTCA

In the presence of a coronary artery obstruction, complex cardiovascular reflexes may lead to changes in heart rate and even to the precipitation of malignant arrhythmias (Malliani et al., 1969). Percutaneous transluminal coronary angioplasty (PTCA) is a technique used for opening the blocked coronary arteries caused by atherosclerotic plaques and to restore arterial blood flow to the myocardium. During PTCA, a balloon is inflated inside a coronary artery, inducing a localized heart ischemia for a short time. PTCA provides a good model to evaluate ischemia-induced HRV changes because it simulates early and acute stages of ischemic episodes (Benitez et al., 2009; Magrans et al., 2010). Monitoring of heart rate before, during and after balloon occlusion may provide an insight into autonomic cardiac function, in response to ischemia. Linear HRV methods were used on PTCA HRV data which indicated an increase in the sympathetic activity during and a few minutes immediately following angioplasty (Castro et al., 2005). In addition, changes in parasympathetic tone adapt to myocardial ischemia in patients undergoing PTCA, suggesting that autonomic regulation may play an important role in ischemic preconditioning (Wu et al., 2005).

17.1.3 Aortic Stenosis

Aortic stenosis (AS) causes left ventricular outflow obstruction, increases left ventricular pressures and leads to compensatory left ventricular hypertrophy (Orłowska-Baranowska, 2007). When the aortic valve becomes progressively stenotic, a pressure gradient is created between the left ventricle and aorta since blood cannot be adequately pumped through a narrow orifice (Lilly, 2003). Stroke volume is maintained within normal limits because of increased left ventricular pressures, compensatory hypertrophy of the left ventricle and increased ejection time. Another mechanism that prevents the reduction of stroke volume and cardiac output involves peripheral vasoconstriction in less important tissues and organs, which enables larger amounts of blood to be directed to cerebral, coronary and renal arteries. As stenosis progresses, left ventricle becomes increasingly dilated and insufficient and a secondary transaortic pressure gradient reduction ensues (Braunwald, 2005). AS induces left ventricular hypertrophy and heart failure and is characterized by altered short-term autonomic responses (e.g., sympathetic modulation is decreased in the presence of a high sympathetic tone) and by modified long-term regulations (e.g., the renin-angiotensin-aldosterone system is overactivated) (Dampney et al., 2002; Morner et al., 2005b). AS has become the most frequent type of valvular heart disease in Europe and North America. It primarily presents as calcific AS in adults of advanced age. The second most frequent etiology that dominates the younger

age group is congenital, whereas rheumatic AS is rare (Task Force, 2007). According to recent studies conducted in the United States, the prevalence of AS is 2.5%, and it is estimated to affect about 5 million patients. The prevalence of the disease increases with age, ranging from 0.7% in the population of patients up to 45 years of age to over 13% among patients aged 75 years or more. In the elderly population, AS is more prevalent among men (Nkomo et al., 2006). Risk factors associated with AS are similar to the risk factors associated with atherosclerosis (Stewart et al., 1997); indeed, factors such as hypertension, diabetes mellitus, hyperlipoproteinemia and uremia may speed up the AS process, which is bound to increase in the future. This is due to the increasing life expectancy and increasing rate of incidental echocardiographic diagnosis in asymptomatic patients (Orłowska-Baranowska, 2007). However, no effective drug treatment for AS is available and symptomatic patients with significant AS should be referred to surgery.

In this chapter, we present the most recent studies using state-of-the-art HRV signal processing techniques in patients with ischemic cardiomyopathy and AS. We also examine the HRV signal during the ischemic process generated by PTCA, which is an excellent experimental platform to study dynamical changes taking place in the cardiac control system.

17.2 Clinical Studies for Evaluating the Efficacy of Time Domain, Frequency Domain and Non-Linear Parameters

The literature on heart failure, including that related to ischemic cardiomyopathy, is vast, since this is a common cause of heart failure. However, there are relatively few new publications that document an evaluation of the HRV of patients with ischemic cardiomyopathy (Truebner et al., 2006; Voss et al., 2009; Valencia et al., 2009b, 2010). Table 17.1 describes databases, patient population and computational methods which document research in this area.

Truebner et al. (2006) conducted a study that included 153 ischemic patients. Two end points were defined. The first end point was death due to cardiac causes, which was termed as the high-risk group (HRG). These patients were compared to survivors, called the low-risk group (LRG). The second end point was death due to sudden cardiac death (HRG_{SCD}), and these patients were again compared to survivors (LRG). For the first analysis, 121 ischemic patients constituted the LRG, while 25 patients were identified as belonging to the HRG. The second analysis was done on 121 ischemic patients constituting the LRG and 14 patients belonging to the HRG_{SCD} . Linear time domain and frequency domain analyses (Task Force, 1996) were performed, while the compression entropy (CE) from non-linear methods was assessed.

Voss et al. (2009) conducted a study that compared healthy subjects (REF) with IHF. A total of 40 subjects were considered for HRV analysis under different pathophysiological conditions, although only 10 subjects were included in the IHF group and 10 subjects in the REF group. In this work, time domain and frequency domain analyses combined with detrended fluctuation analysis (DFA), CE, symbolic dynamics and Poincaré plots were performed. Valencia et al. (2009b) analyzed a total of 194 male ischemic patients, under two end points of analysis: Analysis A, 139 survivor patients (SVPs) as an LRG and 12 sudden cardiac death (SCD) patients as an HRG. Analysis B, 168 SVPs as an LRG and 26 patients who suffered cardiac mortality (CM) as an HRG. Both analyses A and B

TABLE 17.1

Summary of Recent Publications Related to the HRV of Ischemic Cardiomyopathy Patients

References	Analyzed Data	Analysis	Methods
Truebner et al. (2006)	Total: 153 ischemic patients LR: 121 patients HR: 25 patients HR_{SCD} : 14 patients 24 h ECG Holter Follow-up of 2 years	LRG vs. HRG LRG vs. HRG_{SCD}	Time domain analysis Frequency domain analysis Compression entropy
Voss et al. (2009)	Total: 40 subjects REF: 10 healthy subjects IHF: 10 ischemic patients REF and IHF groups were gender- and age-matched	REF vs. IHF	Time domain analysis Frequency domain analysis Detrended fluctuation analysis Compression entropy Symbolic dynamics Poincaré plots
Valencia et al. (2009b)	Total: 194 male ischemic patients Analysis A: SVP: 139 patients SCD: 12 patients Analysis B: SVP: 168 patients CM: 26 patients 24 h ECG Holter Follow-up of 3 years	Daytime: SVP vs. SCD SVP vs. CM Nighttime: SVP vs. SCD SVP vs. CM	Time domain analysis Frequency domain analysis Conditional entropy
Valencia et al. (2010)	Total: 222 ischemic patients SVP: 30 patients CM: 192 patients 24 h ECG Holter Follow-up of 3 years SVP and CM groups were age-matched	Daytime: SVP vs. CM Nighttime: SVP vs. CM	Refined multiscale entropy

were studied during the daytime and nighttime. The methodologies applied were based on time domain, frequency domain and conditional entropy (H_C) analyses. In a study by Valencia et al. (2010), 222 ischemic patients were involved. The HRV behavior of 192 ischemic SVPs as the LRG was compared to that of 30 patients as the HRG who suffered CM by applying a refined multiscale entropy (RMSE).

Few papers (Table 17.2) document the dynamical changes taking place within the cardiac control system during PTCA, using HRV as a quantitative marker of the autonomic nervous system (Gomis et al., 2006; Benitez et al., 2009; Magrans et al., 2010). During a PTCA procedure, a balloon is inflated inside a coronary artery, inducing localized heart ischemia for a short time period. The behavior of HRV was studied by comparing RR series recorded before (pre-PTCA) and during the inflation (PTCA) and following balloon deflation (post-PTCA). In particular, the spectral power law and DFA were applied by Gomis et al. (2006) to compare the HRV behavior between pre-PTCA and PTCA. Benitez et al. (2009) applied average mutual information (AMI) and Magrans et al. (2010) used multifractal fluctuation analysis to study the HRV dynamics of PTCA.

The research on the analysis of HRV in patients with AS is summarized in Table 17.3. In these publications (Carvajal et al., 2002; Valencia et al., 2009a), the HRV of AS patients was compared to HRV of healthy subjects. Carvajal et al. (2002) applied the correlation dimension (D_C) function to characterize the dynamics of HRV, during morning (7–12 h),

TABLE 17.2

Summary of Recent Publications Related to the HRV on Ischemic Process Generated by a Percutaneous Transluminal Coronary Angioplasty Procedure

References	Analyzed Data	Analysis	Methods
Gomis et al. (2006)	Total: 50 patients pre-PTCA: Pre-occlusion: 3 min PTCA: During occlusion: 3 min	pre-PTCA vs. PTCA	Spectral power law Detrended fluctuation analysis
Benitez et al. (2009)	Total: 67 patients pre-PTCA: Pre-occlusion: 3 min PTCA: During occlusion: 3 min post-PTCA: Post-occlusion: 3 min	pre-PTCA vs. PTCA PTCA vs. post-PTCA pre-PTCA vs. post-PTCA	Average mutual information
Magrans et al. (2010)	Total: 55 patients pre-PTCA: Pre-occlusion: 3 min PTCA: During occlusion: 3 min post-PTCA: Post-occlusion: 3 min	pre-PTCA vs. PTCA PTCA vs. post-PTCA pre-PTCA vs. post-PTCA	Multifractal detrended fluctuation analysis

TABLE 17.3

Summary of Publications of HRV of Patients with Aortic Stenosis

References	Analyzed Data	Analysis	Methods
Carvajal et al. (2002)	Total: 274 subjects AS: 206 aortic stenosis patients NRM: 68 healthy subjects 24 h ECG Holter	Morning: AS vs. NRM Afternoon: AS vs. NRM Night: AS vs. NRM	Correlation dimension
Valencia et al. (2009a)	Total: 210 subjects AS: 148 aortic stenosis patients NRM: 62 healthy subjects 24 h ECG Holter	Daytime: AS vs. NRM Nighttime: AS vs. NRM	Frequency domain analysis Multiscale entropy Refined multiscale entropy

afternoon (15–20 h) and nighttime (0–5 h). Valencia et al. (2009a) applied both linear frequency domain analysis and non-linear analysis, including multiscale entropy (MSE) and RMSE, for data recorded from patients with AS over a 24 h cycle.

Some of the methods reported in Tables 17.1 through 17.3 are described in the following sections. Although all are based on known non-linear analysis techniques, they contain new approaches that were developed to better characterize the non-linear dynamics of HRV.

17.3 Advanced Algorithms for Non-Linear HRV Analysis

17.3.1 Compression Entropy

Compression entropy (CE) quantifies the extent to which the RR time series can be compressed (Voss et al., 2009). CE uses the algorithm developed by Lempel and Ziv (1977), which produces a symbol series that is shorter than the original one. This algorithm achieves compression by replacing portions of the data with reference to matching data

that have already passed through both an encoder and a decoder. The basic idea is to encode sequences of the series by referencing (Baumert et al., 2004): (i) the position of a previous sequence that is identical to the sequence to be encoded, (ii) the length of the detected identical sequence and (iii) the next symbol of the encoded sequence. The output consists of a three-column matrix of length M , where M is the number of the encoded sequences. The CE is estimated by dividing the length of the compressed series and that of the original series, if the length of the latter tends to infinity. A decrease in the CE is associated with an increase in HRV regularity, reflecting a change in the sympathetic/parasympathetic activity control (Baumert et al., 2004).

17.3.2 Conditional Entropy

Conditional entropy (H_C) is based on the conditional probability obtained as the probability of occurrence of variable y , given the occurrence of variable x . Therefore, H_C permits the entropy of a random variable y to be quantified, when a second variable x is known (Papoulis, 1984). Indeed, H_C is defined as an entropy rate, which measures the quantity of the information per sample of the signal, once the predictable part of the signal is eliminated (Porta et al., 1998). Changes in the entropy rate have been mainly related to aging and illnesses (Lake et al., 2002; Pikkujamsa et al., 1999; Voss et al., 1996), and they have also allowed HRV complexity within short time scales to be related to cardiac autonomic modulation (Porta et al., 2007b). In this way, regularity of the HRV signal can be a general indicator of the state of cardiovascular control mechanisms (Porta et al., 1998).

Usually, the entropy of HRV data is calculated using patterns of length L samples instead of individual RR-interval data points. Consequently, H_C provides a global index of the complexity of the sample distribution of length L , conditioned on previous $L - 1$ samples. H_C quantifies the regularity of the signal (Porta et al., 2001).

Given a temporal series $x = \{x(i), i = 1, \dots, N\}$, an L -dimensional phase space is constructed using delay coordinates with $\tau = 1$ (Takens, 1981), where each point in this phase space is represented by the vector $u_L(j) = \{x_j, \dots, x_{j+L-1}\}$ with $1 \leq j \leq N - L + 1$. Indeed, the vector $u_L(j)$ corresponds to a pattern of L consecutive samples and the regularity of the series $x(i)$ can be measured by estimating the probability that the two patterns of length $L - 1$ samples that are similar in the $L - 1$ dimension phase space remain similar after adding a new sample. This definition can be expressed as follows:

$$H_C\left(\frac{u_L}{u_{L-1}}\right) = -\sum_{k=1}^{N_k} p(u_{L-1}(k)) \sum_{j=1}^{N_j} p\left(\frac{u_L(j)}{u_{L-1}(k)}\right) \log p\left(\frac{u_L(j)}{u_{L-1}(k)}\right) \quad (17.1)$$

Normally, for computing H_C , the dynamic range of the series $x(i)$ is uniformly quantized in different disjoint regions, partitioning the phase space into hypercubes (Porta et al., 2007a). Hence, vectors inside the same hypercube are considered similar or indistinguishable. It has been demonstrated that H_C suffers a serious limitation when a finite number of samples are considered, since it is possible to have hypercubes with a single point and therefore $\log p(u_L(j)/u_{L-1}(k))$ is equal to zero in Equation 17.1. Consequently, H_C will tend to zero as the number of hypercubes with single points increases, indicating a false impression of determinism. This effect is more evident when patterns of high length L are compared in series of short length (Porta et al., 1998). This limitation has been addressed by

Porta et al. (1998), who introduced a correction factor, and by Valencia et al. (2009b), who proposed a non-uniform quantization of the series in disjoint regions. However, ischemic patients were studied only by Valencia et al. (2009b), where the following non-uniform quantization was proposed:

$$\hat{x}_i = \begin{cases} 1 & \text{if } (1+a)\bar{x} < x(i) < \infty \\ 0 & \text{if } \bar{x} < x(i) \leq (1+a)\bar{x} \\ 2 & \text{if } (1-a)\bar{x} < x(i) \leq \bar{x} \\ 3 & \text{if } 0 < x(i) \leq (1-a)\bar{x}, \end{cases} \quad i = 1, \dots, N \quad (17.2)$$

where a is a parameter that quantifies the standard deviation of the series $x(i)$ of length N , \bar{x} is the mean of the series $x(i)$ and \hat{x}_i represents the symbol sequence under consideration. Parameter a was set to 0.07 (Valencia et al., 2007). An L -dimensional phase space can be reconstructed as $\hat{u}_L(j) = \{\hat{x}_i, \dots, \hat{x}_{i+L-1}\}$ and H_C calculated using Equation 17.1. Although H_C commonly bases its calculation on Shannon entropy, Valencia et al. (2009b) propose a general expression of H_C (Equation 17.3) by including the Rényi entropy definition, which is a generalization of Shannon entropy:

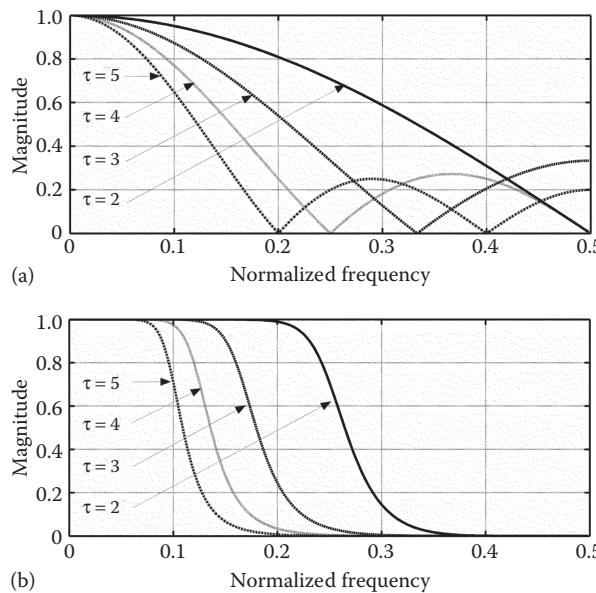
$$H_C\left(\frac{u_L}{u_{L-1}}\right) = \frac{1}{1-q} \sum_{k=1}^{N_k} p(u_{L-1}(k)) \log \left(\sum_{j=1}^{N_j} \left(p\left(\frac{u_L(j)}{u_{L-1}(k)}\right) \right)^q \right), \quad (17.3)$$

where q is a real number, $q > 0$ and $q \neq 1$, which determines the manner in which the probabilities are weighted. When $q \rightarrow 1$, Rényi entropy converges to Shannon entropy.

17.3.3 Refined Multiscale Entropy

RMSE (Valencia et al., 2009a) characterizes the complexity of a time series as a function of time scale factor τ in a manner similar to MSE (Costa et al., 2005), but it overcomes two limitations of MSE. The first shortcoming of MSE is the suboptimal elimination of fast time scales that produce uncontrolled effects on the assessment of complexity at any scale and the second shortcoming is the coarse-graining procedure that tends to artificially decrease the entropy rate as a function of time scale.

To produce a new time series at each time scale factor, MSE uses a procedure that is equivalent to the application of a low-pass finite impulse response (FIR) filter to the original RR series and to the downsampling of the filtered RR series with a factor τ (Nikulin and Brismar, 2004). This FIR filter is characterized by a very slow roll-off of the main lobe, a large transition band and important sidelobes in the stopband (Figure 17.1a). As a result, the FIR filter does not eliminate fast temporal scales above the cutoff frequency (f_c) and thus, subsequent downsampling procedure produces aliasing, generating spurious oscillations in the frequency range from 0 to f_c (Valencia et al., 2009a). Consequently, the evaluation of the complexity of downsampled signal is biased by the inclusion of these artifactual components. This shortcoming has been eliminated in RMSE by a replacement of the FIR filter with a low-pass Butterworth filter, although any anti-aliasing filter would be useful. The magnitude of the frequency response of the Butterworth filter is flat in the passband, sidelobes in the stopband are not present and the roll-off is fast (Figure 17.1b).

**FIGURE 17.1**

The magnitude of the frequency response for different scale factors ($\tau = 2-5$): (a) the FIR filter and (b) the sixth-order low-pass Butterworth filter. The frequency axis is expressed in terms of normalized Nyquist frequency. (Adapted from Valencia, J.F., Porta, A., Vallverdú, M., Claria, F., Baranowski, R., Orlowska-Baranowska, E., and Caminal, P., *IEEE Trans. Biomed. Eng.*, 56, 2202–2213 © 2009 IEEE.)

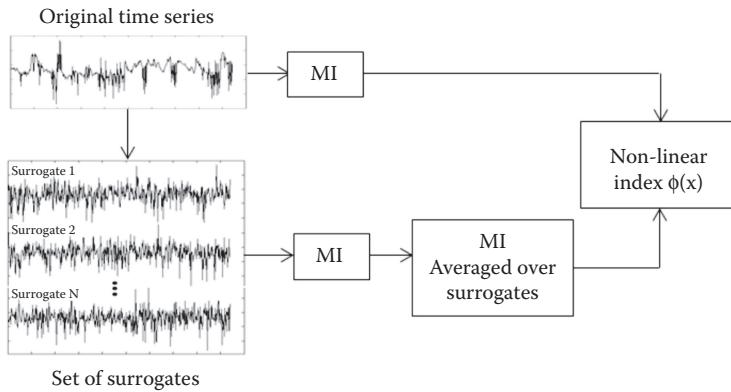
Therefore, the Butterworth filter ensures a more accurate elimination of components with a frequency above f_c with respect to the FIR filter, thereby reducing aliasing when the filtered series are downsampled.

MSE uses a coarse-graining procedure to define similarity between patterns of length L if these are closer than a parameter r in the L -dimensional phase space, according to a given definition of distance. In MSE, the parameter r is set as a percentage of the standard deviation (SD) of the original time series and remains constant for all scale factors. Since the procedure for the elimination of the fast temporal scales acts as a low-pass filter, the filtered series is characterized by a lower SD as a function of the scale factor τ , and accordingly, the cloud of points in the L -dimensional phase space occupies a smaller region. Therefore, given a constant parameter r , more patterns will be considered indistinguishable while increasing τ , thus artificially decreasing the entropy rate and increasing the regularity with the scale factor. This shortcoming has been eliminated in RMSE by continuously updating the parameter r as a percentage of the SD of the filtered series, $r^\tau = \text{SD}(x^\tau)\%$ (Nikulin and Brismar, 2004).

The complexity of the time series in RMSE was assessed by applying sample entropy (SE) (Richman and Moorman, 2000) as a function of the time scale factor τ , $\text{SE}(\tau)$. It was calculated with $r^\tau = 0.15 \times \text{SD}(x^\tau)$ for $L = 2$ samples in a pattern.

17.3.4 Average Mutual Information

Benítez et al. (2009) used the average mutual information (AMI) function to analyze the response of the autonomic control system to an ischemic process. This function is a measure of the information content of the system and estimates how much, on average, the

**FIGURE 17.2**

A description of the non-linear content index. Surrogate data-keeping autocorrelation (histogram) and power spectrum. The Nonlinear content index $\Phi(x)$ is defined as the root-mean-squared error between the average mutual information (MI) of the original segment and the mean MI of the surrogates. As the surrogate set reproduces the same linear features as the original data, the differences should be due to the non-linear content of the analyzed segment.

value of the time series can be predicted from the values of the time series during preceding points. The AMI of a time series x is defined as

$$A_k(x) = \sum_{x_i, x_{i+k}} p(x_i, x_{i+k}) \log_2 \left(\frac{p(x_i, x_{i+k})}{p(x_i)p(x_{i+k})} \right) \quad (17.4)$$

where $p(x_i, x_{i+k})$ is the joint probability distribution function of the values x_i and x_{i+k} obtained from a normalized histogram with a certain binning, and $p(x_i)$ and $p(x_{i+k})$ are the marginal probability distribution functions of x_i and x_{i+k} , respectively. A non-linear index $\Phi(x)$, measuring the non-linear content of x , was defined as the root-mean-squared error of the AMI of x with respect to the AMI averaged over surrogate data (Figure 17.2). These surrogate time series were generated by means of a constrained randomization method (Schreiber and Schmitz, 1996; Schreiber, 1998) in order to have the same histogram and power spectrum as x , while maintaining the same linear properties and entropy as x .

17.3.5 Multifractal Detrended Fluctuation Analysis

Multifractal detrended fluctuation analysis (MF-DFA) method (Kantelhardt et al., 2002) uses the conventional DFA (Peng et al., 1995). Indeed, MF-DFA consists of the following five steps:

Step 1: Integrate the series $x(i)$, obtaining $Y(i)$.

Step 2: Divide $Y(i)$ into $N_s = \text{int}(N/s)$ non-overlapping segments of length s .

Step 3: Calculate the local trend for each segment. Then determine the variance for each segment v , where $v = 1, \dots, N_s$:

$$F^2(s, v) = \frac{1}{s} \sum_{i=1}^s \left\{ Y[(v-1)s+i] - y_v(i) \right\}^2. \quad (17.5)$$

Step 4: Average over all segments to obtain the n th order fluctuation function:

$$F_n(s) = \left\{ \frac{1}{Ns} \sum_{v=1}^{Ns} [F^2(v, s)]^{\frac{n}{2}} \right\}^{\frac{n}{2}}. \quad (17.6)$$

Step 5: Determine the scaling behavior of the fluctuation functions by analyzing the log–log plots $F_n(s)$ versus s for each value of n . If the series x is long-range power-law correlated, $F_n(s)$ increases, for large values of s , as a power-law:

$$F_n(s) \sim s^{\tau(n)}, \quad (17.7)$$

where $\tau(n)$ is the generalized Hurst exponent. Using a Legendre transform (Muzy et al., 1993), the singularity exponent α and the singularity spectrum $f(\alpha)$ are obtained as

$$\alpha = \frac{d\tau(n)}{dn} \quad \text{and} \quad f(\alpha) = n\alpha - \tau(n). \quad (17.8)$$

Magrans et al. (2010) applied this method to study HRV before, during, and after ischemia generated by the PTCA procedure. In this work, four indices were defined to detect the degree of multifractality: R_p , defined as the ratio of the slope of $\tau(n)$ over $n \in (-5;0)$ to the slope of $\tau(n)$ over $n \in (0;5)$, since $\tau(n)$ is a straight line for monofractal signals, whereas it displays non-linear features for multifractal signals; $\Delta\alpha = \alpha_{\max} - \alpha_{\min}$, where α_{\min} and α_{\max} are the minimum and the maximum values in the set of singularity exponents, respectively; α_m , defined as the singularity exponent when $f(\alpha)$ is the maximum; and $\alpha(2)$, defined as the singularity exponent when $n = 2$.

17.3.6 Correlation Dimension Index

Based on the definition of the correlation dimension (D_c), Carvajal et al. (2002) proposed an index named D_{ck} . This index was defined as the product of two parameters, D_c and k , which characterize the fitted exponential curve

$$d(L) = D_c (1 - e^{-kL}), \quad (17.9)$$

where L is the embedding dimension of the phase space. Geometrically, this product represents the slope of the curve $d(L)$ versus L , where the embedding dimension L tends to zero.

17.4 Results

Tables 17.4 through 17.6 show the main results related to HRV analysis in ischemic cardiomyopathy patients (Table 17.4), ischemic process generated by PTCA (Table 17.5), and

TABLE 17.4

Results of the Group Comparisons in Ischemic Cardiomyopathy Patients

References	Truebner et al. (2006)	Analyzed Groups				Valencia et al. (2010)
		LRG vs. HRG	HRG _{SCD}	REF vs. IHF	SVP vs. SCD	
Clinical factors	Age	n.s.	n.s.	n.s.	n.s.	n.s.
	LVEF	*	*		n.s.	*
	NYHA	**	**		*	**
	LVDD	n.s.	n.s.			
	Indexed LA size				*	**
	Indexed LVEDD				n.s.	n.s.
Time domain indices	Mean NN	n.s.	n.s.	n.s.	n.s.	n.s.
	SDNN	*	*	n.s.	* ^a	** ^a
	rMSSD			n.s.		
Frequency domain	LF	*	*			
Indices	LF/HF	*	n.s.	n.s.	n.s.	n.s.
	LFn	*	n.s.	n.s.	* ^a	** ^a
	HFn			n.s.	n.s.	n.s.
Compression entropy	CE	**	*	*		
	CE _{mv}	*	*			
	CE _{diff}	*	n.s.			
DFA	α1			n.s.		
	α2			n.s.		
Poincaré plot	SD1			***		
	SD2			n.s.		
Symbolic dynamics	Shannon			n.s.		
	Forbword			n.s.		
	Renyi025			n.s.		
	pW321			***		
Conditional entropy	H_C ($L = 2, q = 0.1$)				* ^{a,b}	* ^{a,b}
Refined multiscale entropy	SE(τ)					* ^{a,b}

Notes: Cardiac mortality: LRG and SVP, low-risk group; HRG and CM (cardiac morbidity), high-risk group. Sudden cardiac death: LRG and SVP, low-risk group; HRG_{SCD} and SCD, high-risk group. IHF, ischemic heart failure group; REF, healthy subjects group; LVEF, left ventricular ejection fraction; NYHA, the New York Heart Association functional classification; LVDD, left ventricular diastolic diameter; LVEDD, left ventricular end-diastolic diameter; indexed LVEDD, left ventricular end-diastolic diameter indexed to body surface area; n.s., not significant.

^a Daytime analysis.

^b Nighttime analysis.

* $p < .05$; ** $p < .01$; *** $p < .001$.

TABLE 17.5

Results of the Group Comparisons in Ischemic Process Generated by PTCA

References	Gomis et al. (2006)		Benitez et al. (2009)		Magrans et al. (2010)	
	Analyzed Segments					
Indices	Pre-PTCA vs. PTCA	Pre- PTCA vs. PTCA	Post-PTCA	PTCA vs. Post-PTCA	Pre- PTCA vs. PTCA	PTCA vs. Post- PTCA
β	*					
β_1	n.s.					
α_1	n.s.					
$\Phi(x)$		**	**	*		
R_p					n.s.	*
$\Delta\alpha$					*	*
α_m					*	*
α ($n = 2$)					*	*

Note: n.s., not significant.

* $p < .05$; ** $p < .001$.

AS patients (Table 17.6). In these tables, clinical factors, time and frequency domains and indices that contain complexity information of the HRV were measured in order to characterize various groups. The significant statistical differences were $p < .05$ or better.

17.4.1 HRV in Ischemic Cardiomyopathy Patients

Table 17.4 presents a summary of results reported by Truebner et al. (2006), Voss et al. (2009) and Valencia et al. (2009b, 2010). It can be observed that in all cases, the age did not differ significantly between various groups, since most studies were conducted with age-matched cohorts. The New York Heart Association functional classification (NYHA) and the left ventricular ejection fraction (LVEF) showed statistically significant differences in results reported by Truebner et al. (2006) and Valencia et al. (2009b), with the exception of LVEF when SVP and SCD were compared (Valencia et al., 2009b).

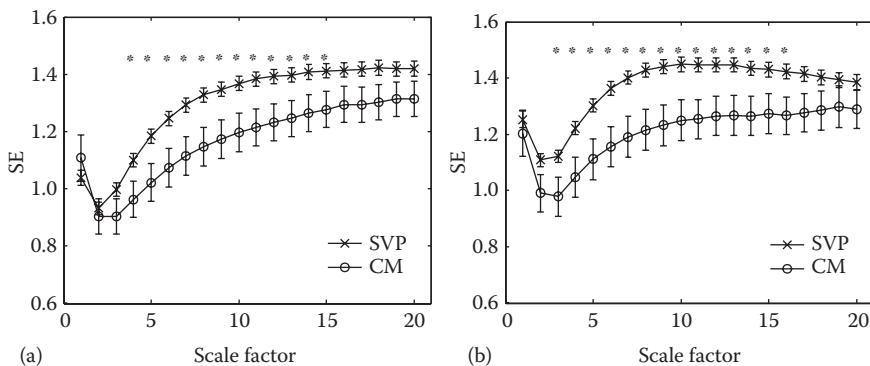
TABLE 17.6

Results of the Group Comparisons in Aortic Stenosis Patients

References	Carvajal et al. (2002)	Valencia et al. (2009a)
	Analyzed Groups	
	NRM vs. AS	NRM vs. AS
Frequency domain indices	LFn	* ^a
	HF	n.s.
Multiscale entropy	SE(τ)	* ^{a,b}
Refined multiscale entropy	SE(τ)	* ^{a,b}
Correlation dimension index	D _{ck}	** ^{a,b}

Note: NRM: Healthy subjects; AS: Aortic stenosis patients; n.s., not significant.

^a denotes daytime analysis.^b denotes a nighttime analysis.* $p < .05$; ** $p < .0005$.

**FIGURE 17.3**

Mean values (\pm standard error) of RMSE as a function of the scale factor derived from the RR series in the ischemic cardiomyopathy patients classified in low (SVP) and high (CM) risk groups of cardiac death. The SVP and the CM are compared during the daytime (a) and during the nighttime (b). Significant statistical differences with $p < .05$ are marked with an *.

There were no consistent time domain or frequency domain indices (Table 17.4) that could differentiate between survivors and non-survivors, with the exception of standard deviation of all normal-to-normal intervals between adjacent QRS complexes (SDNN) in the studies by Truebner et al. (2006) and Valencia et al. (2009b). Indeed, the value of SDNN was lower in the HRGs (HRG, HRG_{SCD}, SCD and CM) when compared to the LRGs (LRG and SVP). Values of the LF, the LF/HF and normalized LF (LFn) in the studies by Truebner et al. (2006) and Valencia et al. (2009b) were higher in LRGs (LRG and SVP) than in HRGs (HRG, HRG_{SCD}, SCD and CM).

Different indices related to non-linear studies were able to classify various groups analyzed (Table 17.4). The CE was also calculated from RR time series after subtracting the mean (CE_{mv}) and from consecutive differences of RR intervals (CE_{diff}). The values of CE were decreasing from the LRG to the HRGs (HRG and HRG_{SCD}) (Truebner et al., 2006) and from the healthy group (REF) to the IHF group (Voss et al., 2009). The index SD1, obtained from Poincaré map analysis, had higher values in the REF group than in the IHF group (Voss et al., 2009). It was not possible to know the tendency of pW321, a non-linear index, from one group to the other because there was no information about its value in the REF group (Voss et al., 2009). The value of the H_C ($L = 2$, $q = 0.1$) was significantly lower in the HRG (SCD and CM) than in the LRG (SVP) (Valencia et al., 2009b). From a multiscale analysis perspective, applying RMSE (Valencia et al., 2010), the risk group (SVP vs. CM) showed significant differences over a large interval of scales both during the daytime (Figure 17.3a at $\tau = 4\text{--}15$) and during the nighttime (Figure 17.3b at $\tau = 3\text{--}16$), the entropy being smaller in the CM group than in the SVP group.

17.4.2 HRV in Ischemic Process Generated by PTCA

A summary of the results presented by Gomis et al. (2006), Benitez et al. (2009) and Magrans et al. (2010) is shown in Table 17.5. This table contains different proposed indices for the HRV recorded during the ischemic process generated by PTCA and takes into account the entire set of the three occluded arteries. Gomis et al. (2006) applied the fractal indices β (0.003 to 0.0316 Hz), β_1 (0.003 to 0.1 Hz) and for small time scales α_1 to compare the RR intervals recorded pre-PTCA and during PTCA. The value of β , which measures the slope of the

spectral power, significantly decreased from pre-PTCA to PTCA. Benitez et al. (2009) applied an index obtained from AMI, $\Phi(x)$, and found it significantly increased from pre-PTCA to post-PTCA. The proposed indices (R_p , $\Delta\alpha$, αm and $\alpha[n = 2]$) by Magrans et al. (2010) could differentiate between all segments, presenting an increase from pre-PTCA to post-PTCA.

17.4.3 HRV in Aortic Stenosis Patients

Table 17.6 summarizes recent results of an HRV analysis of AS patients and healthy subjects (NRM). The results obtained in the studies by Valencia et al. (2009a) indicated that the LFn obtained from the frequency domain analysis was significantly lower in the AS group than in the NRM group. The non-linear indices $SE(\tau)$, obtained by applying MSE and RMSE, permitted a differentiation between the two groups during the daytime and the night time (Figure 17.4). The differences between the groups were presented over a larger interval scale in the daytime (MSE, $\tau = 2-10$; RMSE, $\tau = 2-9$) than in the nighttime (MSE, $\tau = 2-3$; RMSE, $\tau = 2$). Both methods (MSE and RMSE) offered the same tendency in the value of $SE(\tau)$, being significantly higher in the NRM group than in the AS group during the daytime and the nighttime. The non-linear index D_{ck} , introduced by Carvajal

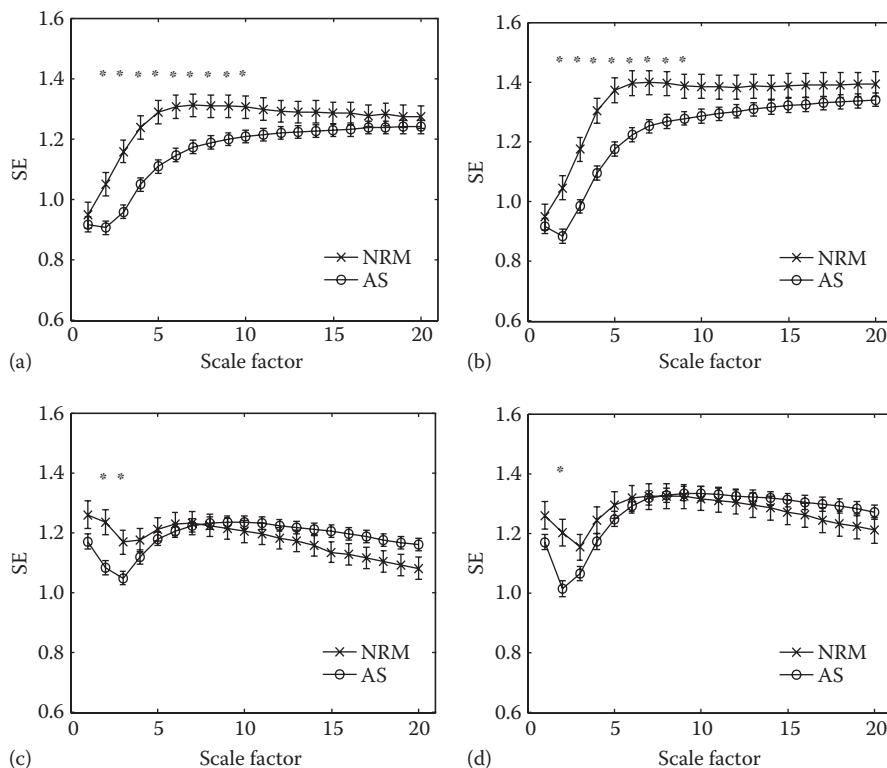


FIGURE 17.4

Mean values (\pm standard error) of MSE (a, c) and RMSE (b, d) as a function of the scale factor derived from the RR series compared in healthy subjects (NRM) and aortic stenosis patients (AS). The NRM and the AS are compared during the daytime (a, b) and during the nighttime (c, d). Significant statistical differences with $p < .05$ are marked with an *. (Adapted from Valencia, J.F., Porta, A., Vallverdú, M., Claria, F., Baranowski, R., Orlowska-Baranowska, E., and Caminal, P, *IEEE Trans. Biomed. Eng.*, 56, 2202–2213 © 2009 IEEE.)

et al. (2002), showed a significantly higher value in the AS group than in the NRM group during the daytime, but a contrary behavior was observed during the nighttime, that is, the AS group presented lower values than the NRM group.

17.5 Discussion

17.5.1 Ischemic Cardiomyopathy Patients

A statistical analysis of the clinical factors identified by Truebner et al. (2006) and Valencia et al. (2009b) showed that LVEF, NYHA and indexed left atrial (LA) size were the best factors in the characterization of HRGs and LRGs of ischemic cardiomyopathy patients. These results were consistent with similar studies published previously (Bayés-Genis et al., 2007; Voss et al., 2008), where heart failure patients were included. An increment of NYHA and indexed LA size and a reduction of the LVEF are directly related to a dysfunction of the cardiac regulation due to ischemic cardiomyopathy. Although all patients analyzed in the study suffered from ischemic cardiomyopathy, values of LVEF, NYHA and indexed LA size indicated a higher level of neurocardiac dysfunction in patients from the HRGs (HRG, HRG_{SCD}, SCD and CM) than in the patients from the LRGs (LRG and SVP). Despite the clinical applicability of LVEF, NYHA and indexed LA size, these measures have some potential limitations as specific risk markers of ischemic cardiomyopathy because of their low sensitivity when the HRGs and the LRGs are analyzed (Bax, 2008; Voss et al., 2008; Valencia et al., 2009b).

Among time domain indices (Truebner et al., 2006; Voss et al., 2009; Valencia et al., 2009b), only SDNN was suitable for an enhanced risk classification with the exception of results reported by Voss et al. (2009). From these results (Table 17.4), it is deduced that the main statistical differences are contained in the daytime, that is, the statistical differences were detected in the RR series during both 24 h and the daytime, but not during the night. The lower value of SDNN in the HRG implies a reduction in HRV in ischemic cardiomyopathy patients with the highest risk of cardiac death.

A spectral analysis contributes to an understanding of the autonomic regulation of HRV (Task Force, 1996). Because chronic heart failure is characterized by a high sympathetic drive, a spectral analysis of the RR series could be reasonably expected to manifest a predominantly LF component. However, published results in the case of ischemic cardiomyopathy patients with chronic heart failure (Truebner et al., 2006; Valencia et al., 2009b) have revealed a decreased LFn component in the HRGs in comparison with the LRGs. The interpretation of the reduced LFn in chronic heart failure patients is still an open question. Explanations include a depressed sinus node responsiveness, central abnormality in autonomic modulation, limitation in the responsiveness to high levels of cardiac sympathetic activation, depressed baroreflex and increased chemoreceptor sensitivity (Guzzetti et al., 2005). Again, as with the time domain index SDNN, Table 17.4 suggests that the main statistical differences of LFn are during daytime, since statistical differences were detected in the RR series both in 24 h and during daytime, but not during the night.

The indices extracted from the time domain HRV analysis and the frequency domain HRV analysis have been shown to contain useful information (Task Force, 1996; Guzzetti et al., 2005). However, these indices only describe linear features of systems involved in heart rate control and may not capture non-linear features of such control. The non-linear indices such as entropy used for the study of ischemic cardiomyopathy patients, CE (Truebner et al., 2006), H_C (Valencia et al., 2009b) and SE(τ) (Valencia et al., 2010) indicated

an increase in HRV regularity in the evolution of disease severity. Since regularity is under sympathetic control (Porta et al., 2007b), increased regularity might suggest that high-risk patients have higher levels of sympathetic tone. For risk stratification, the CE calculated on the RR time series seems to be more useful than the CE_{diff} calculated on the consecutive difference of the RR intervals as reported by Truebner et al. (2006). Although the performance of the H_C can be improved by enlarging the number of uniform quantization regions as reported by Porta et al. (2007b), it was demonstrated by Valencia et al. (2009b) that a non-uniform quantization of the dynamic range of RR series can also improve the performance of H_C even with a few number of quantization regions. The results of the multiscale analysis performed using the index $SE(\tau)$ (Valencia et al., 2010) suggest a reduced complexity of the mid-term and the long-term cardiovascular regulation in the HRGs (possibly including even the regulation in the LF band), as a likely result of the overwhelming action of fewer regulatory mechanisms. Furthermore, a decreased level in the short-term variability indicated by SD1 was observed in IHF patients, estimated from the Poincaré plots of RR time series. This may be the result of an increased vagal suppression (Tulppo et al., 1996) in IHF patients.

17.5.2 Ischemic Process Generated by PTCA

Gomis et al. (2006) have shown that the fractal indices that describe the dynamics of HRV can be associated with ischemic events, such as those that occur during PTCA (Table 17.5). Thus, RR signals before and during coronary occlusion were characterized using the fractal power law index β . Since the index β decreased significantly during coronary occlusion and myocardial ischemia, authors suggested that the long-range correlation in the heartbeat dynamics breaks down because such correlation is characterized by a lower negative exponent. An analogous behavior was observed by Magrans et al. (2010), where the indices α_m and $\alpha(n = 2)$ that contain information similar to β also indicated a breakdown in the long-range dependence of heartbeat fluctuations from the pre-PTCA to the post-PTCA process. Variations in the multifractal spectrum slopes and a wider range of singularity exponent values that characterize the fluctuations in heartbeat intervals were assessed by an increase in the R_p and $\Delta\alpha$ indices throughout the PTCA procedure. The interpretation of the results of R_p and $\Delta\alpha$ indices suggests that PTCA procedures cause a progressive increase in the non-linear multifractal complexity of the autonomic nervous system during ischemia (PTCA) and reperfusion periods (post-PTCA), compared to the baseline periods measured just prior to balloon inflation (pre-PTCA). However, according to the hypothesis in which complexity is reduced with disease progression, a decrement in the complexity of the RR series during the ischemia process compared to the period before the arterial occlusion was expected. Authors tried to explain this counterintuitive finding by hypothesizing the existence of a complex interplay between two branches of the autonomic nervous system in heart rhythm control when myocardial ischemia starts. The index $\Phi(x)$ obtained from the AMI by Benitez et al. (2009) showed a progressive increase in the non-linear content from pre- to post-balloon inflation stage. Therefore, the non-linearity of the system not only increased during balloon occlusion (PTCA) but also continued rising shortly after reperfusion. This can be thought of as an indication that cardiac autonomic responses take place in a time scale longer than few minutes over which a PTCA is performed. From a physiological point of view, this would correspond to changes in non-linear content of the sympathetic regulation of the cardiac control system. It should be noted that use of RR series of short length could diminish the reliability of multifractal estimates and may

lead to erroneous interpretations. Although these authors characterized changes during the ischemic process generated by PTCA, it is recommended that a series with enough data points be used whenever possible, to reduce the finite sample error.

17.5.3 Aortic Stenosis Patients

Although results of correlation dimension index D_{ck} published by Carvajal et al. (2002) showed statistically significant differences, the physiological significance of this index is still unknown. Nevertheless, the index D_{ck} , by definition, is a function of the D_c (Carvajal et al., 2002). The D_c is an approximation of the fractal dimension, where a high value means a more complex system. The multiscale analysis developed by Valencia et al. (2009a) shows that the entropy-based HRV complexity, measured by $SE(\tau)$, decreased with the disease and that this reduction could not be attributed to aging alone, thus confirming the hypothesis that pathology reduces the complexity of cardiovascular control (Costa et al., 2005). The drop in complexity in the AS population was more evident during daytime (Figure 17.4a,b) than at the night (Figure 17.4c,d). This finding suggests that the reduction in the complexity of cardiovascular regulation involved temporal scales that were slower than those corresponding to vagal control and were more evident during the daytime, when these processes are more active. On a short time scale, the main features of RMSE can be explained in terms of short-term fluctuations present in the HRV data in the range from 0.04 to 0.5 Hz. At these time scales, the course of RMSE was different in AS population, especially during daytime. Indeed, a clear local minimum followed by a rapid recovery was present during both daytime and at night. This finding suggests that the HF rhythms are prominent in the AS population. In addition, the presence of local minimum at short time scales suggests that entropy-based complexity of HRV is reduced in the range of temporal scales corresponding to the LF band. Indeed, the complexity was high at $\tau = 1$ and decreased significantly when the filtering procedure eliminated HF oscillations responsible for a large portion of the complexity at short time scales (Porta et al., 2007b). These observations were confirmed by a short-term spectral analysis. More specifically, in agreement with Fei et al. (1995), the LFn was significantly decreased in the AS group, while respiratory sinus arrhythmia measured by the HF was not significantly modified, as expected in the case of AS population. The different information derived at short and long temporal scales stresses the importance of assessing the entropy at different time scales. Indeed, indices based on a single-scale analysis, such as LFn and HF, seem to ignore such subtle and non-linear aspects of information embedded within the HRV signal.

17.6 Limitations

Although some of the linear and non-linear indices, described in this chapter, have been able to characterize HRV recorded from patients with ischemia and AS, there are several factors that can influence the results of various analysis, procedures and algorithms.

One limitation of signal processing techniques, such as power spectral density, power law correlation, MSE and RMSE, is due to the inherent non-stationarity of long-term RR series. Although HRV was calculated from 24 h ECG Holter recordings in many of the studies described in this chapter (Carvajal et al., 2002; Truebner et al., 2006; Valencia et al.,

2009a,b, 2010), physiological mechanisms that modulate the heart rate cannot be considered stationary during the entire 24 h (Furlan et al., 1990). The spectral analysis performed during a 24 h period or in the shorter segments averaged over the entire 24 h period, generates an average of the modulations attributable to LF and HF components and obscures finer and detailed information about autonomic modulation of RR intervals (Task Force, 1996). Bollt et al. (2009) have suggested that changes in the entropy of measured physiological signals indicate changes in the underlying constraint of the system of interest.

Techniques such as CE, DFA, H_C , MSE, RMSE and Dc have serious drawbacks because their consistency is progressively lost as the number of data points decreases (Voss et al., 2009; Porta et al., 1998; Richman and Moorman, 2000). Another limitation that directly affects the estimation of the various entropy measures or other indices derived from recurrence plots is the dependency on the sampling rate or the resolution of the time series (Garcia-Gonzalez et al., 2008; Voss et al., 2009). Ectopic beats, detection of missing beats, artifacts and noise also may alter the estimation of these indices. Indeed, signal preprocessing based on an adaptive filter (Truebner et al., 2006; Valencia et al., 2009b, 2010) or a linear predictor optimized by the least squares approach (Valencia et al., 2009a) may minimize these negative effects.

17.7 Conclusions

Due to the complex interaction between the autonomic control system and several regulatory mechanisms of heart rate, and the fact that many biological systems have an intrinsically non-linear behavior, it is reasonable to assume that the control system regulating the heart is affected by several non-linear variables. Taking into consideration that indices such as CE (Truebner et al., 2006; Voss et al., 2009), H_C (Valencia et al., 2009b), SE(τ) (Valencia et al., 2009a, 2010), $\Phi(x)$ (Benitez et al., 2009), Rp and $\Delta\alpha$ (Magrans et al., 2010) are defined as non-linear measures, results obtained in the analysis of ischemic cardiomyopathy patients and ischemic process generated by PTCA stress the importance of assessing the non-linear dynamics that is present in HRV signal. These indices have shown that the intrinsic non-linearity of the autonomic response provides clinically useful information about physiological mechanisms underlying an ischemia.

Computed values of various measures of entropy are lower when the HRV signal is more regular and higher when the HRV signal is more irregular. Therefore, low values of CE, H_C , and SE(τ), which were obtained from patients in HRGs (patients with more severe disease) in both ischemic heart disease and AS, indicate an increase in heart rate regularity at short time scales. Since heart rate regularity is believed to be under sympathetic control, the increased regularity suggests that patients with more severe disease have higher levels of sympathetic tone. Treatment aimed at reducing the sympathetic activity may be useful.

The use of non-uniform quantization regions using H_C appears to be an excellent method for improving the characterization of HRV (Valencia et al., 2009b). Increasing the number of quantization regions also works well (Porta et al., 2007b). A combination of these two computational methods, using a higher number of regions with non-uniform quantization, could be considered in future research.

The research presented in this chapter (Valencia et al., 2009b, 2010) has confirmed the hypothesis that multiscale activity is present in HRV (Costa et al., 2005; Hoyer et al., 2005; Baumert et al., 2007). The degree of complexity of such multiscale activity depends on the

physiological state of the subject and the time of day that the HRV data are recorded (Costa et al., 2005; Valencia et al., 2009b). Major differences have also been found in the multiscale behavior of the HRV complexity between healthy subjects and patients with AS, especially during the daytime and for both short and medium time scales. A comparison between these two populations indicates that the entropy-based HRV complexity decreases with the disease, thus supporting the hypothesis that pathology reduces the complexity of cardiovascular control (Goldberger et al., 2002; Costa et al., 2005; Porta et al., 2007a).

Our results suggest that different types of information are derived from HRV analysis over both short and long time scales, and estimation of entropy at different time scales is needed to characterize the HRV complexity. Therefore, it is essential to develop a robust and a reliable method for computing a suitable multiscale analysis of HRV. A new measure called RMSE proposed by Valencia et al. (2009a, 2010) provides a refinement of the MSE index and overcomes two limitations of MSE, that is, the dependence of MSE on variance and on the shape of power spectrum. In addition, both RMSE and MSE methodologies are based on the estimation of the entropy rate and assess the complexity of a time series for a particular scale. Any method to estimate the entropy rate, such as approximate entropy, SE and H_C , can be used in RMSE and MSE. However, it is necessary that those methods include ad-hoc corrections of the bias arising from its evaluation at large embedding dimensions over limited data sequences.

Currently, the interpretation of the features of RMSE (or MSE) on real HRV data at long time scales remains uncertain because these non-linear parameters are not meaningfully linked to specific physiological regulatory mechanisms, either in the short term or in the long term. Because the method of RMSE allows simultaneous estimation of the complexity of the cardiovascular regulation for both short and long time scales, the design of experimental protocols, targeting long-term control and interactions between short-term autonomic regulations and long-term hormonal controls, might help in clarifying the extra information that RMSE provides compared to simpler approaches based on single-scale entropy rate or symbolic dynamics (Porta et al., 2001, 2007a,b; Wessel et al., 2003). Pharmacological protocols involving small animals (e.g., mice) and use of telemetry for gathering RR intervals from such animals for several days may provide greater insights.

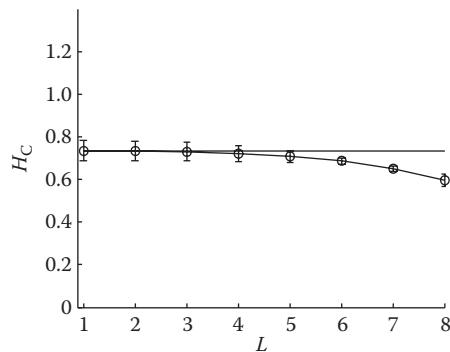
More research is needed to explain the effects of coronary artery occlusion at specific sites on the non-linear dynamics of heart rate. Further research is also needed to explain the reduction of complexity of the cardiac control system during a myocardial ischemia induced by coronary artery occlusion. Because changes in non-linearity during PTCA were observed (Benitez et al., 2009; Magrans et al., 2010), possibly due to the complex interplay between various regulatory systems involved in generating the HRV, future studies on the physiological mechanisms of cardiac control should take into account the non-linear coupling between different subsystems in order to describe the dynamical breadth of the system.

Conventional time domain, frequency domain and non-linear indices reflect different aspects of HRV. However, none of these indices are consistently superior to others (Kleiger et al., 2005). Moreover, a single index cannot adequately describe the complexity of heart rate control (Goldberger et al., 2002). Therefore, multivariate approaches that take into account non-linear dynamical indices in combination with standard linear indices and clinical factors should be considered (Truebner et al., 2006; Voss et al., 2008; Valencia et al., 2009b).

Finally, a rich array of complex physiological signals is available at www.physionet.org. This website contains computer software, including algorithms for power spectral analysis, Dc, DFA, multifractal analysis and MSE computation. In addition, it has a database of RR time series from patients with different cardiac pathologies.

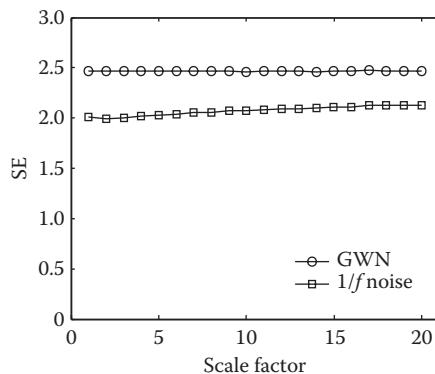
17.8 Appendix

17.8.1 Conditional Entropy

**FIGURE A17.1**

The mean and the standard deviation values of $H_C(L, q)$ obtained from 30 random series with a Gaussian distribution. In this figure, H_C was calculated with $q = 1$, and 1000 samples were considered for each realization.

17.8.2 Refined Multiscale Entropy

**FIGURE A17.2**

The mean values of RMSE as a function of the scale factor derived from 50 realizations of a simulated series: Gaussian white noise (GWN) and $1/f$ noise. Thirty thousand samples were considered for each realization.

Abbreviations

α	Fractal scalar exponent
α_m	Index of multifractality degree
β	Power law slope index
$\Delta\alpha$	Index of multifractality degree

$\Phi(x)$	Nonlinear content index
AMI	Average mutual information
AS	Aortic stenosis
CAD	Coronary artery disease
CE	Compression entropy
CM	Cardiac mortality
Dc	Correlation dimension
DCM	Dilated cardiomyopathy
DFA	Detrended fluctuation analysis
ECG	Electrocardiogram
FIR	Finite impulse response
H_C	Conditional entropy
HF	High-frequency spectral power
HFn	Normalized HF
HRG	High-risk group/patients who died due to cardiac causes
HRG _{SCD}	Patients who died due to sudden cardiac death in high-risk group
HRV	Heart rate variability
IHF	Ischemic heart failure
LA	Left atrial
LF	Low-frequency spectral power
LFn	Normalized LF
LRG	Survivor patients in low-risk group
LVDD	Left ventricular diastolic diameter
LVEDD	Left ventricular end diastolic diameter
LVEF	Left ventricular ejection fraction
MF-DFA	Multifractal detrended fluctuation analysis
MSE	Multiscale entropy
NRM	Healthy subjects
NYHA	New York heart association functional classification
PTCA	Percutaneous transluminal coronary angioplasty
R_p	Index of multifractality degree
REF	Healthy subjects
RMSE	Refined multiscale entropy
rMSSD	Square root of the mean squared differences of successive normal-to-normal intervals
SCD	Sudden cardiac death
SDNN	Standard deviation of all normal-to-normal intervals between adjacent QRS complexes
SE	Sample entropy
SVP	Survivor patients

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18

Heart Rate Variability and Blood Pressure Variability in Respiratory Disease: Effects of Pharmaceutical Compounds, Non-Invasive Ventilation and Physical Exercise

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18.1 Introduction

Chronic obstructive pulmonary disease (COPD) is a highly prevalent pathological condition that causes substantial morbidity and mortality in the adult population (Rabe et al., 2007). COPD is characterized by the presence of a chronic obstruction or limitation of expiratory airflow in lungs that is generally progressive and is not fully reversible (Rabe et al., 2007). As COPD progresses, worsening lung inflammation and tissue damage in the proximal and peripheral airways, lung parenchyma and pulmonary vasculature are observed. In addition, mucus hypersecretion and ciliary dysfunction lead to cough with sputum, often in the early morning. The airflow limitation in COPD patients is usually progressive and is associated with an abnormal inflammatory response of lungs to noxious particles and gases. The airflow limitation leads to hyperinflation, which occurs when air is trapped in lungs after each breath due to an imbalance in the volume of air being inhaled and exhaled (Rabe et al., 2007; Fromer and Cooper, 2008).

Smoking is the leading cause of COPD. However, it is known that COPD can also result from environmental factors, including passive smoking, air pollution, chemical inhalation or dust from the environment or workplace (Salvi and Barnes, 2009). The risk of developing COPD depends on the total amount of particles inhaled over time. Additionally,

long-term inhalation of occupational dust, chemicals, indoor pollution from heating and cooking with biomass fuels and outdoor pollution increase the risk of developing COPD (Rabe et al., 2007). However, approximately 3% of COPD patients have an α 1-antitrypsin (AAT) deficiency, a genetic factor predisposing them to the development of COPD. The onset of COPD in AAT-deficient individuals often occurs earlier in life than in those without the deficiency.

Many severe COPD patients experience intermittent or continuous hypoxemia (Barbara et al., 1991) in addition to a limitation of the expiratory airflow. Increased airway resistance, insufficient ventilation, hyperinflation, mechanical disability of the respiratory muscles and gas exchange abnormalities are all associated with dyspnea and contribute to ventilatory limitation during respiratory effort in these patients (O'Donnell, 2008; Dantzker and D'Alonzo, 1986). As a consequence, pulmonary ventilatory adjustments, especially dynamic hyperinflation and its sensorial perception (dyspnea), are centrally related to exercise impairment in patients with COPD. Moreover, hypercapnia is present when a considerable reduction in ventilation occurs (Barbara et al., 1991; O'Donnell, 2001; Dantzker and D'Alonzo, 1986).

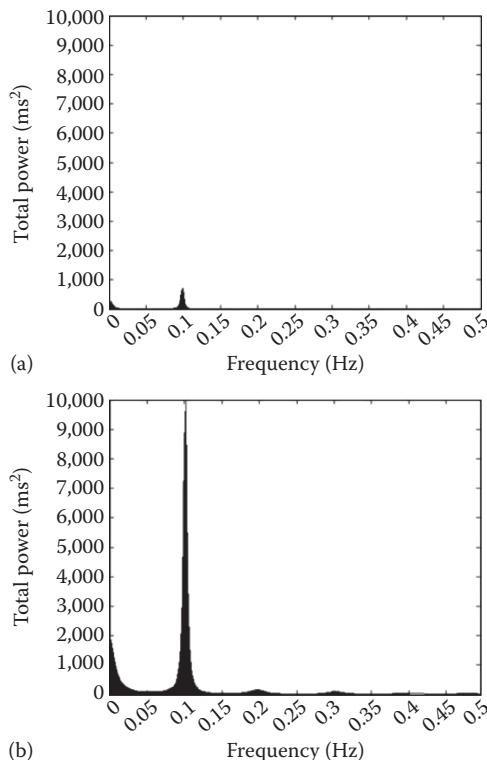
However, more recently, an emphasis has also been placed on peripheral muscle abnormalities, since systemic consequences constrain exercise tolerance in this population (ATS/ERS, 1999; Borghi-Silva et al., 2008a). All these abnormalities lead to considerable disability, morbidity and mortality, especially with increasing severity of COPD.

18.2 Heart Rate Variability and Baroreflex Activity in COPD Patients

Cardiovascular autonomic neuropathy is a common consequence of COPD (Chhabra and De, 2005; Volterrani et al., 1994; Sin et al., 2007). Previous studies have demonstrated that COPD patients have a depressed heart rate variability (HRV), indicating an increased sympathetic activity at rest (Chhabra and De, 2005; Volterrani et al., 1994) as well as during sleep (Fromer and Cooper, 2008) and physical exercise (Bartels et al., 2004). As a result, arrhythmias are common in patients with COPD, contributing to a documented increased risk of sudden cardiac death in chronic COPD patients (Senior et al., 1979; Tükek et al., 2003; Yıldız et al., 2002).

The main cause of reduced HRV in patients with COPD is not well understood. Plausible pathophysiologic mechanisms leading to a reduced HRV in COPD include bronchoconstriction (Volterrani et al., 1994), hypoxia (Chen et al., 2006), hypercapnia (Sin et al., 2007), medications (Senior et al., 1979; Tükek et al., 2003; Yıldız et al., 2002), weight loss (Takabatake et al., 2001) and systemic inflammation (Takabatake et al., 2001; Lampert et al., 2008). Some research, however, suggests that despite a reduced overall HRV, parasympathetic modulation is increased (Volterrani et al., 1994; Borghi-Silva et al., 2008b), while others point to an increase in sympathetic activation (Chen et al., 2006; Pagani et al., 1996). In our laboratory, we have observed both a reduced index of parasympathetic modulation and an increased index of sympathetic modulation in COPD patients based on HRV analysis (Reis et al., 2010a; Pantoni et al., 2007), as shown in Figure 18.1. Furthermore, cardiac adjustments caused by postural changes are depressed in these patients (Pantoni et al., 2007).

Studies in a rat model have shown that repeated hypoxemia alters HRV and baroreflex activity before it induces hypertension (Iturriaga et al., 2010). Moreover, Patakas et al. (1982) showed that baroreflex sensitivity (BRS) was lower in COPD patients compared

**FIGURE 18.1**

Decomposition of the spectrum into single spectral components—very low frequency (VLF), low frequency (LF) and high frequency (HF)—during a respiratory sinus arrhythmia maneuver in a representative COPD patient (a) and a healthy matched control (b).

to age-matched controls and a significant inverse relationship between BRS and pulmonary arterial pressure. This mechanism has been linked to oxidative stress caused by hypoxia, which is a potential mediator of both chemosensory and cardiorespiratory alterations (Iturriaga et al., 2009; Del Rio et al., 2010), as well as impaired baroreceptor feedback control (Costes et al., 2004). Thus, when persistent hypoxia is provoked in other conditions, it may be associated with a cardiac autonomic dysfunction (Watson et al., 1999). Somers et al. (1988) demonstrated that in normal subjects, both hypoxia and hypercapnia result in sympathetic nerve activation, and, when combined (i.e., hypoxia plus hypercapnia), they synergistically increase sympathetic activity. Systemic manifestations have also been associated with sympathetic overactivity (Andreas et al., 2005). Heart rate turbulence, which measures heart rate response to premature ventricular beats, is reduced in COPD patients (Gunduz et al., 2009), implying a loss of normal autonomic regulation.

Recently, it has been suggested that cardiac autonomic function in patients with COPD is related to their physical activity level and their muscle strength (Garet et al., 2005). Such a relationship would be similar to that reported in patients with chronic heart failure (Larsen et al., 2004). Reis et al. (2010b) found that the impairment of sympathovagal balance was associated with inspiratory muscle weakness in COPD patients, which confirms the observations by Somers et al. (1988) that dyspnea and an increase in respiratory drive

are associated with increased sympathetic modulation. In addition, Costes et al. (2004) found depressed spontaneous BRS in COPD patients.

18.3 Strategies for Restoring Heart Rate Variability and Baroreflex Activity in COPD Patients

18.3.1 Physical Exercise

COPD and its sequelae negatively impact exercise tolerance and accentuate the level of disability. In this context, physical activity programs appear to ameliorate consequences of COPD, both reducing the severity of dyspnea and improving health-related quality of life (Borghi-Silva et al., 2010). The positive effects of aerobic exercise training on autonomic modulation have been reported in healthy subjects (Melo et al., 2005; American College of Sports Medicine Position Stand, 1998) as well as in post-acute myocardial infarction (Santos-Hiss et al., 2010), post-coronary bypass (Mendes et al., 2010) and chronic heart failure patients (Selig et al., 2004; Arena et al., 2006), which may help explain the documented prognostic improvement in patients with COPD, since both diseases culminate in important systemic manifestations and considerable disability (Gosker et al., 2003).

Type of exercise may also be an important factor in whether exercise restores autonomic nervous system (ANS) balance in patients with COPD, because aerobic physical training seems to improve cardiac autonomic modulation in healthy older men (Melo et al., 2005a; De Meersman, 1993; Stein et al., 1999) and in those with pathological conditions (Santos-Hiss et al., 2010; Mendes et al., 2010; Selig et al., 2004; Arena et al., 2006; Pollock et al., 2000), while effects of aging on the muscular system (i.e., the loss of muscle mass and a reduction in muscle strength and power) can only be impeded by resistance (strength) training (Mazzeo et al., 2001). In addition to improving muscular function, strength training appears to decrease resting blood pressure both in normotensive adults (Kelley and Kelley, 2000) and in hypertensive elderly subjects (Taylor et al., 2003), with an increased vagal modulation in the latter group (Taylor et al., 2003). Melo et al. (2008b) reported that eccentric strength training in healthy older men increased peak torque (assessed by an isokinetic dynamometer) and reduced systolic blood pressure. However, it also caused an autonomic imbalance toward sympathetic dominance in resting conditions, produced by an as yet unidentified mechanism. In summary, whether resistance training can alter HRV or systolic blood pressure in COPD patients remains to be seen.

In a randomized clinical trial, Borghi-Silva et al. (2009a) demonstrated that in COPD patients who underwent whole-body aerobic physical training, sympathetic activity decreased and parasympathetic modulation increased. This may be due to the significant improvements that were also recorded in submaximal and maximal exercise capacities. The reduction in respiratory rate and the increase in tidal volume that result from training would reduce sympathetic activity. Increases in tidal volume in healthy volunteers during spontaneous respiration have also been shown to increase the HF component of HRV, a parameter associated with parasympathetic activity (Pöyhönen et al., 2004).

Another plausible explanation related to physical training would be the positive adaptations of respiratory and peripheral muscles. In this context, Heindl et al. (2001) observed

that there was marked sympathetic activation in patients with chronic respiratory failure. Ischemic metabolites generated during muscle contraction have been shown to stimulate local receptors and cause increases in heart rate, arterial pressure and sympathetic activity (Heindl et al., 2001; Mitchell et al., 1983). Another explanation is that lung inflation reflexes can modulate the influence of vagal modulation on heart rate (Pöyhönen et al., 2004).

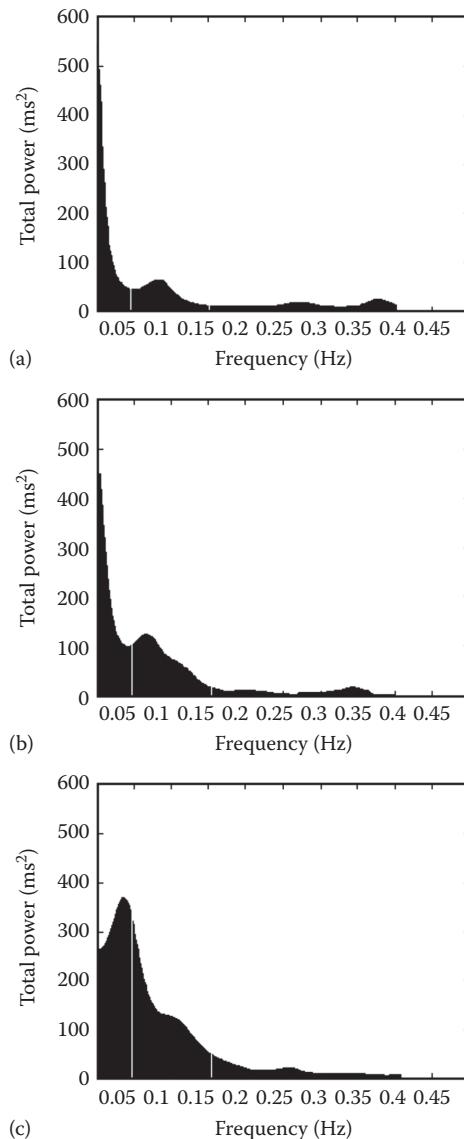
In another study, an analysis of cardiac BRS in COPD patients after a whole-body physical training program showed that physical training was associated with a gain in spontaneous BRS, which confers cardiovascular benefits (Costes et al., 2004). By contrast, Marquis et al. (2008) observed that aerobic exercise training either alone or with antihypertensive drugs was not associated with beneficial alterations of HRV or blood pressure in a subgroup of COPD patients with systemic arterial hypertension.

Respiratory exercise and biofeedback using HRV are other strategies that have been investigated in COPD patients. In a recent study, Raupach et al. (2008) found that slow breathing significantly reduced sympathetic activity and tended to increase BRS in COPD patients, indicating a positive modulation of the sympathovagal balance. In a study by Giardino et al. (2004), 20 patients with COPD participated in five weekly sessions of HRV biofeedback and four weekly sessions of walking with oximetry feedback and instructions for walking at home. After 10 weeks of training, the participants showed statistically and clinically significant improvements in the distance they walked in 6 min and in their quality of life (Giardino et al., 2004).

18.3.2 Non-Invasive Ventilation

Several studies have shown that non-invasive positive pressure ventilation (NPPV) can be successfully used to reduce respiratory work, the need for intubation, respiratory complications, mortality and morbidity during acute exacerbations of respiratory failure (Hess, 2004; BTS, 2002). NPPV administered to patients with stable COPD reduced inspiratory effort (Borghi-Silva et al., 2009a; Vanpee et al., 2002), reduced dyspnea and improved exercise tolerance (Van't Hul et al., 2002; Borghi-Silva et al., 2009a). Consequently, some modes of NPPV have been tested as an adjunct therapy during short-term interventions (Borghi-Silva et al., 2009b; Puhan et al., 2004) in such patients.

Bilevel positive airway pressure (BPAP) has been shown to be effective in improving ventilation and does not create a significant hemodynamic instability (Palasiewicz et al., 1997). Moreover, Skyba et al. (2007) demonstrated that BPAP may improve neural regulation of heart rate by reducing the blood pressure during acute exacerbation of COPD in such patients. In patients with severe but stable COPD, Borghi-Silva et al. (2008a) observed that BPAP reduced parasympathetic cardiac modulation and increased sympathetic cardiac modulation. Similarly, Reis et al. (2010c) showed that progressive increase in continuous positive airway pressure (CPAP) could reduce parasympathetic modulation and increase sympathetic modulation (Figure 18.2). These results are important since Volterrani et al. (1994) had previously found that the parasympathetic modulation of heart rate is increased in the absence of bronchodilators. Furthermore, there was a consistent reduction in end-tidal carbon dioxide due to an increase in ventilation, which was associated with a decrease in vagal activity in these patients. On the other hand, in another study that applied BPAP during acute exacerbation of COPD, there was an improvement in the parasympathetic indices of HRV, which concomitantly included a reduction in sympathetic activation (Yazici et al., 2008). Three months of non-invasive mechanical ventilation (BPAP or CPAP) improved HRV, reduced circulating natriuretic

**FIGURE 18.2**

Decomposition of the spectrum into single spectral components—very low frequency (VLF), low frequency (LF) and high frequency (HF)—during sham continuous positive airway pressure (CPAP) (a), CPAP of 5 cmH₂O (b) and CPAP of 10 cmH₂O (c).

peptide levels and enhanced the functional performance of patients with stable but advanced COPD (Sin et al., 2007).

18.3.3 Long-Term Oxygen Therapy

Long-term oxygen therapy (LTOT) can increase survival and reduce secondary complications in COPD patients (BTS, 2002; Güell, 2008). In the short term, oxygen supplementation can reverse cardiac autonomic dysfunction (Stewart et al., 1991; Hjalmar森 et al., 1996;

Scalvini et al., 1999; Bartels et al., 2000). Recently, Lewis et al. (2009) found evidence that LTOT of patients with severe COPD provided oxygen supplementation, a positive cardiac benefit, as well as an improvement in HRV indices. LTOT can reduce intermittent nocturnal hypoxia, which is associated with a high risk of sudden death due to nocturnal arrhythmias (Kleiger et al., 1976). By contrast, intermittent hypoxia (Haider et al., 2009) with or without physical exercise has been investigated as a therapeutic strategy for the treatment of COPD and asthma patients (Vogtel and Michels, 2010). It has been generally observed that LTOT leads to higher levels of ventilation, especially during physical training. However, physiological effects and the potential harm, if any, of LTOT to cardiac autonomic activity need to be further investigated.

18.4 Medications

The ANS plays a primary role in regulating airway caliber, and its dysfunction is likely to contribute to the pathogenesis of airway diseases (Canning and Fischer, 2001). COPD and asthma patients are usually treated pharmacologically. Considering that HRV is modified by various medications, it is necessary to investigate how such therapies affect the ANS. Specifically, we will review the effects and implications of β_2 -agonists and anticholinergic drugs on cardiovascular autonomic function.

Selective β_2 -adrenoceptor agonists, such as salbutamol, are in widespread use as bronchodilators in the treatment of COPD, asthma (Cekici et al., 2009) and other reversible obstructive airway diseases (Jartti et al., 1997a). Asthmatic children have autonomic nervous dysfunction (Kazuma et al., 1997), characterized in both asymptomatic and acute patients by a significantly lower sympathetic index (manifested in lower normalized low-frequency [LF] power). These findings are consistent with the altered sympathetic/parasympathetic balance of HRV found in adult (Garrard et al., 1992) as well as pediatric patients with bronchial asthma.

On the other hand, the literature suggests that in COPD patients, the sympathetic excitatory modulation of the sinoatrial node is depressed and that the respiratory modulation of RR interval variability is significantly reduced when compared to age-matched healthy controls (Pagani et al., 1996). Such abnormalities in the autonomic control may represent a functional correlation with the pulmonary hyperinflated state present in this clinical condition (Pagani et al., 1996).

Using spectral analysis, Jartti et al. (1997b) assessed the acute effects of inhaled salbutamol on the heart rate and blood pressure variability of pediatric COPD patients. They concluded that acute salbutamol inhalation decreased cardiovagal responsiveness, increased sympathetic dominance and tended to decrease BRS as well as improve pulmonary function.

Eryonucu et al. (2001a) found that salbutamol (200 μ g inhaled) and terbutaline (500 μ g inhaled) had similar acute effects on autonomic cardiovascular function in adults with asthma (who did not receive β_2 -agonists during the 2 months prior to the study). Both drugs decreased total power and increased LF/HF ratio and sympathetic modulation (LF), possibly due to an increased β -receptor stimulation. However, because the study patients had not been on β_2 -agonists for 2 months prior to the study, these results probably cannot be extrapolated to asthmatic patients who use β_2 -agonists regularly. β -Receptor sensitivity may be downregulated with regular β_2 -agonist use.

The cardiovascular effects of β -adrenergic agonists result from direct myocardial effects that increase heart rate, which may result in a shortening of ventricular diastole, and an increase in myocardial oxygen consumption and cardiac work, resulting in an increase in the force of contraction, thereby reducing the time for coronary artery perfusion (Cekici et al., 2009; Skorodin, 1993; Penna et al., 1993; Scheinin et al., 1989).

β -Adrenergic agonists have been associated with increased cardiovascular risks in asthma patients (Barnes, 1997; Au et al., 2000; Kallergis et al., 2005; Salpeter et al., 2004), since they may interfere with autonomic regulation of cardiovascular function (Jartti et al., 1997b; Skorodin, 1993). They could result in tachycardia, palpitation, tremors, peripheral vasodilation, hyperactivity, various metabolic effects, dysrhythmias, exacerbation of myocardial ischemia and hypotension or hypertension (Jartti et al., 1997b; Eryonucu et al., 2001a).

Moreover, myocardial infarction has been reported as a possible complication of β_2 -adrenergic agonist therapy (Salpeter et al., 2004). Rossinen et al. (1998), however, showed that salbutamol inhalation did not induce myocardial ischemia, arrhythmias or an alteration in HRV in patients with coronary artery disease and asthma or COPD. Cekici et al. (2009), in a placebo-controlled study, showed that the inhalation of therapeutic doses of salbutamol (0.2 mg) in healthy subjects resulted in significant hemodynamic changes (an increase in cardiac output and a decrease in total peripheral resistance) and a shift toward a sympathetic dominance (an increase in the LF and a decrease in the HF spectral component) in the absence of baroreceptor activation. Cekici et al. (2009) suggested that observed changes in cardiac autonomic function as reflected by HRV measures could contribute to the cardiac risk associated with inhaled β -adrenergic agonists.

Formoterol and salmeterol are two long-acting β_2 -adrenergic agonists (Palmqvist et al., 1999) used to treat asthma. These drugs are given by inhalation and produce bronchodilating effects that last for at least 12 h after a single administration (Ullman and Svedmyr, 1990). They have been used in the regular treatment of asthmatic patients who are not controlled with inhaled corticosteroids (BGMA, 2009). Palmqvist et al. (1999) studied 15 asthmatic patients in a double-blind, crossover, placebo-controlled design study. They found that, at the highest doses, formoterol caused a significantly higher tremor score and a larger drop in serum potassium than salmeterol.

The effects of these β_2 -adrenergic agonists on HRV have been studied. Eryonucu et al. (2005b) studied the effects of salmeterol (50 μ g) and formoterol (12 μ g) on HRV in 39 adult asthmatic patients with no heart disease. The time domain measures of the HRV (the standard deviation of normal-to-normal RR intervals [SDNN], the standard deviation of the mean of consecutive 5 min segments of normal-to-normal RR intervals [SDANN] and the root-mean-squared value of differences between successive RR intervals [RMSSD]) at baseline were not significantly different between the salmeterol and the formoterol groups. Moreover, there were no significant differences in HRV parameters after inhalation of both drugs. These authors concluded that salmeterol and formoterol have no short-term adverse effects on HRV in patients without heart disease. However, further studies are needed to evaluate the long-term effects of these drugs on HRV in asthmatic patients with heart disease.

Pichon et al. (2005) studied subjects who had suspected asthma with chronic cough and unexplained exercise-induced dyspnea or cough. Using HRV spectral analysis, they tested the relationship between airway hyperresponsiveness and cardiac parasympathetic modulation in patients who underwent a diagnostic methacholine bronchial challenge (MBC). Their results demonstrate that responsive or hyperresponsive subjects

have a significantly higher parasympathetic modulation than subjects without airway responsiveness at baseline before MBC. The hyperresponsive subjects also had a significant increase in HF(nu) after the bronchial challenge, suggesting a significant increase in parasympathetic modulation. Moreover, a significant relationship was found between the normalized units of the HF component of HRV and hyperresponsiveness. These data showed that bronchial autonomic modulation seems to be linked with the cardiac parasympathetic autonomic modulation in those subjects with airway hyperresponsiveness (Pichon et al., 2005).

Regarding anticholinergic drugs that act by antagonizing the muscarinic receptors located in airway smooth muscle, tiotropium is a long-acting bronchodilator of bronchial smooth muscle. It reduces airway tone and improves expiratory flow limitation, pulmonary hyperinflation and exercise capacity in patients with COPD (Hanania and Donohue, 2007). In year-long, placebo-controlled trials (Casaburi et al., 2002), dry mouth was the most commonly reported side effect of tiotropium. An increased risk of glaucoma and urinary retention has also been associated with the use of this drug (Hanania and Donohue, 2007). Vincken et al. (2002) observed no clinically significant alterations either in vital signs or in 12-lead electrocardiogram during a year-long treatment with tiotropium.

Unlu et al. (2006), in a randomized, double-blind, crossover design study, investigated the effects of inhaled tiotropium and placebo on HRV of healthy volunteers before and after drug administration. These drugs were administered in two different sessions. Time domain parameters (mean RR interval, the standard deviation of the RR intervals and the RMSSD) and power spectral analysis of HRV were assessed in the supine position, during handgrip exercise and controlled breathing, before and after drug administration. There were no significant differences in HRV parameters (in the time and frequency domains) after administration of each drug in the conditions studied. The authors concluded that a single 18 µg dose of tiotropium did not affect cardiac autonomic modulation in healthy volunteers. However, these results may not be applicable to patients with respiratory disease, since they studied only healthy young males and administered only a single dose of the drug. Thus, the long-term effects of tiotropium in patients with respiratory diseases and of different ages need further investigation (Unlu et al., 2006).

18.5 Conclusions

HRV analysis is a useful tool for the clinical evaluation of pharmacological and non-pharmacological interventions that have the potential to influence the cardiac ANS in COPD patients. Strategies to reverse and control pulmonary function abnormalities and its systemic effects, which are associated with autonomic dysfunction that leads to elevated mortality and morbidity from cardiovascular disease in this population, need to be extensively investigated.

In addition, future research should examine long-term efficacy and safety of different combinations of bronchodilators, as well as the effects of different types of physical exercise on HRV, BRS and the clinical outcomes of COPD patients. In this context, new non-pharmacological therapies, such as resistance training of the lower and upper limbs, combined aerobic/resistance exercise, respiratory muscle training and new modes of non-invasive ventilation should be investigated in future studies.

Abbreviations

BPAP	Bilevel positive airway pressure
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
LTOT	Long-term oxygen therapy
MBC	Methacholine bronchial challenge
NPPV	Non-invasive positive pressure ventilation

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19

Effects of Spinal Cord Injury on Heart Rate Variability and Blood Pressure Variability

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19.1 Introduction

The incidence rate of spinal cord injury (SCI) varies widely across different parts of the world. While the incidence rate is estimated at 35 per million in Canada, in the United States, the incidence rate is estimated at 50 per million per year (Sekhon and Fehlings, 2001). While these incidence rates seem relatively small, they translate to approximately 1,100 new injuries in Canada and approximately 12,000 new injuries in the United States each year (Rick Hansen Foundation, 2010), numbers that are added to the estimated 41,000

Canadians and 306,000 Americans already living with an SCI. Globally, there are 223–755 million individuals living with an SCI, a number that increases annually by 10.4–83 million individuals (Wyndaele and Wyndaele, 2006).

An SCI results, perhaps most notably, in partial or complete muscular paralysis and a loss of mobility. These functional impairments are the most obvious consequences of an SCI and, in many cases, are the greatest initial concern for the injured person. Unfortunately, in the weeks and months that follow, many individuals come to realize that the full impact of an SCI extends well beyond the already devastating loss of ambulation. Several of these more insidious consequences of an SCI result from (i) the damage that is sustained to the autonomic nervous system (ANS), or, simply, its disconnection from the control of higher centers; and (ii) the level of inactivity that is regrettably characteristic of the SCI population. Thus, many of the body's physiological systems become impaired following an SCI, often resulting in daily obstacles for the injured individual as well as a heightened risk of morbidity and mortality from a variety of pathologies.

The ANS is responsible for maintaining a homeostatic balance within a variety of systems by means of both sympathetic and parasympathetic innervations. An SCI results in a unique form of ANS dysfunction, characterized by a disruption in the balance of these autonomic subsystems. Due to the anatomical distribution of sympathetic and parasympathetic fibers, much of the sympathetic outflow is lost following a spinal trauma, while parasympathetic outflow is largely maintained. Specifically, much of the parasympathetic outflow to the body is provided by fibers traveling within the vagus nerve (with the exception of parasympathetic innervation to the bladder, bowel and sexual organs), and as such, it is largely preserved following a spinal trauma. Conversely, sympathetic fibers originate between the first thoracic and second lumbar segments of the spinal cord, making this system susceptible to extrication from the regions rostral to actual lesion. As such, those with cervical and high thoracic SCIs would be expected to exhibit a parasympathetic-dominated nervous system. In addition, the immobility that is often characteristic of an SCI, and the disruption of the ANS function in a way that is contradictory to this supposed parasympathetic predominance, leads to cardiovascular disease. Thus, the ability to reliably estimate the autonomic function after an SCI is of extreme importance.

19.2 Cardiovascular Disease and Dysfunction after SCI

The health and proper function of the cardiovascular system are dependent on the neural outflow from higher centers as well as the maintenance of an active lifestyle, and therefore, it is particularly vulnerable after an SCI. Accordingly, the increased risk of a multitude of cardiovascular diseases becomes a serious long-term concern for the SCI population (Cowan and Nash, 2010; Grigorean et al., 2009; Wahman et al., 2010; Rosado-Rivera et al., 2011). Following an SCI, abnormalities in blood pressure (BP) and heart rate (HR) are common manifestations of autonomic dysfunction and contribute to an increased cardiovascular risk. These risks are in addition to those due to obesity, lipid disorders, metabolic syndrome and diabetes, which are common in the SCI population (Myers et al., 2007).

Causes of mortality in the SCI population have changed dramatically in the last few decades, largely due to improved bladder care and the reduction in corresponding deaths due to urinary complications (Frankel et al., 1998). Likewise, improved care of both acutely and chronically injured individuals has had the very positive effect of increasing the life

expectancy of the SCI population (Frankel et al., 1998). As a result, however, there has been a parallel increase in the association between SCI and typical age-related diseases. Accordingly, van Duijnhoven et al. (2010) published a systematic review of literature on survival analysis of patients with traumatic and non-traumatic SCI worldwide. These authors found that age at injury, neurological level, the extent of lesion and the year of injury are the major factors in predicting survival. Similarly, while mortality rates due to urinary complications have steadily decreased over the last several decades, mortality rates due to cardiovascular and respiratory diseases have emerged as the most common causes of death among the SCI population (DeVivo et al., 1993). These health risks are apparent both acutely and in the long term after an SCI. For example, multiple organ failure has been frequently observed during the acute phase in patients with cervical SCI (Stein et al., 2010), and the most common system to fail was observed to be the cardiovascular system at 84%, based on the Multiple Organ Dysfunction Score (MODS).

Heart disease has been consistently cited as the second predominant cause of mortality in individuals with an SCI (DeVivo et al., 1993, 1999; Frankel et al., 1998; Soden et al., 2000). A detailed examination of mortality in the SCI population was provided by DeVivo et al. (1993), who tabulated various causes of death after an SCI as well as their corresponding standardized mortality ratios in a cohort of 9135 injured individuals (all of whom survived the first 24 h). Non-ischemic heart disease ranked as the second most common cause of death in the SCI population after pneumonia, although specific mortality risks differed widely across injury types. For example, those with incomplete paraplegia showed a similar risk to the able-bodied population, while those with complete tetraplegia exhibited a significantly increased risk of 23-fold. Ischemic heart disease was the fifth most common cause of death in the SCI population, and again, those with incomplete paraplegia showed a similar mortality risk to the able-bodied population, while those with complete tetraplegia showed a significantly increased risk of 2.6-fold.

Heart disease is not the only cardiovascular consequence of an SCI. In the aforementioned study, individuals with complete tetraplegia were found to be at a significantly increased risk (5.4-fold) of death due to a cerebrovascular disease such as stroke, while the risk of death due to a pulmonary embolism was increased in all types of SCI, regardless of the level or severity. Remarkably, even those with incomplete paraplegia (the mildest injury group) possessed a 23-fold increased mortality risk due to a pulmonary embolism, while those with complete tetraplegia possessed a 107-fold risk compared to the able-bodied population. Finally, each of these deficits persisted as a major concern long after the acute phase of injury (DeVivo et al., 1993).

In addition to a heightened risk of cardiovascular disease, individuals with an SCI are susceptible to various forms of cardiovascular dysfunction, with two particularly common forms being autonomic dysreflexia and orthostatic intolerance. Autonomic dysreflexia, a potentially serious sequel of an SCI, is a sympathetic reflex in response to noxious stimuli below the level of injury (Krassioukov et al., 2009a). The sympathetic response below the lesion level causes an uninhibited vasoconstriction and thus, potentially dangerous increases in BP, especially in those with injuries at or above the sixth thoracic level due to the involvement of the splanchnic vascular bed. Accordingly, while the clinical definition of autonomic dysreflexia is an increase in systolic BP of at least 20%, in its most severe form, this condition may be associated with life-threatening increases in systolic BP to roughly 250–300 mmHg. Thus, autonomic dysreflexia is not only an isolated cardiovascular dysfunction that can severely limit independence and quality of life, but more seriously, it may be a catalyst for the deadly cardiovascular diseases previously mentioned. Specifically, full-blown episodes of autonomic dysreflexia have been reported to cause cerebrovascular events such as seizures

TABLE 19.1

Current Literature Regarding HRV and BPV after SCI

References	Participants	Design	Main Findings
Inoue et al. (1991)	$n = 14$ 7 tetra males AIS: A Time post-injury: 10 months to 2 years 7 able-bodied male controls	Design: Prospective, observational Measures: BPV (BP waveforms, SBP variability) (supine position) Methods: Arterial tonometry, autoregressive power spectral analysis	• Disappearance of the LF component of SBP in tetra subjects
Inoue et al. (1990)	$n = 12$ 6 tetra males AIS: A Time post-injury: 13 months to 13 years 6 able-bodied male controls	Design: Prospective, observational Measures: HRV (HF, LF) (supine) Methods: Autoregressive power spectral analysis	• Disappearance of the LF component in tetra subjects
Inoue et al. (1995)	$n = 25$ 15 tetra males AIS: A Time post-injury: >6 months 10 able-bodied male controls 9 para males (T10–11) AIS: A Time post-injury: >6 months 9 able-bodied male controls	Design: Prospective, observational Measures: HRV (LF, HF, LF:HF) (supine) Methods: Autoregressive power spectral analysis	• Tetra subjects = maintenance of the LF component in six subjects • LF and HF = ↓ than controls • LF:HF = ↑ than controls • Para subjects = ↓ the HF and LF components than controls
Grimm et al. (1997)	$n = 40$ 10 tetra males AIS: A Time post-injury: 11 ± 2.9 years 10 tetra males AIS: B–D Time post-injury: 8 ± 1.3 years 10 para males AIS: not stated Time post-injury: 13 ± 2.5 years 10 able-bodied male controls	Design: Prospective, observational Measures: HRV (HF, LF, HF:LF) (supine/head-up tilt/cold pressor test/isometric test) Methods: Spectral analysis (Fourier transform)	• Tetra = ↓ spectral components in baseline and provocative measure • Para = ↓ the HF and LF components • No difference in the LF:HF ratio among all groups

Grimm et al. (1995)	<i>n</i> = 14 7 tetra males AIS: A Time post-injury: 14 ± 4 years 7 tetra males AIS: B–D Time post-injury: 7 ± 2 years	Design: Prospective, observational Measures: HRV (HF and LF) (supine and provocative maneuvers) Methods: Power spectral analysis (Fourier transform)	<ul style="list-style-type: none"> The LF component apparent in complete tetra Supine = ↓ the LF component in complete tetra compared to incomplete Provocation = ↓ the LF and HF components in complete tetra
Wang et al. (2000)	<i>n</i> = 31 14 para males (T10–L2) AIS: A Time post-injury: 6.7 ± 5.3 years 17 tetra males AIS: A Time post-injury: 6.6 ± 5.8 years	Design: Prospective, observational Measures: HRV (time and frequency domains) Methods: 24 h Holter monitoring	<ul style="list-style-type: none"> Tetra = ↓ VLF/LF/HF and RR intervals compared to para No difference in the LF:HF ratio between groups
Ditor et al. (2005a)	<i>n</i> = 8 8 tetra: 6 males/2 females AIS: 7 = C/1 = B Time post-injury: 9.6 ± 7.5 years	Design: Exercise intervention (6 months pre/post) Measures: LF and HF power/LF:HF ratio/systolic and diastolic LF power (pre/post 6-month BWSTT) Methods: 10 min HR and finger arterial pressure (supine/orthostatic stress)	<ul style="list-style-type: none"> ↓ in HR and LF:HF ↓ in LF systolic BP No change in BP No change in HRV or BPV during orthostatic stress
Ditor et al. (2005b)	<i>n</i> = 6 3 Para AIS: A 3 Tetra AIS: B 4 males/2 females Time post-injury: 7.6 ± 9.4 years	Design: Exercise intervention (4 months pre/post) Measures: HRV, BPV, peripheral muscle/artery dimension and function (pre/post 4-month BWSTT) Methods: Ultrasound (artery dimension), HR and BP (HRV/BPV)	<ul style="list-style-type: none"> No change in carotid or femoral artery dimension/blood flow/resistance No change in carotid artery compliance Exercise induced ↑ femoral artery compliance Subgroup (<i>n</i> = 3) increased vagal predominance and ↓ BPV
Ditor et al. (2005c)	<i>n</i> = 10 6 tetra AIS: B 4 tetra AIS: A 6 males/4 females Time post-injury: 5.4 ± 7.7 years	Design: Prospective, observational Measures: HRV and BPV reproducibility (2 measures/2-week period) Methods: 10 min supine electrocardiogram and Finapress BP recording	<ul style="list-style-type: none"> High reproducibility of HR, LF and LF:HF ($R = 0.82$–0.88) Poor reproducibility of HF High reproducibility of BP and systolic BPV ($R = 0.71$–0.89) Lower reproducibility of diastolic BPV but acceptable ($R = 0.71$–0.89)

(continued)

TABLE 19.1 (Continued)

Current Literature Regarding HRV and BPV after SCI

References	Participants	Design	Main Findings
Millar et al. (2009)	$n = 7$ 2 tetra AIS: A–C 5 para AIS: A–C 6 males/1 female Time post-injury: 5 ± 4.4 years	Design: Randomized crossover design Measures: HRV (rest/before and after exercise) Methods: 4 weeks BWSTT and HUTT (thrice weekly)	<ul style="list-style-type: none"> • No difference in linear HRV following training • Change in sample entropy after BWSTT
Millar et al. (2010)	$n = 9$ 5 tetra AIS: B–D Time post-injury: 13 ± 13 years 4 able-bodied controls	Design: Cross-sectional Measures: Non-linear HR dynamics (before and after autonomic blockade) Methods: Atropine sulfate and metoprolol tartrate administration in supine and cardiac stress conditions	<ul style="list-style-type: none"> • ↑ in HR after vagal blockade • ↓ in sample entropy • Baseline sample entropy and correlation dimension lower in SCI during CV stress
Wecht et al. (2009)	$n = 24$ 17 tetra AIS: not stated Time post-injury: 1–41 years 7 para AIS: not stated Time post-injury: 1–41 years 18 able-bodied controls (10 young/8 old)	Design: Prospective, observational Measures: Time–frequency analysis of HR (HFIn) Methods: Cold face test	<ul style="list-style-type: none"> • HFIn reduced in SCI compared to young able-bodied controls • HFIn was similar between SCI compared to old
Wecht et al. (2006)	$n = 32$ 7 tetra AIS: A–C Time post-injury: >2 years 7 para AIS: A–C Time post-injury: >2 years 8 able-bodied controls	Design: Prospective, observational Measures: HR, HF and LF HRV and LF/HF ratio Methods: 45° head-up tilt (HUT)	<ul style="list-style-type: none"> • HR and LF power ↓ in tetra compared to para and able-bodied at 45° HUT • No between-group differences in the HF component at 45° HUT • LF/HF ratio ↓ in tetra than able-bodied at 45° HUT

Wecht et al. (2006b)	<i>n</i> = 18 18 para (9 fit/9 unfit) AIS: not stated Time post-injury: fit: 12 ± 7 years; unfit: 10 ± 7 years	Design: Exercise intervention Measures: LF and HF HRV and LF/HF ratio (baseline vs. recovery) Methods: Hand cycling	• VO ₂ and peak watts ↑ in fit group • HF recovery ↑ in fit group • LF and LF/HF recovery ↓ in fit group
Wecht et al. (2003)	<i>n</i> = 28 19 para AIS: A–C Time post-injury: 11 ± 7 years 9 able-bodied controls	Design: Prospective, observational Measures: HR, HF and LF HRV, LF/HF ratio and LF SBP Methods: Head-up tilt (HUT)	• LF ↑ and HF ↓ across tilt angle in control • In para LF = no change and HF ↓ across tilt angle • Interaction for LF/HF • LF SBP ↓ in para
Takahashi et al. (2007)	<i>n</i> = 15 6 tetra AIS: A Time post-injury: 7–22 years 9 able-bodied controls	Design: Exercise intervention Measures: HF component and HF/total HR Methods: Static elbow flexor contractions	• No difference in resting HR, HF, and HF/total between groups • During exercise HF and HF/total HR ↓ 67%–90% in tetra • Blunted initial ↑ in HR and delayed recovery in tetra • LF power ↑ in able-bodied only during HUT • SV and MAP ↓ in tetra more than able-bodied or para
Houtman et al. (2000)	<i>n</i> = 27 9 para Time post-injury: >2 years 9 tetra Time post-injury: >2 years AIS: A (15), B (1), C (2) 9 able-bodied controls	Design: Prospective, observational Measures: LF peak of BPV/stroke volume/MAP Methods: 12 min head-up tilt (HUT)	

Notes: AIS, American Impairment Scale; CV, cardiovascular; HF, high frequency; HR, heart rate; HRV, heart rate variability; HUT, head-up tilt; LF, low frequency; Para, paraplegia; SBP, systolic blood pressure; Tetra, tetraplegia.

(Yarkony et al., 1986) as well as potentially fatal intracerebral and subarachnoid hemorrhages (Eltorai et al., 1992; Kursh et al., 1977). Furthermore, due to the HR alterations that may accompany autonomic dysreflexia, this condition has also been associated with deleterious cardiac events (Pine et al., 1991).

Another common cardiovascular dysfunction after an SCI is orthostatic intolerance, a condition defined as an acute or progressive decline in mean arterial pressure of more than 10 mmHg during upright posture (Blackmer, 1997; Krassioukov et al., 2009b). The inability to maintain BP is due to sympathetic decentralization that is characteristic of an SCI and the resulting inability to vasoconstrict below the level of injury. Again, this condition is most problematic in individuals with injuries at or above the sixth thoracic level due to the involvement of the large splanchnic vascular bed, which is extremely vital in regulating the BP. While orthostatic intolerance is not generally considered a fatal condition in the able-bodied population, the decreases in BP can be severe in patients with an SCI and lead to potentially dangerous bouts of syncope. For many individuals with an SCI, orthostatic intolerance can be a daily obstacle that seriously limits their independence and ability to participate in many forms of rehabilitation.

A great deal of work has shown that indices of cardiovascular disease respond favorably to exercise training in the able-bodied population (Kingwell, 2002; Powers et al., 2004; Seals, 2003), and SCI populations are no exception (Brenes et al., 1986; de Groot et al., 2003; Ditor et al., 2005a,b; Jacobs and Nash, 2001). The effects of exercise training on cardiovascular dysfunction after an SCI, such as autonomic dysreflexia and orthostatic intolerance, are not fully understood.

The remainder of this chapter reviews and discusses the use of heart rate variability (HRV) and blood pressure variability (BPV) as the indices of autonomic control in individuals with SCI. [Table 19.1](#) provides a list of references and the significance of each paper.

Valid and reliable measures of cardiovascular autonomic control would be highly valuable to the SCI population as a means of gauging autonomic damage and tracking potential improvements with exercise rehabilitation, pharmacological treatment or even future neuroregenerative strategies. As cardiovascular disease and dysfunction are prevalent in this population, measures of HRV and BPV could be very useful as predictors of risk. However, while studies to date have shown promise for HRV and BPV as reliable and valid measures of cardiovascular autonomic control after an SCI, no large-scale clinical trials have been conducted at this time, although such studies are certainly warranted.

19.3 Measures of Autonomic Regulation of the Cardiovascular System

19.3.1 HRV as an Index of Autonomic Control of the Heart

The analysis of HRV has become a common, non-invasive method used to measure the autonomic control of the heart (Akselrod et al., 1981; Kamath and Fallen, 1993; Malik and Camm, 2004). This method is based on the principle that even during constant resting conditions, the heart does not beat with perfect metronome-like regularity. Moreover, an analysis of the temporal variability between successive heartbeats (specifically, between successive RR intervals obtained from an electrocardiogram) can be used to estimate the relative predominance of cardiac sympathetic outflow and cardiac parasympathetic outflow over a given period of time.

From a biochemical perspective, techniques that are used to analyze HRV take advantage of the fact that sympathetic and parasympathetic nervous systems use different neurotransmitters to exert their influence on the heart and, further, that different mechanisms are used to terminate the effects of each neurotransmitter. Specifically, the postganglionic parasympathetic fibers release acetylcholine (ACh) that (i) acts relatively quickly to decrease HR due to the direct G protein link between muscarinic ACh receptors and potassium channels and (ii) is rapidly hydrolyzed by the abundance of cholinesterase located at sinoatrial and atrioventricular nodes (Hockman, 1987; Warner and Cox, 1962). By contrast, postganglionic sympathetic fibers release norepinephrine that (i) acts relatively slowly to increase the HR due to the requirement of a second messenger system; and (ii) has its effects more slowly terminated mainly by the pre-synaptic reuptake of this neurotransmitter, and to a lesser extent its diffusion out of the synaptic cleft into surrounding extracellular fluids (Hockman, 1987; Warner and Cox, 1962). Therefore, the parasympathetic system may exert a beat-to-beat influence on the cardiac control, while the sympathetic system cannot alter cardiac behavior within one cardiac cycle. Several methods can be used to analyze HRV, depending on whether the variability of the successive RR interval is expressed in the time or frequency domain (Task Force, 1996). Time domain analysis through a computation of statistical indices, derived from a 24 h HR signal usually obtained from a Holter recorded signal, can provide the indices of autonomic regulation. The standard deviation of the normal-to-normal RR intervals (SDNN) primarily quantifies the parasympathetic outflow. The power spectral analysis of HRV in the frequency domain serves as an estimate of both parasympathetic and sympathetic cardiac regulation.

When successive RR intervals are plotted against time, a complex but reproducible signal is typically produced in healthy, able-bodied subjects. This plot, which is referred to as a tachogram, is treated as the summation of several distinct signals, each oscillating at a distinct frequency. The relative strength of each frequency, or power, in the complex signal can then be quantified and graphically represented as a power spectrum. In healthy, able-bodied individuals, the distribution of these frequencies tends to be bimodal with a predominance of frequencies in the low-frequency range (LF; 0.04–0.15 Hz, centered around 0.10 Hz) and the high-frequency range (HF; 0.15–0.4 Hz, centered around 0.25 Hz). Various investigations, utilizing either biochemical blocking agents (Pomeranz et al., 1985) or maneuvers known to provoke certain autonomic responses (Montano et al., 1994), have shown that the HF oscillation corresponds to the parasympathetic outflow to the heart, while the LF oscillation corresponds to both sympathetic and parasympathetic outflows to the heart. Thus, the LF:HF ratio has become an acceptable and reproducible estimation of the relative contribution of sympathetic and vagal outflows.

19.3.2 HRV as a Predictor of Cardiovascular Risk

A large number of studies have noted the predictive power of HRV for gauging the risk of mortality from various cardiovascular diseases. In particular, there appears to be an association between an increased risk of cardiovascular mortality and indices of reduced cardiac parasympathetic modulation and/or increased cardiac sympathetic modulation of HRV (Algra et al., 1993; Kleiger et al., 1987; Myers et al., 1986).

Studies by Lombardi et al. (1987, 1992) have shown an increase in the LF:HF ratio in patients who recently suffered an acute myocardial infarction compared to healthy, age-matched controls. Ajiki et al. (1993) also showed similar results in patients with

cardiomyopathies. Although such results have established altered HRV in cardiac patients, they unfortunately do not associate specific values of the LF:HF ratio with corresponding relative increases in cardiovascular risk. Likewise, differences in HRV measurement techniques between laboratories restrict the general clinical use of any specific value for the LF:HF ratio as a critical point for cardiovascular risk. Nevertheless, several investigations have shown cardiovascular disease to be characterized by a shift in cardiac sympathovagal balance away from a parasympathetic predominance and toward a sympathetic predominance, as indicated by HRV measures (Vybrial and Glaeser, 1995; Singer and Ori, 1995). Accordingly, HRV may be a better predictor of mortality than the commonly used clinical measures such as left ventricular ejection fraction, cardiac wall motion abnormalities and exercise capacity (Singer and Ori, 1995). Finally, HRV has been shown to be a valid predictor of cardiovascular and all-cause mortality in a variety of populations without any previous cardiovascular disease (Ewing et al., 1980; Gordon et al., 1984) and therefore, HRV may provide valuable information to individuals with an SCI, with or without coexisting cardiovascular complications.

19.3.3 Neurovascular Control

The ANS also plays a major role in the control of BP via the innervation of the systemic vasculature. Specifically, adrenergic neurons originating between the first thoracic and second lumbar levels of the spinal cord eventually synapse with and innervate the entire arterial tree down to the arterioles. This adrenergic innervation exerts a constrictor effect that increases the resistance of the vessels. As mean arterial BP is the product of cardiac output and total peripheral resistance, adrenergic vasoconstriction is vital to the maintenance of BP at rest and in response to the cardiovascular challenge. In fact, in circumstances such as an upright posture, when ventricular filling pressure is limited and increases in cardiac output are prevented, only peripheral vasoconstriction can maintain the BP (Rowell, 1986).

Autonomic control of the vasculature differs significantly from that of the heart in that there is no evidence of parasympathetic outflow to the vessels. Furthermore, adrenergic nerves are not completely quiescent at rest and exert a resting sympathetic tone. Increases in sympathetic outflow above this basal tone constrict the vessel and increase resistance, while the withdrawal of sympathetic outflow below this basal level causes a relative “passive” vasodilation (Calendar, 1954). Of note, some evidence exists for sympathetic cholinergic vasodilators, but they do not appear to play an important role in human circulation (Rowell, 1986).

19.3.4 BPV as an Index of Neurovascular Control

Resting values of arterial BP are not perfectly stable, and like HR, systolic and diastolic BP values are characterized by small beat-to-beat variations that have a physiological significance. Specifically, beat-to-beat values of systolic or diastolic BP may also be plotted against time and then analyzed in the frequency domain. Similar to HRV, the LF variations in BP, also known as the Mayer waves, oscillate around 0.1 Hz (0.04–0.15 Hz), and HF variations in BP oscillate around 0.25 Hz (0.15–0.40 Hz).

Several studies have investigated physiological correlates of the LF and HF components of BPV. Specifically, it has been demonstrated that increases in the LF component of BPV during nitroglycerin infusion, coronary occlusion and exercise are associated with an increased sympathetic outflow to peripheral vessels (Rimoldi et al., 1990), and

decreases in the LF component are associated with a reduced sympathetic activation of vessels during an α -adrenergic blockade (Parati et al., 1995). Furthermore, a significant correlation has been shown between direct measures of muscle sympathetic nerve activity (MSNA) at the peroneal nerve and the LF component of BPV over a wide range of BPs evoked by either nitroprusside or phenylephrine infusion (Pagani et al., 1997). Nonetheless, there is some debate as to the most appropriate interpretation of the LF component of BPV because α -adrenergic blockade decreases but does not completely eliminate the LF signal (van de Borne et al., 2001). It is more likely that while sympathetic outflow to the vasculature is a major modulator of the LF component of BPV, it is not the sole contributor. The physiological correlate of the HF component of BPV is not as analogous to the HF component of HRV, as there is no parasympathetic outflow to the vasculature. Therefore, HF components of BPV have been assumed to represent mechanical effects of respiration, which may act directly on pressure gradients of intra-thoracic vessels (Pagani et al., 1986).

19.3.5 BPV and Risk of Cardiovascular Disease

Several groups have explored the potential association between an increased LF component of BPV and the risk of cardiovascular disease (Miao and Su, 2002; Parati et al., 1987, 1992). Although the majority of research in this area has been cross-sectional, a longitudinal study conducted by Frattola et al. (1993) has provided evidence for the cause-and-effect relationship between increases in BPV and organ damage, and furthermore, has shown that deleterious effects of increased BPV are independent of the effects of increases in BP. Specifically, Frattola et al. (1993) recorded 24 h ambulatory BP measures in 73 hypertensive patients, from which a time domain measure of BPV, called "among half-hour standard deviation" (defined as the standard deviation of the average of the half-hour mean values of the BP), was calculated. Patients were also divided into quartiles based on their 24 h mean arterial pressure. At follow-up, approximately 7 years later, measures of end-organ damage (as indicated by several electrocardiogram and chest X-ray measures) were determined. The results showed that for any given quartile of mean arterial pressure, those patients with lower values of BPV determined at the initial examination had a lower severity of end-organ damage at follow-up, especially for measures of left ventricular hypertrophy. Moreover, this relationship held true even at the lowest quartile of mean arterial pressure, which was approximately 80–85 mmHg.

Notably, in the study by Frattola et al. (1993), the relationship between BPV and cardiovascular disease was determined via time domain measures of BPV. Although there seems to be a strong link between time domain measures of BPV and end-organ damage, there is a paucity of literature regarding such a relationship when frequency domain measures of BPV are considered. However, one recent study has provided evidence supporting the protective effect of reductions in the LF component of BPV. Taylor et al. (2003) examined frequency domain measures of BPV before and after exercise training in a cohort of 17 older adults with hypertension, who were otherwise healthy. Nine of these individuals performed a low-intensity isometric handgrip exercise for 10 weeks, while eight served as non-exercising controls. Following the training protocol, those who exercised had significantly greater reductions in systolic and mean arterial pressures than controls, accompanied by significantly greater reductions in the LF power of systolic BPV. Although the researchers did not measure indices of end-organ damage, their results are suggestive of an association between reductions in the LF power of BPV and protection from cardiovascular disease. It is also interesting to note that the median frequency,

rather than just the power, of the LF component of BPV may serve as an index of cardiovascular risk, such that lower frequencies were associated with coronary artery disease (Kiviniemi et al., 2010).

Measures of HRV and BPV may be particularly valuable and interesting in individuals with an SCI for several reasons. First, as the SCI population is at an increased risk of cardiovascular disease, measures of HRV and BPV may be able to quantify and help predict this risk as well as determine the potential to reduce such cardiovascular risk with exercise or pharmacological interventions. Second, individuals with an SCI theoretically possess a unique autonomic imbalance since sympathetic nerves that innervate the heart are partially or completely disconnected from the influence of higher centers, while the parasympathetic influence provided by the vagus nerve is spared after an SCI. On the other hand, the inactivity associated with an SCI may cause the typical enhancement of any spared sympathetic outflow and overcompensate for any loss due to partial disconnection resulting from the cord lesion. Therefore, the measures of HRV and BPV may be helpful in defining the nature of autonomic regulation of the cardiovascular system after an SCI and in determining if individuals with an SCI, despite the damage sustained to their central nervous system, retain the ability to make positive adaptations to this regulation with exercise training, pharmacological intervention or even future nerve regeneration strategies.

19.4 Effects of SCI on Measures of HRV and BPV

19.4.1 HRV in Individuals with SCI

19.4.1.1 Debating the Presence or Absence of the LF Component after SCI

Several studies have employed the analysis of HRV to determine the autonomic control of the heart in individuals with an SCI. The initial work done by Inoue et al. (1990) examined frequency domain measures of HRV in individuals with a chronic, neurologically complete SCI (C6–C7) and age-matched, healthy, able-bodied controls during supine rest. While control subjects displayed both LF and HF components of HRV, individuals with an SCI only exhibited the HF component. Furthermore, comparisons of HF power between the two groups showed a non-significant reduction in individuals with an SCI compared to able-bodied controls. However, subsequent work by Inoue et al. (1995), which included a wider range of injury types and a larger sample of subjects, found somewhat different results. Specifically, 6 of 15 individuals with chronic, complete tetraplegia (C6–C7) exhibited both LF and HF components of HRV during supine rest. The researchers hypothesized, however, that the LF component shown in individuals with an SCI was simply the reflex sympathetic outflow caused by stimuli from the periphery (bladder or bowel distension or spasms from the limbs) rather than cardiac sympathetic innervation originating from higher centers.

By contrast, results from studies conducted by Grimm et al. (1995, 1997) have shown that there is some maintenance of cardiac sympathetic innervation following even a complete cervical SCI. These researchers (Grimm et al., 1997) examined individuals with complete tetraplegia (above C7), incomplete tetraplegia (above C7) and complete paraplegia (below T7) and age-matched, able-bodied control subjects, during supine resting conditions and various “provocative maneuvers” (60° head-up tilt, cold pressor test and isometric jaw

contractions). The results of these investigations showed that both LF and HF components of HRV were present in individuals with an SCI, although the power of each component appeared to be inversely proportional to the level and severity of the injury. There were no differences observed between groups in the LF:HF ratio, indicating a maintenance of sympathovagal balance to the heart regardless of the type of injury sustained. Because of the preservation of the LF:HF ratio, researchers concluded that the withdrawal of cardiac sympathetic tone that results from a cervical SCI causes a compensatory reduction of cardiac parasympathetic tone in an attempt to maintain cardiac sympathovagal balance. This conclusion was also drawn by Wang et al. (2000), who also found a maintenance of sympathovagal balance in individuals with tetraplegia. Thus, despite the sparing of the vagus nerve, individuals with an SCI may experience a reduction in parasympathetic outflow to the heart. This may be a particularly discouraging scenario for individuals with SCI, since a withdrawal of cardiac parasympathetic tone is associated with an increased cardiac mortality in other populations (Algra et al., 1993; Kleiger et al., 1987; Myers et al., 1986). A compensatory reduction of this kind would also be problematic for another reason. If the body does, in fact, strive to maintain cardiac autonomic balance after an SCI, as others have suggested (Grimm et al., 1997; Wang et al., 2000), then the compromise to the sympathetic system in this population may preclude the normal exercise-induced enhancements of cardiac parasympathetic tone. Conversely, the decreased parasympathetic tone that has been shown to accompany an SCI may only be a reflection of the reduced activity levels in this population, in which case exercise-induced enhancements in the resting parasympathetic tone may be expected. Fortunately, recent work that is detailed in this chapter supports the latter, which is a more encouraging scenario (Ditor et al., 2005a,b). Still, it is unclear as to why such stark discrepancies exist between the initial work provided by Inoue et al. (1990) and more recent literature regarding HRV after an SCI, especially with respect to the presence or absence of the LF power in individuals with a long-term, complete SCI. These incongruities may become clear when considering the limitations of the neurological examination that is used to determine the injury classification and the resulting confusion regarding what is meant by a complete SCI. First, the neurological examination is strictly a reflection of somatic motor and sensory functions and makes no consideration of the autonomic function. Thus, those who have been classified as having complete tetraplegia may have differing amounts of autonomic innervation below the level of injury. This may be a contributing factor to the infrequent, but periodically noted, observation of individuals with *complete* tetraplegia showing greater orthostatic tolerance or maximal exercise HRs compared to those with *incomplete* tetraplegia. Second, while the term "complete tetraplegia" may connote an absolute loss of neural transmission to all levels below the injury, this is certainly not always the case, as the term "complete" strictly describes no sensory or motor function in the S4–S5 dermatomes and myotomes. There is commonly a zone of partial preservation associated with a complete SCI, such that several segments below the neurological level of injury do have neural outflow, although it is impaired. This could explain the evidence of sympathetic outflow to the heart in many individuals with complete injuries above the T1 level. Accordingly, in the study by Inoue et al. (1990) (in which no LF component of HRV was detected), the participants were, in fact, described as having not only complete tetraplegia but also no detectable somatic motor or sensory function below the level of the lesion as determined by a physical examination, and thus, no zone of partial preservation. It is therefore reasonable to conclude that the discrepancies between the work by Inoue and colleagues and other subsequent studies (Ditor et al., 2005a,b; Grimm et al., 1995, 1997; Wang et al., 2000) are because of the fact that the former examined a particular subset of individuals with an SCI with no zone of

partial preservation, while the latter examined the more typical individual with complete tetraplegia. Finally, it would therefore appear that the presence of LF power of HRV after an SCI does depend on some degree of connection between higher centers and the spinal segments that provide sympathetic outflow to the heart.

19.4.1.2 Validity and Reliability of HRV Measures after SCI

Although aforementioned studies have shown that HRV can be measured after an SCI (i.e., both sympathetic and parasympathetic components are represented in the power spectrum), there is still some question as to the validity of these components as the indices of cardiac autonomic control. While no large-scale validation study has been conducted to date in the SCI population, there is some promise for these measures. Specifically, if measures of HRV are truly indices of cardiac autonomic regulation after an SCI, then they should display the following properties, in increasing order of importance: (1) the LF:HF ratio and HF power should change with exercise or a postural challenge in a way that would reflect expected changes in cardiac autonomic outflow, (2) the LF:HF ratio should be at least loosely correlated with other validated measures of sympathetic activity and (3) the LF:HF ratio should be significantly reduced after the administration of drugs that block sympathetic outflow to heart, and the HF power should be significantly reduced after the administration of drugs that block cholinergic outflow to heart. The first of these criteria is discussed in detail in the following section. The remainder of the current section, therefore, is focused on the other two criteria, namely the clinical correlates of HRV and the recent data regarding the pharmacological validation of HRV in individuals with an SCI.

Regarding the former, Claydon and Krassioukov (2008) recorded continuous HR from 26 individuals with a chronic (greater than 1 year post-injury) cervical or thoracic SCI and 17 able-bodied controls, from which they computed the power spectra of HRV. In addition, various indices of autonomic function were measured, and authors investigated whether meaningful correlations existed between these autonomic indices and the measures of HRV. Their results showed that the frequency domain measures of LF power and the LF:HF ratio were independently correlated with several parameters of cardiovascular autonomic function. Specifically, LF power was independently correlated with palmar and plantar sympathetic skin responses and maximum HR, while LF:HF ratio was independently correlated with resting serum epinephrine concentrations and systolic BP during orthostatic stress. In addition, HF power was negatively correlated (although not independently) with resting serum epinephrine concentrations, maximum HR and systolic BP during orthostatic stress.

However, the most rigorous test for the validity of HRV must be the analysis of such measures before and after a pharmacological blockade of cardiac autonomic outflow. If the HF power is truly an index of cardiac parasympathetic control and the LF:HF ratio is an index of sympathetic control, then these measures should be substantially reduced, if not abolished, following the administration of cholinergic and β -blocking agents, respectively. In fact, Pomeranz et al. (1985) conducted such a study in a cohort of eight able-bodied participants and the results still stand as perhaps the most compelling evidence for the validity of the HRV measures as the indices of cardiac autonomic control. Although a large-scale pharmacological validation study has not been conducted in the SCI population, recent pilot data strongly suggest that measures of HRV are, in fact, valid indices of cardiac autonomic regulation after an SCI. Specifically, in a study conducted by Cotie et al.

(in press), measures of HRV were determined both before and after the administration of intravenous atropine sulfate (0.02 mg/kg; a cholinergic blocker) and metoprolol tartrate (3×5 mg; a β -sympathetic blocker) in three individuals with incomplete tetraplegia (C4–C7; American Spinal Injury Association (ASIA) classification B–D; 13.4 ± 13.4 years post-injury) and three age-matched, sex-matched, weight-matched, height-matched, able-bodied controls.

Results of their study showed that the HF power appears to be a close reflection of cardiac parasympathetic outflow as the administration of atropine sulfate virtually abolished the HF signal during supine resting conditions in all three SCI participants. Furthermore, a β -blockade with metoprolol tartrate produced no significant effect on the HF power, signifying no link between this measure and the cardiac sympathetic innervation. Likewise, the LF:HF ratio was shown to be associated with the cardiac sympathetic outflow as the administration of metoprolol tartrate caused a significant decrease ($61.8 \pm 19.8\%$) in this measure during cardiovascular stress (induced by 40° head-up tilt, with the right hand submerged in 10°C water and a sustained submaximal jaw clench). Importantly, there was no difference between the SCI group and able-bodied controls, with respect to changes in HF power or the LF:HF ratio following the administration of atropine sulfate or metoprolol tartrate, respectively. Therefore, similar to what has been shown in the able-bodied population by Pomeranz et al. (1985), the measures of HRV appear to be valid indices of cardiac autonomic control after an SCI. Still, a large-scale pharmacological study would need to be conducted in order to definitively validate the measures of HRV in individuals with an SCI, although the aforementioned pilot data certainly show promise and highlight the justification for such research. It is also interesting to note that non-linear HR dynamics were also determined before and after a pharmacological blockade described previously (Millar et al., 2010). In both SCI and able-bodied participants, vagal blockade with atropine sulfate resulted in significant reductions in sample entropy and correlation dimension in both supine and cardiovascular stress positions. It was concluded that the vagal modulation is a primary modulator of non-linear HR signals in individuals with an SCI as well as the able-bodied population, while the relation between the β -adrenergic system and non-linear HR signals remains less defined and possibly absent.

Finally, in addition to the validity of HRV measures after an SCI, day-to-day reproducibility of these measures has also been investigated. Specifically, in a study by Ditor et al. (2005c), the day-to-day reproducibility of resting HRV and BPV in 10 individuals (age 35.9 ± 13.2 years) with complete and incomplete SCI (C4–T12; 5.4 ± 7.7 years post-injury) was determined. On two occasions within a 2-week period, 10 min supine electrocardiogram and Finapress BP recordings were obtained, and frequency domain measures of HRV and BPV were calculated. Intra-class correlation coefficients (R) were used as an index of day-to-day reproducibility and analyses were conducted on (i) all participants and then (ii) only those with tetraplegia. For HRV, the measures of HR, LF and LF:HF ratio were found to be highly reproducible ($R = 0.82$ – 0.88); however, the reproducibility of HF was found to be poor (all participants: $R = 0.53$, tetraplegia: $R = 0.66$). Measures of BP as well as systolic BPV also showed high reproducibility ($R = 0.72$ – 0.93), although measures of diastolic BPV were less reproducible but still acceptable ($R = 0.71$ – 0.89). Taken together with the validation study described earlier, it would appear as though measures of HRV are valid and reliable indices of cardiac autonomic regulation after an SCI, and as such they hold promise for estimating the integrity of autonomic function in this population, as well as possible improvements in the autonomic function with exercise rehabilitation, drug therapies or even future nerve regeneration strategies.

19.4.2 Effects of Exercise Training on HRV: Comparisons between Able-Bodied Population and SCI Population

In the able-bodied population, it is well established that aerobic exercise training is associated with an increased cardiac parasympathetic outflow, as illustrated by the frequently observed training-induced bradycardia at rest, and enhancements of HRV measures are indicative of resting cardiac parasympathetic tone (De Meersman, 1993a,b; Dixon et al., 1992; Melanson and Freedson, 2001; Seals and Chase, 1989). With respect to frequency domain measures of HRV, cross-sectional studies have shown significantly lower LF:HF ratios in aerobic athletes compared to healthy sedentary controls (Dixon et al., 1992). In addition, longitudinal studies have shown training-induced decreases in the LF:HF ratio in able-bodied individuals, be they healthy (Tulppo et al., 2003) or suffering from cardiac disease (Malfatto et al., 2002; Taylor et al., 2003). For example, individuals with heart failure experienced a 36% reduction in the LF:HF ratio after 6 months of low-intensity (40%–50% $\text{VO}_{2\text{max}}$) exercise training (Malfatto et al., 2002), while healthy, middle-aged individuals showed reductions in the LF:HF ratio of approximately 25% after 8 weeks of moderate-intensity exercise training (Tulppo et al., 2003). In general, the majority of evidence suggests that aerobic exercise training in the able-bodied population may typically produce reductions in the LF:HF ratio of approximately 20%–50%, depending on the intensity of exercise and initial fitness levels of the participants, with more sedentary individuals experiencing the largest benefit.

The effects of exercise training on HRV after an SCI have been explored to a much lesser extent and a small number of studies have been conducted on this topic. Ditor et al. (2005a) evaluated eight individuals with an incomplete SCI before and after a 6-month body-weight-supported treadmill training (BWSTT) program at a frequency of three times per week. The study participants were only included if they were at least 1 year post-injury and free of any coincident cardiac disease. Medications were not interrupted during the investigation and were identical at pre- and post-testing sessions for each participant. In terms of the training modality, BWSTT program entails suspending an individual, with the use of a harness, above a motorized treadmill. Counter-balances, attached to the harness via a pulley system, allow any percentage of the individual's body weight to be supported while therapists assist in the production of gait. BWSTT program was chosen as the form of training because it is an upright exercise that utilizes the large muscles of the leg, and therefore, it may be ideal to bring about a cardiovascular change. Furthermore, the supporting, or partial supporting, of body weight allows for a prolongation of exercise, which may be required to yield maximum cardiovascular benefit.

In agreement with previous findings (Grimm et al., 1995; Wang et al., 2000), results obtained by Ditor et al. (2005a) showed the presence of both LF and HF components of HRV, indicating the presence of both sympathetic and parasympathetic outflows to the heart in individuals with an SCI during resting conditions. The presence of LF component should not be surprising in this group as their injuries were incomplete and therefore, some amount of cardiac sympathetic control from the higher centers would be expected. More importantly however, following 6 months of BWSTT, resting HR was found to decrease from 61.9 ± 6.9 to 55.7 ± 7.7 beats/min, while the LF:HF ratio showed a decrease of 20%.

The results of the study by Ditor et al. (2005a) have both physiological and clinical relevance. First, these data strengthen the evidence that measures of HRV are valid indices of cardiac autonomic regulation after an SCI, as they changed in a predictable manner

following an exercise training program, with a significant decrease in the LF:HF ratio. Furthermore, these results demonstrate that individuals with an incomplete cervical SCI retain the ability to make positive changes to the autonomic regulation of the heart with exercise training, despite damage sustained to the central nervous system. Finally, these data also strongly suggest that the previously observed decrease in the HF power after an SCI (Grimm et al., 1995; Wang et al., 2000) is not a compensatory mechanism attempting to maintain cardiac autonomic balance but is more likely a reflection of the inactivity that often accompanies a SCI. Although it is not known if such shifts in cardiac autonomic balance actually conferred a reduced risk of cardiovascular mortality, work in animals has shown an association between the training-induced shift toward cardiac parasympathetic predominance and a reduced risk of cardiac mortality. Specifically, in a study conducted by Hull et al. (1990), dogs without myocardial infarction, but at high risk as indicated by the occurrence of ventricular arrhythmia during acute ischemia, completed 6 weeks of daily exercise. Following the training program, the dogs exhibited significant changes in HRV, indicative of a shift toward parasympathetic predominance, which were accompanied by the disappearance of ventricular fibrillation during a new trial of myocardial ischemia induced by an exercise stress test.

Despite the encouraging results provided by the 6-month BWSTT study conducted by Ditor et al. (2005a), it is important to note some caveats to the data. First, the 20% reduction that was observed in the LF:HF ratio was accounted for by a significant reduction in the LF power and only a non-significant increase in the HF power. Thus, changes that were noted in the cardiac autonomic balance seemed to be driven more by reductions in sympathetic tone rather than increases in parasympathetic tone (although the LF power contains both sympathetic and parasympathetic components, the present finding of a decreased LF power in conjunction with an increased or a maintained HF power strongly suggests a reduction in the sympathetic outflow, per se). The absence of parasympathetic enhancement may make any associated health benefits questionable, as the majority of studies regarding HRV and cardiovascular risk have used time domain measures (Kleiger et al., 1987) and have thus primarily commented on the cardioprotective nature of parasympathetic outflow. Still, Lanza et al. (1997) did find an association between reductions in the LF:HF ratio and protection from cardiovascular mortality. Furthermore, norepinephrine, per se, has been shown to have deleterious effects on myocardial tissue (Brouri et al., 2002; Masuda et al., 2002). Second, participants in the BWSTT study exhibited a fairly well-preserved sympathetic outflow to the cardiovascular system as seen by the relatively high HRs that were experienced during exercise training. Therefore, it is unclear if individuals with more severe sympathetic decentralization would be able to experience the same exercise-induced changes in the LF:HF ratio. However, participants with the lowest peak HRs during exercise training (two of the eight participants achieved average training HRs of 120 beats/min) still experienced representative decreases in the LF:HF ratio (of 19% and 32%) following a 6-month training protocol. Moreover, in a subsequent study conducted by the same group, the effect of exercise training in individuals with motor-complete SCI was investigated (Ditor et al., 2005b). In that study, one participant with a severe C4 injury (ASIA B) experienced a 40% reduction in the LF:HF ratio following 4 months of BWSTT. This adaptation was achieved despite a severe sympathetic dysfunction as evidenced by pronounced orthostatic intolerance and an average training HR of only 103 beats/min (Ditor et al., 2005b).

Although non-linear HR dynamics seem to be somewhat less understood, recent studies have investigated the effects of exercise on this index of cardiac autonomic control after an SCI. In particular, Millar et al. (2009) evaluated the efficacy of BWSTT

versus head-up tilt in modifying the ANS in individuals with an SCI, as determined by the linear measures of HRV as well as the non-linear measures of sample entropy and the fractal scaling distance score. Seven participants with an SCI (C5–T10, ASIA A–C, 5.0 ± 4.4 years post-injury) completed a randomized crossover exercise protocol involving the above two exercise modalities, three times a week for 4 weeks. The linear indices of HRV did not show significant differences following either training protocol. However, both sample entropy (1.05 ± 0.14 to 1.42 ± 0.12 , $p < .05$) and fractal scaling distance score (0.54 ± 0.06 to 0.26 ± 0.05 , $p = .001$) demonstrated significant reductions following BWSTT. Although more research is required to fully understand the physiological significance of such changes, these measures provide strong evidence that exercise training (in particular BWSTT) in SCI patients is associated with the positive effect of increasing the complexity of HRV. Recent research by Agiovlasitis et al. (2010) shows that individuals with paraplegia exhibit a lower HR complexity at rest and during static exercise.

19.4.3 BPV in Individuals with SCI

The effects of an SCI on BPV remain somewhat controversial. Inoue et al. (1991) observed an intact HF component but an absent LF component of systolic BPV in individuals with complete tetraplegia. These researchers concluded that the LF oscillation in BP, or Mayer waves, is dependent on the connection between the supraspinal centers and preganglionic sympathetic fibers and that this connection is completely disrupted in individuals with a complete SCI. Subsequent studies, however, have found the existence of Mayer waves in individuals with a complete SCI (Guzzetti et al., 1994; Koh et al., 1994; Munakata et al., 2001), although the power of these oscillations may be reduced with higher injury levels. Munakata and colleagues determined BPV measures in individuals with either a high-level SCI (C4–T3) or a low-level SCI (T4–T12) and in able-bodied controls matched for age and sex. Mayer waves were apparent in all but one individual in the high-level SCI group, although the power of Mayer waves (the LF power of BPV) in this group was considerably reduced compared to the low-level SCI group and able-bodied controls (by approximately 50% and 65%, respectively). In addition, the power of the LF component tended to decrease during a 60° head-up tilt in the high-level SCI group, whereas it significantly increased in the other two groups.

Again, the discrepancy between the early findings of Inoue et al. (1991) and subsequent work in the field probably stems from the subtle differences in the neurological status of the respective participant groups. While Inoue et al. (1991) investigated individuals with no sensory or motor function at or below the lesion level, recent studies have included more typical individuals with a complete SCI in which a zone of partial preservation is expected. Taken together, these studies suggest that as long as some partial neural outflow is preserved in the T1 segment or below, sympathetic outflow to the vasculature will be maintained, and thus, the estimate of this outflow (the LF component of BPV, or Mayer waves) will be detectable. In addition, although the LF component may be diminished in healthy individuals with an SCI, it may continue to increase over the years (as it would in the able-bodied population) as the injured individual progresses into cardiovascular disease. Therefore, a reduction in the LF component of BPV may still be considered an important exercise-induced adaptation in individuals with a long-term SCI, despite the attenuated sympathetic control that is initially characteristic of this population.

19.4.4 Effects of Exercise Training on BPV: Comparisons between Able-Bodied Population and SCI Population

Recent longitudinal studies have found exercise-induced decreases in the LF component of BPV in both the healthy population (Portier et al., 2001) and those with hypertension (Taylor et al., 2003). Specifically, older adults with hypertension were found to have the LF power of systolic BPV reduced by nearly 30% after 10 weeks of low-intensity handgrip training (Taylor et al., 2003), while marathon runners were found to have an approximate reduction of 17% in the LF power of systolic BPV after the training portion of their season (Portier et al., 2001). Thus, exercise-induced changes in BPV may be possible in a wide spectrum of people, regardless of initial BP, age or fitness levels. However, it is inconclusive whether these changes in BPV were actually associated with a reduced risk of cardiovascular mortality, although such a hypothesis would be reasonable considering the data from other experiments (Frattola et al., 1993).

Recent studies by Ditor et al. (2005a,b) demonstrate exercise-induced reductions in BPV in individuals with an SCI, and furthermore, these studies have helped to clarify the nature of the measure in the SCI population. In the aforementioned 6-month BWSTT study in individuals with an incomplete SCI, resting measures of BP and BPV were determined before and after the training program (Ditor et al., 2005a). Although there were no changes in the resting systolic, diastolic or mean arterial pressures after the training, results did show a significant 13.5% reduction in the LF power of systolic BPV. In a subsequent study (Ditor et al., 2005b), individuals with a motor-complete SCI completed 4 months of BWSTT at a frequency of three times per week. The study included individuals with a motor-complete SCI with levels of injury ranging between C4 and T12, all of whom would be expected to have some disruption of the sympathetic outflow to the vasculature. Although the results showed no exercise-induced changes in BP or BPV when the group was considered as a whole, a detailed analysis showed that those who responded to the BWSTT with relatively high training HRs (greater than 100 beats/min) did experience a significant 19% decrease in the LF component of systolic BPV. Although the lack of change in mean arterial pressure may seem to detract from these findings, it should be reiterated that previous work has shown that reductions in BPV confer a protective effect against cardiovascular disease independent of the BP (Frattola et al., 1993). Importantly, these data also help support the validity of BPV as an index of neurovascular control after an SCI. In the absence of any pharmacological validation study, the finding of a reduced LF component of systolic BPV following an exercise training program does speak to the validity of this measure in individuals with SCI. Still, large-scale pharmacological validation studies for BPV after an SCI are needed.

In summary, individuals with an SCI are capable of achieving positive changes in the measures of BPV despite damage to their central nervous system and its connection to the vasculature. The potential for change, however, seems to be dependent on the intensity of exercise and the ability to achieve modest increases in the HR during exercise. While individuals with a complete SCI above T1 may not be able to experience large increases in HR due to the loss of cardiac sympathetic outflow, it should be noted that relatively modest increases in HR to approximately 100 beats/min seemed to be sufficient to evoke decreases in BPV and that such modest increases in HR may be achieved via a parasympathetic withdrawal alone. Other forms of exercise training, such as functional electrical stimulation, may also be sufficient to evoke the HR response that seems to be required for changes in BPV; however, further research is needed to address this issue.

19.5 Discussion

The successful application of HRV and BPV to the SCI population would be extremely valuable. As mentioned earlier, the accepted neurological classification provided by the ASIA considers only the motor and sensory functions. Accordingly, despite a significant need, there is no established classification system for autonomic impairments that accompany SCI. Clinical tests of autonomic function, such as those provided by HRV and BPV, would allow an estimation of autonomic damage after SCI as well as help gauge potential improvements with exercise rehabilitation, pharmacological treatment or even future nerve regeneration. Furthermore, in the able-bodied population, measures of HRV and BPV are well established as powerful predictors of cardiovascular morbidity and mortality. Since the SCI is characterized by a substantially increased risk of cardiovascular disease and dysfunction, non-invasive clinical tests that have diagnostic or predictive properties would be a great advantage. This is especially important since individuals with severe cervical injuries may lack the sensory function needed to perceive angina. These individuals experience what is known as "silent ischemia" and therefore, only seek medical attention when the symptoms become very severe.

Thus, the potential utility of HRV and BPV for individuals with an SCI is unquestionable, but these tests have yet to be used widely in the SCI population. Several studies have shown promise for the use of HRV and BPV after an SCI. In general, results from most studies suggest the that HRV and BPV are measurable in the SCI population. They are reproducible over time after an SCI and they change with postural stress and exercise training in a manner similar to that observed in the able-bodied population. Finally, a pilot study with a pharmacological blockade has been recently conducted and results strongly suggest that the HF component of HRV is reflective of cardiac vagal control and that the LF:HF ratio is reflective of sympathovagal balance in individuals with chronic incomplete tetraplegia.

19.6 Future Research

Perhaps the most clinically relevant application of measures computed from HRV would be their potential use as predictors of cardiovascular disease and dysfunction. For example, in an acute in-patient care setting, it would be very advantageous to be able to test the future vulnerability to autonomic dysreflexia or orthostatic hypotension, before a patient is discharged into the community. Likewise, in the chronic condition, it would be very useful to gauge an individual's susceptibility to cardiac morbidity and mortality, especially in those who lack the sensory function to detect angina. However, before such applications can be realized, a great deal of research must be conducted to test the predictive power of HRV and BPV after an SCI and to determine if such an application depends on such factors as the level, severity and perhaps the time post-injury.

In addition, many therapeutic strategies are aimed at enhancing the function after SCI. These include exercise rehabilitation, pharmacological treatment and neuroprotective and neuroregenerative strategies. The majority of outcome measures that are used to gauge the effectiveness of these strategies concern the motor and sensory functions and histological

analysis when studies are conducted in animals. However, there is a growing appreciation for including autonomic outcomes when testing the efficacy of various therapeutic strategies. In this way, measures derived from HRV and BPV could be invaluable to researchers as certain treatments may have modest effects on the motor and sensory functions but profound effects on the autonomic function and vice versa. Thus, HRV and BPV could help provide a more robust view of the somatic and autonomic effects of various therapeutic treatments.

19.7 Conclusions

An SCI is a life-altering event that is characterized by sensory, motor and autonomic impairments, all of which contribute to a variety of secondary health complications. While the standard neurological examination provided by the ASIA is a widely accepted clinical test for the motor and sensory functions, there is a scarcity of easily administered clinical tests of autonomic function for those with a SCI. Measures of HRV and BPV are highly valuable for this population as a means of evaluating an autonomic impairment as well as evaluating improvements in autonomic function with various therapeutic strategies. These measures may be particularly useful in predicting cardiovascular disease and dysfunction, both of which are common and potentially life-threatening in those with SCI.

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Abbreviations

ACh	Acetylcholine
ANS	Autonomic nervous system
ASIA	American spinal injury association
BPV	Blood pressure variability
BWSTT	Body-weight-supported treadmill training
HF	High frequency
HRV	Heart rate variability
LF	Low frequency
MSNA	Muscle sympathetic nerve activity
SCI	Spinal cord injury

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20

Autonomic Dysfunction in Stroke

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20.1 Introduction

Stroke is the third leading cause of mortality and one of the leading causes of adult disability in the United States and Canada (American Heart Association, 2010; Heart and Stroke Canada, 2010). The two main types of stroke are ischemic and hemorrhagic. Ischemic stroke, which accounts for about 80% of all strokes (Heart and Stroke, 2010), occurs when a thrombus or an embolus blocks blood flow to a part of the brain for a sufficient amount of time to cause permanent damage. Hemorrhagic stroke occurs when a vessel ruptures and the increased pressure caused by the leaking fluid damages the brain. The specific disability and dysfunction resulting from a stroke depend on the areas affected by the infarct or hemorrhage. While the cardiovascular autonomic network remains incompletely understood, baroreceptor unloading (i.e., lower body negative pressure to reduce baroreceptor afferent information) has been shown to increase the activation of the right superior posterior insula and left cerebellar hemisphere and to decrease the activation of the bilateral anterior insula, right anterior cingulated amygdala, midbrain and mediodorsal thalamus (Kimmerly et al., 2005). The middle cerebral artery (MCA) supplies the insular cortex and other important parts of the autonomic network; therefore, stroke involving the MCA can have dramatic effects on autonomic cardiovascular control. This chapter discusses the changes in heart rate

variability (HRV) and baroreflex sensitivity (BRS) that occur with stroke, the implications of autonomic dysfunction and potential interventions used to improve autonomic function. In addition, challenges in interpretation of the HRV data unique to the stroke population, including lesion localization and disability, will be discussed.

20.2 Heart Rate Variability in Stroke

HRV is usually found to be reduced in stroke survivors, although the affected parameters differ from one study to another. For example, one study of chronic stroke survivors showed that the high-frequency (HF) component of HRV was reduced (Dütsch et al., 2007), while another study conducted in elderly stroke survivors showed preservation of HF, along with reduced total power (TP), low frequency (LF) and standard deviation of normal-to-normal interval (SDNN) (McLaren et al., 2005). The conflicting findings may be due to several factors. The study by Dütsch et al. (2007) used controlled respiration at 15 cycles/min, while the elderly patients in the second study (McLaren et al., 2005) were allowed to breathe naturally. All HRV parameters, with the exception of LF, are higher during free breathing than during controlled breathing, according to a systematic review (Nunan et al., 2010). This fact would have biased the results of first study toward showing reduced HF, but does not explain the reduced TP and SDNN in the second study. Secondly, HRV parameter values, in general, are known to decrease with age. Patients in the first study were aged less than 75 and those in the second were over 75. Thirdly, the length of time from stroke to HRV measurement was longer at 18–43 months in the first study, compared to 4–28 months in the second. There had been more time for HRV parameters to recover in the first study population, possibly explaining why only one HRV parameter was found to be reduced.

Long-term recordings show greater autonomic dysfunction as represented by the HRV, but again, there is much variation among different studies. In a study by Lakusic et al. (2005), of 78 stroke survivors, multiple time domain parameters (RR interval, SDNN, standard deviation of sequential 5 min interval [SDANN], root-mean-square successive difference [rMSSD] and percentage of differences between adjacent normal-to-normal intervals greater than 50 ms [pNN50]) and frequency domain parameters (TP, very low frequency [VLF], LF, normalized LF [LFnu], HF and normalized HF [HFnu]) were found to be reduced. The only parameter that was not reduced was the LF/HF ratio. Another study found that the LF/HF ratio was increased, but only in those stroke survivors who also had documented arrhythmias (Orlandi et al., 2000). Other studies have shown reduced SDNN (Korpelainen et al., 1999; Kwon et al., 2008) and SDANN (Kwon et al., 2008) with no differences in HF (Korpelainen et al., 1999; Kwon et al., 2008) or other frequency domain measures (Kwon et al., 2008). Non-linear HRV is less studied in stroke survivors, but the Poincaré plot SD2 (standard deviation of long-term continuous RR interval variability measured from a Poincaré plot) parameter is reduced compared to control subjects with no differences in Poincaré plot SD1 parameter, approximate entropy (ApEn) or short-term (α_1) and long-term (α_2) scaling exponents (Korpelainen et al., 1999). Normal HRV reference values and post-stroke values from select studies are listed in Table 20.1.

BRS is also impaired following a stroke. Cardiac BRS was found to be lower in both ischemic (Eveson et al., 2005; Robinson et al., 2003; Sykora et al., 2009a) and hemorrhagic (Sykora et al., 2009a) stroke patients, compared to controls. It has been hypothesized that

TABLE 20.1

HRV Values from Selected Studies in Healthy Population and Stroke Patients

Study	Sample Characteristics	Time Post-Event	HRV Analysis	SDNN (ms)	rMSSD (ms)	LF (ms ²)	HF (ms ²)	LF/HF
Task Force (1996)	Reference Healthy Population		24 h Holter	141 ± 39	27 ± 12	1170 ± 416	975 ± 203	1.5–2.0
Bassi et al. (2007)	n = 85 (60.0 ± 12.4 years)	<30 days	24 h Holter	117.3 ± 40.3	38.5 ± 33.0	NR	NR	NR
Bassi et al. (2010)	n = 126 (59.7 ± 11.6 years)	<30 days	24 h Holter	116.4 ± 38.9	39.4 ± 31.9	NR	NR	NR
Colivicchi et al. (2005)	n = 208 (69.5 ± 7.8 years)	<72 h	24 h Holter	107.1 ± 11.5	26.5 ± 4.3	837 ± 451	341 ± 213	2.6 ± 1.1
Korpelainen et al. (1999)	n = 31 (52.1 ± 11.2 years)	1–7 days	24 h Holter	109 ± 38	NR	494 ± 298	331 ± 369	NR
		6 months		127 ± 39	NR	595 ± 410	436 ± 530	NR
Lakusic et al. (2005)	n = 78 (59 ± 11 years)	<10 weeks	24 h Holter	96 ± 21	23 ± 16	362 ± 291	154 ± 126	2.4 ± 1.4
		6 months		107 ± 24	27 ± 18	576 ± 316	212 ± 107	2.6 ± 1.3
Nunan et al. (2010)	Reference Healthy Population		5 min	50 ± 16	42 ± 15	519 ± 291	657 ± 777	2.8 ± 2.6
Katz-Leurer and Shochina (2007)	n = 64 (62 ± 10 years)	<30 days	5 min	NR	NR	1242 ± 1692	531 ± 86	NR
McLaren et al. (2005)	n = 76 (80.1 ± 4.0 years)	9 ± 4 months	5 min	3.21 ± 0.44 ^a	NR	4.65 ± 1.05 ^a	4.33 ± 1.23 ^a	NR
Tokgözoglu et al. (1999)	n = 62 (61.5 ± 10.6 years)	<3 days	5 min	31 ± 11	NR	243 ± 174	83 ± 86	NR

Note: NR = Not reported.

^a Logarithmic transformation of results.

this may be mechanistically related to an increase in blood pressure variability (Sykora et al., 2009b), which has also been noted following a stroke. In addition, BRS was negatively correlated with the grade of hypertension ($r = -0.52$) in a study of 26 hypertensive stroke survivors and 30 hypertensive control participants (Čelovská et al., 2010). BRS was also correlated with systolic blood pressure (SBP), diastolic blood pressure (DBP), occurrence of acute hypertension on hospital admission and the number of hypertensive episodes in the first 72 h of hospital admission (Sykora et al., 2010). Therefore, autonomic dysfunction, including the BRS, may be related to blood pressure control in stroke survivors.

20.3 Autonomic Indices and Stroke Prognosis

Measurement of autonomic indices following a stroke may be important in light of the prognostic utility of HRV and BRS. Studies have shown that reduced time domain and non-linear indices of HRV predict mortality, while the frequency domain parameters demonstrate no prognostic significance (Colivicchi et al., 2005; Mäkipallio et al., 2004). SDNN and rMSSD were reduced in non-survivors compared to survivors 12 months following a stroke (Colivicchi et al., 2005). In fact, those with an SDNN less than 100 ms were over three times more likely to die than those with an SDNN greater than 100 ms. Univariate analysis showed that both β -slope less than -1.5 and α_1 less than 0.75 were predictors of mortality (Mäkipallio et al., 1999). When multivariate analysis was used to adjust for age, only β -slope less than -1.5 predicted death. Fractal dimension (FD) ≤ 1.05 from 1 h recordings of HRV was also shown to predict mortality (He et al., 2010). Further, 47.62% of non-survivors and only 17.54% of survivors had FD ≤ 1.05 in this study (He et al., 2010). Although long-term frequency domain analysis of HRV lacks predictive value of mortality, short-term frequency domain analysis of HRV from 5 min recordings was able to predict the outcome as assessed by the modified Rankin Scale (ranging from 0—no symptoms at all—through levels of disability to 6—dead) following a severe stroke (Gujar et al., 2004). Low LFnu and increased %VLF predicted survival, but when adjusted for artificial ventilation and dopamine use, reduced LFnu and increased absolute VLF predicted clinical outcome.

BRS has also shown promise as a predictor of mortality after acute ischemic stroke. Patients with impaired BRS (≤ 5) had higher mortality rates than those with normal BRS (28% compared to 8% mortality) (Robinson et al., 2003). Interestingly, patients with reduced BRS also had an average SDNN less than those with normal BRS (25.4 ms compared to 51.0 ms). Since the prognostic value of SDNN was not discussed by Robinson et al. (2003), it cannot be determined whether BRS has a greater prognostic value than traditional HRV indices. However, it has been suggested that BRS may offer greater insight into autonomic cardiovascular regulation as the single index takes into account both neural health (from the reflex loop) and vascular health (from the mechanical changes in the blood vessels that have been shown to alter BRS) as opposed to HRV, which only reflects neural control (Kaushal and Taylor, 2002).

HRV may also be useful for predicting functional outcome in stroke survivors, although again, studies to date have had small sample sizes. SDNN and SDANN from 24 h Holter monitoring were lower in stroke patients with an unfavorable functional outcome (Barthel Index Score <75) compared to those with favorable rehabilitation outcomes (Bassi et al., 2007). In fact, patients with an SDNN <100 ms were over nine times more likely to have

a poor functional outcome than those with an SDNN >100 ms. A follow-up study by the same researchers showed that gender differences do exist. In this study, an SDNN <100 ms was an independent predictor of the functional outcome after 60 days of rehabilitation in men (odds ratio, OR = 15.29) but not in women (Bassi et al., 2010). Insular damage was an important independent predictor of dependency after the rehabilitation program in women (OR = 18.89) but not in men. Interestingly, a number of studies have reported that women experience less functional recovery after a stroke, compared to men. Fukuda and colleagues (2009) showed that women had worse functional outcome and lower survival ratio at 1 and 5 years post-stroke, compared to men, despite no gender differences in stroke recurrence. In Canada, women were more likely to be discharged to long-term care and had greater disability than men at 6 months, although mortality and quality of life were similar between genders (Kapral et al., 2005). Further studies are needed to determine how gender differences in functional outcomes are related to HRV.

A study examining short-term HRV indices (10 min recordings) showed that rMSSD and HF were correlated with motor impairment at 2 weeks and 3 months post-stroke (Katz-Leurer and Shochina, 2005), but authors did not assess whether there were actual differences in the outcome. A 10 min HRV analysis was inadequate to predict aerobic exercise outcome in stroke rehabilitation (Katz-Leurer and Shochina, 2007). Both of these studies had small sample sizes ($n = 39, 64$) and, therefore, may not have had adequate power to predict the outcome. In addition, long-term recordings may have a greater prognostic value as the autonomic function is being assessed during the course of usual activity as opposed to during a short rest period.

It is apparent that autonomic dysfunction is present following a stroke and marked by both altered HRV and BRS. However, to date, most studies have been relatively small, and results have been somewhat inconsistent, highlighting the need for larger-scale studies. In the following section, we discuss some of the unique factors affecting results in stroke patients compared to other patient populations.

20.4 Factors Affecting Studies Involving Stroke

Due to the complexity of stroke, there are a number of factors affecting HRV and BRS that are not a result of stroke per se, but rather due to concurrent issues. The following section discusses in detail some of the factors affecting the autonomic nervous system in stroke patients, including time post-event, location and lateralization of lesions, arterial stiffness and comorbidities.

20.4.1 Time Post-Event and Lesion Location

One reason for the disparity between results from different laboratories may be the timing of HRV measurement post-event. Studies have revealed that ANS function improves throughout recovery. Orlandi and colleagues (2000) found that SDNN, pNN50 and variability were decreased and the LF/HF ratio and catecholamines were increased 3 days post-event in stroke survivors with arrhythmia. By day 7, values had recovered to the point that there were no statistically significant differences between stroke survivors and controls. Conversely, in ischemic hemispheric stroke, all time domain (mean RR interval, SDNN, SDANN, SDNN-I, rMSSD and pNN50) and frequency domain HRV parameters

(TP, VLF, LF, LFnu, HF and HFnu) studied were reduced, compared to controls, at 2 months following stroke (Lakusic et al., 2005). The LF/HF ratio was the only HRV index that was not altered in stroke survivors. At 6 months, all deficits persisted, although there was some recovery in SDNN, SDANN-I, SDNN-I, TP, LF and LFnu (Lakusic et al., 2005). Differences in recovery may, therefore, be related to the location of the lesion. Korpelainen et al. (1999) found reduced SDNN, VLF, LF and SD2 in acute stroke in those patients with hemispheric and medullary infarctions, but the only impaired autonomic parameter in pontine infarcts was the RR interval. At 6 months, those with medullary infarct showed full autonomic recovery, while SD2 was the only index that recovered in the hemispheric group. Within the hemispheric lesion group, there could be differences in recovery depending on the extent of the autonomic cortical network involved. Further research is needed to study this hypothesis.

20.4.2 Stroke Location and Laterality

The central processing is complex, and input from the ANS is not completely understood. However, it is clear that stroke location, whether the insula is involved or not, and stroke laterality have an effect on clinical manifestations of autonomic dysfunction and prognosis. Within the first 7 days following a stroke, more patients with right hemispheric lesions than left hemispheric lesions had recorded arrhythmias (Orlandi et al., 2000). Some of these arrhythmias may have resulted from increased sympathetic drive, because nor-epinephrine was found to be pathologically increased in right insular stroke compared to left insular or non-insular stroke (Meyer et al., 2004). In particular, lesions involving the insula appear to have greater autonomic consequences than those localized outside insular regions. The SDNN was the lowest in right insular lesions compared to all other stroke groups and controls (Tokgözoglu et al., 1999). Patients with right hemispheric lesions had lower HF and LF power values than those with left hemispheric lesions, while those with right insular involvement had the lowest values, although there were no differences in the LF/HF ratio (Tokgözoglu et al., 1999). When comparing right and left hemispheric infarctions with no insular involvement, only the LF/HF ratio was increased in right hemispheric stroke compared to controls, with no statistically significant difference between right- and left-sided lesions or between the left-sided lesions and controls (Dütsch et al., 2007). Another study found no difference between right and left hemispheric lesions and did not report any insular involvement (Korpelainen et al., 1999). The non-linear index FD was measured in both right and left hemispheric stroke patients, and those with right-sided stroke had significantly lower FD compared to those with left-sided stroke (He et al., 2010). Right-sided stroke also had a greater proportion of patients with $FD \leq 1.05$, which predicted mortality (He et al., 2010).

Right insular damage also appears to have an effect on sudden cardiac death and mortality, as it has been shown to be an independent indicator of 1-year mortality (Colivicchi et al., 2005). Similarly, 16.76% of patients with right-sided stroke compared to 8.44% of patients with left-sided stroke died after 1 month (He et al., 2010). In a study with 62 stroke patients, 7 sudden deaths occurred during hospitalization (Tokgözoglu et al., 1999). Although the study was not powered to find significance, all 7 patients who died had insular lesions and 5 of the 7 deaths were due to right insular damage, suggesting that larger-scale studies are warranted to determine mortality risk in right insular stroke. As mentioned in the introduction section of this chapter, right superior posterior insula exhibits greater activity and bilateral anterior insulae exhibit lesser activity during sympathetic activation induced by lower body negative pressure testing (Kimmerly

et al., 2005). Increased sympathetic activity that accompanies insular stroke lesions is likely responsible for worse prognosis.

While impaired HRV may be a greater consequence in patients with right-sided stroke, BRS appears to be more strongly affected by left insular damage. Sykora and colleagues (2009a) measured the BRS in 52 ischemic and 44 hemorrhagic stroke patients. In both types of stroke, there was no difference in the BRS between control subjects and patients without insular involvement. However, those with insular involvement on either side presented lower BRS values and those with left insular lesions had lower values than those with right insular lesions. Thus, it appears that while both insulae are involved in baroreflex regulation, the left insula exerts greater control over the reflex loop.

20.4.3 Arterial Stiffness

Since stroke may be considered a consequence of systemic vascular disease, patients are likely to have some degree of atherosclerosis or arterial stiffening. Since baroreceptors are stretch receptors located in the aortic arch and carotid sinus, arterial stiffness could affect the autonomic function. BRS was independently correlated with carotid–femoral pulse wave velocity, an index of central arterial stiffness, both immediately and 14 days following a stroke (Eveson et al., 2005). Conversely, BRS was found to be unrelated to atherosclerosis profiles assessed by an ultrasound examination in the acute stroke group (Sykora et al., 2009a). Differences in the results may have been due to the measurement of arterial stiffness versus atherosclerosis or due to the fact that the latter study took insular involvement into account while the former did not. BRS was reduced in bilateral carotid atherosclerosis compared to unilateral or no atherosclerosis in a population of varying medical histories (Nasr et al., 2005). In both healthy older and younger men, carotid artery compliance was strongly correlated with BRS ($r = 0.69$) (Monahan et al., 2001). Path analysis revealed that both mechanical (i.e., carotid distensibility) and neural components of the baroreflex affect its gain, and this was more pronounced for older adults than for younger adults (Kaushal and Taylor, 2002). Thus, it seems likely that reduced BRS in stroke survivors could be affected by both arterial stiffness and injury to the baroreflex neural network, although further research is necessary to clarify this relationship.

It appears that atherosclerosis is not directly associated with reduced vagal outflow in stroke patients (Kwon et al., 2008) or healthy men (Kaushal and Taylor, 2002). SDNN was correlated with intima media thickness and carotid atherosclerosis in patients with acute ischemic stroke or transient ischemic attack (Kwon et al., 2008). HF was reduced in patients with bilateral carotid atherosclerosis compared to those with unilateral or no atherosclerosis (Nasr et al., 2005). However, HFnu, LF and LF/HF ratio were not correlated with carotid atherosclerosis. The age (30–84 years) as well as health indicators of the patients in this study ($n = 75$) ranged greatly. Most patients were referred to ultrasonography for stroke or transient ischemic attack, but others were referred for palsies, migraines, amnesia and other symptoms, including one who was being screened for asymptomatic carotid atherosclerosis. The heterogeneity of this patient population may have resulted in findings that are not specific to stroke survivors.

20.4.4 Comorbidities

Stroke is a serious disease that often results from poor lifestyle habits. As such, concomitant diseases including hypertension, coronary artery disease, various arrhythmias and type 2 diabetes mellitus are often present. Each of these diseases has its own autonomic

consequences and therefore, care must be taken to either use these comorbidities as exclusion criteria or appropriately account for the presence of these diseases in analysis.

20.5 Pharmacologic Interventions

Hypertension is common in stroke survivors. Antihypertensive therapies may improve clinic blood pressure as well as its regulation, which would be reflected in improved HRV and/or BRS. There is almost no research that has examined the impact of different antihypertensive therapies on autonomic function in stroke survivors. One study showed that β -blocker use prior to stroke resulted in reduced stroke severity (Laowattana and Oppenheimer, 2007), likely in part due to reduced sympathetic activity. Those who had been taking β -blockers had reduced LF/HF ratio compared to those who were not. It was suggested that this potential shift in sympathovagal balance may improve neurologic prognosis (Laowattana and Oppenheimer, 2007). Indeed, a study showed reduced early mortality in ischemic stroke survivors receiving β -blocker therapy (6.8% vs. 19.0% at 30-day follow-up: Figure 20.1) (Dziedzic et al., 2007). This study did not examine the autonomic function and therefore, it is not known whether improvements in HRV or BRS are underlying mechanisms for improved short-term survival. Although β -blockers are no longer considered preferential initial therapy for adults over the age of 65 (Hackam et al., 2010) and

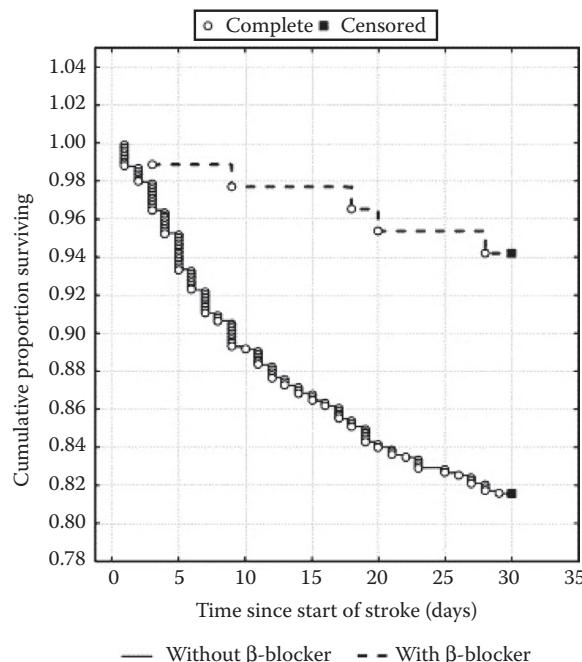


FIGURE 20.1

Kaplan-Meier cumulative survival curves for stroke patients treated with and without β -blockers. (Reprinted from *J. Neurol. Sci.*, 252, Dziedzic, T., Slowik, A., Pera, J. and Szczudlik, A., Beta-blockers reduce the risk of early death in ischemic stroke, pp. 53–56, Copyright (2007), with permission from Elsevier.)

with hypertension, it is still recommended that they be considered for patients with increased sympathetic drive (Sever, 2006).

Antihypertensive medications have varying effects on autonomic function in hypertensive patients, though direct studies on stroke survivors have not been completed. Calcium-channel blockers have been shown to increase LF/HF ratio and decrease HF during night and early morning (Karas et al., 2005) and increase the norepinephrine spillover (Karas et al., 2005; Lindqvist et al., 2007). These changes are indicative of increased sympathetic and decreased parasympathetic activities, despite lower SBP and DBP. It would be expected that those calcium channel blockers with inotropic effects (dihydropyridines) compared with those that do not have direct inotropic effects (non-dihydropyridines) would have a different impact on the HRV. Since most patients require more than one antihypertensive agent to control the blood pressure, it is interesting that a combination therapy with the non-dihydropyridine calcium channel blocker felodipine and the β -blocker metoprolol resulted in improved blood pressure profile accompanied by improved BRS, SDNN and HF power of HRV (Ylitalo et al., 1999). It should be noted that calcium channel blockers tend to reduce heart rate, which in turn affects the HRV. Studies on calcium channel blockers and the HRV in stroke survivors have yet to be conducted.

Angiotensin-II-converting enzyme (ACE) inhibitors have generally shown positive autonomic changes in hypertensives. Compared to a control group, hypertensive patients showed reduced SDNN, pNN50 and LF power (da Silva Menezes et al., 2004). Following 3 months of antihypertensive therapy with ACE inhibitors, blood pressure was reduced, although not all patients achieved optimal blood pressure control. Patients also showed an improved HRV, with values similar to those of control participants (da Silva Menezes et al., 2004). Combination therapy with ACE inhibitor and hydrochlorothiazide resulted in improved BRS and HRV, with no change in heart rate (Ylitalo et al., 1999), suggesting that BRS and HRV modifications were true autonomic improvements, rather than an artifact of altered heart rate. Studies in angiotensin-receptor blockers (ARB) are needed as this class of pharmacological agents is an important contributor to blood pressure management in hypertension including post-stroke.

Despite the shortcomings of limited studies on different antihypertensive classes and specifically those in post-stroke, current evidence in hypertensive patients may suggest the preferential use of ACE inhibitors to attain blood pressure control while improving autonomic function. Studies also need to examine the long-term benefits of such potential improvements. For example, studies are needed to determine whether or not these autonomic modifications actually translate into improved prognosis and or functional outcomes.

20.6 Lifestyle Interventions

Recent research supports the use of exercise rehabilitation post-stroke for improving gait, cardiorespiratory fitness and functional outcome. Although cardiovascular measures are not always reported, SBP was reduced by 10% and the DBP by 11% following 8 weeks of intensive physical training at 80% of maximal heart rate (Jørgensen et al., 2010). In another study, SBP was reduced by 8% and DBP by 11% following 12 weeks of aerobic exercise with progressively increasing intensity (from 40%–49% of heart rate reserve to 60%–69% of heart rate reserve) (Rimmer et al., 2009). Neither SBP nor DBP was modified following 12 weeks of low-intensity exercise (exercise at <50% heart rate reserve) with gradually

increasing duration (from 30 to 60 min/session) or following 12 weeks of therapeutic, non-aerobic exercise (Rimmer et al., 2009). Twelve weeks of moderate-intensity treadmill training at 50%–60% of heart rate reserve resulted in 4% and 5% reduction in SBP and DBP, respectively (Yang et al., 2007). One study reported a reduction in resting heart rate from 78 to 73 bpm (Yang et al., 2007), while another reported no significant changes (Jørgensen et al., 2010). Only one study has assessed the autonomic function before and after exercise in stroke patients using symbolic, rather than spectral, HRV analysis. Following a 30-day cycle of robotic-assisted body weight-supported treadmill training, the HRV profiles of stroke patients more closely matched those of healthy adults (Magagnin et al., 2010). These preliminary HRV results and positive changes in cardiovascular profiles following exercise training support the need for further research to investigate the effects of exercise rehabilitation on autonomic function in stroke survivors. Investigation of effects of exercise on standard HRV and BRS parameters would be helpful, since time and frequency domain measures are more commonly utilized. It would also be interesting to examine whether or not modifications in the ANS translate to better rehabilitative outcomes and reduced mortality.

Exercise rehabilitation is an integral part of stroke therapy in many hospitals in Canada and the United States. Recently, researchers have been studying the means of adapting existing cardiac rehabilitation programs to include transient ischemic attack and stroke patients (Tang et al., 2009, 2010). Trials are currently underway to evaluate cardiovascular risk (Lennon and Blake, 2009; MacKay-Lyons et al., 2010), including secondary vascular events (MacKay-Lyons et al., 2010) in stroke survivors undergoing cardiac rehabilitation. Cardiac rehabilitation has been shown to effectively improve the HRV (Iellamo et al., 2000; Malfatto et al., 2000; Sandercock et al., 2007; Stähle et al., 1999; Tygesen et al., 2001) and BRS (Iellamo et al., 2000; Mimura et al., 2005) in cardiac patients, although not all studies have found positive results (Leitch et al., 1997). Thus, it seems logical that similar exercise programs may elicit improved HRV and BRS in stroke patients. Future studies will reveal whether similar results occur in stroke survivors.

20.7 Limitations and Future Considerations

Most studies on HRV in stroke survivors completed to date are limited by a small sample size and heterogeneity of stroke lesion location. Future investigations should focus on evaluating the autonomic dysfunction specific to stroke localization. This would enable classification of stroke lesion according to the dysfunction and enable implementation of specific, targeted therapies to maximize recovery and rehabilitation. A study of therapies to improve autonomic regulation following stroke is also lacking, and such investigations are needed, as they may translate into improved outcome.

20.8 Summary and Conclusions

Stroke results in autonomic dysfunction as evidenced by impaired HRV and BRS. The extent and type of dysfunction depend upon the lesion location. Lesions of the insula,

especially those of the right side, seem to produce the worst dysfunction and prognosis. Some antihypertensive therapies likely improve the autonomic function, but lifestyle interventions such as increased exercise may be even more beneficial in maximizing recovery and rehabilitation because they have the potential to improve aerobic capacity, gait and the autonomic function.

Acknowledgment

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Abbreviations

ACE	Angiotensin-II-converting enzyme
ApEn	Approximate entropy
BRS	Baroreflex sensitivity
FD	Fractal dimension
HF	High frequency
HFnu	Normalized HF
LF	Low frequency
LFnu	Normalized LF
MCA	Middle cerebral artery
OR	Odds ratio
pNN50	Percentage of differences between adjacent normal-to-normal intervals greater than 50 ms
rMSSD	Root-mean-square successive difference
SDANN	Standard deviation of sequential 5 min intervals
SDNN	Standard deviation of normal-to-normal intervals
TP	Total power
VLF	Very low frequency

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21

Significance of Heart Rate Variability in Patients with Epilepsy

Manjari Tripathi and Navita Choudhary

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21.1 Introduction

21.1.1 Incidence and Prevalence of Epilepsy

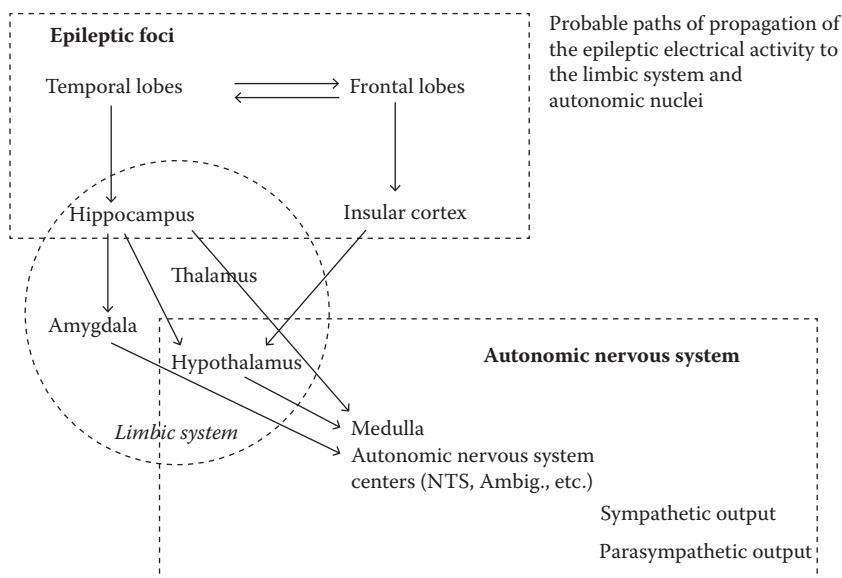
Epilepsy is a very common brain disorder, and it is estimated that about 5.5 million people around the world suffer from it. The general population with active epilepsy (i.e., continuing seizures) at a given time is 4–10 per 1,000 people in industrialized nations and 6–10 per 1,000 in developing countries. In the industrialized nations, annual new cases are 40–70 per 100,000 people, with twice those numbers in developing countries (WHO, 2009). Epilepsy may occur in any age group, but the incidence is higher in infants and the elderly (MacDonald et al., 2000).

21.1.2 Overview of Epilepsy

Epilepsy may occur due to head trauma, birth hypoxia, infections of the central nervous system and tumors. Cerebrovascular disease is also one of the risk factors for epilepsy (Granger et al., 2002). The fundamental characteristics of epilepsy are recurrent, usually unprovoked, seizures. A seizure is a transient occurrence of signs and/or symptoms due to excessive or abnormal synchronous neuronal activity in the brain areas, usually, but not necessarily, involving the cortex (Fisher et al., 2005; Engel, 2006). Seizure presentation depends on the location of seizure onset in the brain, patterns of propagation, maturity of the brain, confounding disease processes, time of occurrence in the sleep–wake cycle, medications and a variety of other factors. Seizures can affect sensory, motor autonomic functions, consciousness, emotional state, memory, cognition and behavior (Fisher et al., 2005). On the basis of seizure onset and propagation, seizures are classified as partial (focal) and generalized seizures. The partial seizure originates from one lobe of the brain, although seizure activity may propagate to both hemispheres. On the basis of the propagation of seizure activity, partial seizures can be further classified as simple partial seizures, complex partial seizures (CPS) and secondary generalized seizures. If seizure activity remains focal, it is called a simple partial seizure. When seizure activity propagates via neuronal pathways and networks to various regions of the same hemisphere, it is called a complex partial seizure (Chabolla, 2002). When partial seizure spreads to involve the majority of both hemispheres, it is said to be a secondary generalized seizure (Chabolla, 2002). The signs and symptoms associated with a partial seizure depend on cortical regions involved and may be somatosensory, motor, autonomic or psychic (Chabolla, 2002). In a generalized seizure, the epileptic activity arises from both cerebral hemispheres simultaneously.

21.1.3 Involvement of the Central Autonomic Network in Seizure

Involvement of the central autonomic network in a seizure, either as the origin of the seizure or as a result of the seizure spreading to it, modifies autonomic nervous system activity. The central autonomic network primarily consists of the insular cortex, medial prefrontal cortex, amygdala, cingulate gyrus and hippocampus. These areas are directly and indirectly connected to subcortical structures, namely, the hypothalamus, periaqueductal gray matter, parabrachial complex, nucleus of the solitary tract and rostroventrolateral medulla (Inui and Nosaka, 1993; Dampney, 1994) and control sympathetic and parasympathetic branches of the autonomic nervous system. The insular cortex plays an important role in the regulation of cardiovascular autonomic state and is highly lateralized. For example, stimulation of the right insula in humans results in tachycardia and hypertension, while stimulation of the left insula causes hypotension and bradycardia (Oppenheimer et al., 1992). Stimulation of the medial prefrontal cortex can produce both pressor and depressor responses (Tavares et al., 2004; Burns and Wyss, 1985). Similarly, cingulate gyrus, amygdala and hippocampus play an important role in the control of cardiovascular autonomic functions (Cechetto, 2000; Benarroch et al., 1999). Stimulation of the left cingulate gyrus has been shown to result in bradycardia (Leung et al., 2007). Thus, an assessment of autonomic function in epilepsy patients has significant clinical relevance, in that clinical signs can suggest the laterality of the focus (Figure 21.1).

**FIGURE 21.1**

Probable pathways of seizures originating in the temporal lobe. (From Nouri S. Epilepsy and the Autonomic Nervous System [Emedicine.medscape.com.] 2011 [updated 2011 March; cited 2011 July 7]. Image reprinted with permission from Medscape.com, 2011; Available from <http://emedicine.medscape.com/article/1186872-overview>.)

21.2 Cardiovascular Autonomic Dysfunction during a Seizure

Autonomic symptoms are very common in epilepsy. The type of autonomic symptoms seen depends on the type of seizure, location and size of the brain area involved (Epstein et al., 1992; Engel et al., 2008). Clinical manifestation of a simple partial seizure is an alteration in the autonomic function, while autonomic auras are a common phenomenon prior to CPS (Devinsky, 2004). Seizure foci can be localized on the basis of autonomic symptoms, but it must be kept in mind that seizure-induced autonomic symptoms may mimic autonomic symptoms associated with syncope or other cardiovascular diseases. Therefore, autonomic symptoms should not be used as the sole tool for seizure localization (Engel et al., 2008; Devinsky, 2004).

Seizure originating in, or propagation of seizure activity to, the central autonomic network may lead to tachycardia, hypertension, apnea, sweating, pupillary changes, salivation, incontinence, etc. (Van Buren, 1958). Study of autonomic changes during seizures was first conducted during electroshock therapy (ECT) (Brown et al., 1953). It was observed that at the start of ECT, there was an abrupt fall in systolic and diastolic blood pressures, along with bradycardia and respiratory arrest. As convulsions continued, both blood pressure and heart rate recovered only to fall below the baseline again after convulsions ceased. This second decrease in blood pressure was followed by yet another recovery that overshot the baseline and then gradually returned to the baseline. Bradycardia persisted throughout the post-ictal period. In a second subgroup of experiments, subconvulsive shocks failed to produce apnea, but variations in blood pressure and heart rate were observed (Brown et al., 1953).

Van Buren et al. investigated autonomic phenomena in 13 temporal lobe epilepsy (TLE) patients during 20 epileptic seizures. They recorded ECG, blood pressure, respiratory movements, skin temperature resistance and esophageal and gastric pressures simultaneously with the electroencephalogram (EEG) and found that the majority of patients showed a fairly stereotypical pattern of initial decrease in skin resistance and swallowing, followed by cessation of respiration and gastric motility and then tachycardia, hypotension and decrease in pulse amplitude. They concluded that this pattern was indicative of the propagation of electrical activity through spatially separate autonomic centers (Van Buren, 1958).

More recent studies using simultaneous recording of EEG and ECG during CPS and generalized tonic-clonic seizures (GTCS) have shown that tachyarrhythmia and pressor responses are more common than bradyarrhythmia and hypotension (Freeman and Schachter, 1995; Hilz et al., 1999; Weil et al., 2005). Tachycardia occurs in 64%–100% of seizures (Blumhardt et al., 1986; Epstein et al., 1992; Schernthaner et al., 1999; Opherk et al., 2002) and is more frequently seen in patients whose seizure onset is in the right temporal lobe (Leutmezer et al., 2003; Saleh et al., 2000), while bradycardia occurs in <6% of seizures (Liedholm and Gudjonsson, 1992; Reeves et al., 1996; Leutmezer et al., 2003; Nei et al., 2000) and is more frequent in patients with seizure foci in the left temporal lobe (Tinuper et al., 2001; Leutmezer et al., 2003).

Most of the structures associated with temporal lobe are involved in the modulation of cardiovascular autonomic functions. Therefore, one would expect major cardiovascular and respiratory changes to occur when the discharge involves the temporal lobe. Heart rate changes usually occur approximately 5–13 s prior to seizure onset as recorded on the scalp EEG in medial TLE (Leutmezer et al., 2003; Di Gennaro et al., 2004), while in lateral TLE, an increase in the heart rate coincides with changes in EEG (Di Gennaro et al., 2004). Ictal tachycardia occurred more prominently after mesial temporal lobe seizures than after non-lesional or extratemporal seizures (Leutmezer et al., 2003; Galimberti et al., 1996; Garcia et al., 2001; Weil et al., 2005).

Patients with bradycardia and asystole during a seizure are said to have bradycardia syndrome (Reeves et al., 1996). Nashef et al. reported bradycardia, asystole, syncope and cardiac arrest in most patients who experienced central apnea during a seizure (Nashef et al., 1996). Bradycardia and asystole have been correlated with postganglionic cardiac catecholamine disturbance. Two studies using MIBG testing suggest that a deficit of sympathetic cardiac innervation may increase the risk of asystole (Kerling et al., 2009; Manitius-Robeck et al., 1998), while another study has shown that a transient increase in vagal tone may be responsible for asystole and bradycardia (Schuele et al., 2008).

It has also been reported that acceleration of heart rate often occurs around the time or even before the earliest scalp EEG abnormality or clinical change (Zijlmans et al., 2002). In most cases, supraventricular tachycardia, paroxysmal atrial tachycardia and sinoatrial heart block are also reported (Pritchett et al., 1980; Rush et al., 1977; Phizackerley et al., 1954) and may be related to sudden death in epilepsy patients (SUDEP). A study of seizure-related cardiac arrhythmia and lateralized effects of seizure on the cardiac function is essential in understanding the mechanism of SUDEP and may lead to treatments in patients having cardiac emergencies due to seizure activity.

Some studies have indicated that focus laterality affects the cardiovascular autonomic disturbances observed in epilepsy patients. For example, seizure onset in the left temporal lobe has been associated with bradycardia (Tinuper et al., 2001; Liedholm and Gudjonsson, 1992). However, others have suggested that there is no relationship between the location and laterality of seizure activity and the autonomic function (Epstein et al., 1992; Britton

et al., 2006). Epstein and colleagues observed the EEG and ECG during seizure onset in 14 right TLE and 13 left TLE patients and found that unilateral limbic discharge, irrespective of the side of origin, usually resulted in tachycardia. Britton and colleagues observed seizure activity with ECG in 13 patients and found that ictal bradycardia occurred in association with bilateral hemispheric seizure activity. They, therefore, suggested that unilateral parasympathetic cardiomotor representation in the left hemisphere did not exist.

21.3 Heart Rate Variability as a Predictor of Mortality and Sudden Death

Reduced heart rate variability (HRV) measured through both time domain and frequency domain methods is considered to be a risk factor associated with mortality and sudden cardiac death in patients with cardiac anomalies (Tomson et al., 1998a; Timmings, 1998; Bigger et al., 1993; Myers et al., 1986; Martin et al., 1986). Sympathetic overdrive or vagal withdrawal is associated with the pathogenesis of ventricular arrhythmias and sudden death in patients with myocardial infarction (De Ferrari et al., 1995). Therefore, reduced HRV could be a marker of increased risk of SUDEP. A preliminary report revealed the death of nine patients, who had significantly lower high-frequency power than epilepsy control as well as non-epilepsy controls (Eppinger et al., 2004).

21.4 HRV during the Inter-Ictal Period

Lathers et al. showed that even minimal epileptogenic activity can alter cardiac neural discharge and cause arrhythmias. They suggested that even inter-ictal activity may alter the cardiovascular autonomic functions (Schraeder and Lathers, 1983; Schraeder and Lathers, 1989; Lathers et al., 1997). Other reports (Druschky et al., 2001; Dütsch et al., 2004, 2006; Kerling et al., 2009; Persson et al., 2005; Hilz et al., 2003; Harnod et al., 2009) are also in agreement.

21.4.1 Measures of Total HRV during the Inter-Ictal Period

Both time domain and frequency domain analyses in TLE have shown a significant decrease in HRV compared to control subjects (Tomson et al., 1998; Ansakorpi et al., 2002, 2004; Isojärvi et al., 1998). The decrement of HRV is more pronounced during night than during day (Ronkainen et al., 2005; Persson et al., 2007). Children with simple seizures and CPS also showed decrement in the HF power, root mean of squared successive RR interval difference (RMSSD) and percent of normal–normal RR intervals whose difference exceeds 50 ms (pNN50) and increment in low frequency/high frequency (LF/HF) ratio (Ferri et al., 2002). These studies suggest that total HRV is reduced in epilepsy patients during the inter-ictal period.

21.4.2 Measures of Sympathetic Activity during the Inter-Ictal Period

There are many reports that the low-frequency (LF) component of HRV, which is a marker of sympathetic modulation of the sinus node, increases in patients with epilepsy (Devinsky

et al., 1994; Faustmann and Ganz, 1994; Dütsch et al., 2006; Li et al., 2006). Studies using other HRV parameters likewise suggest an increased sympathetic tone in epilepsy, such as the observations of increased LF power and LF/HF ratio in GTCS (Evrengul et al., 2005), decreased RMSSD and pNN50 in idiopathic epilepsy in children (El-Sayed et al., 2007), decreased RMSSD in refractory epilepsy patients (Shobha et al., 2007) and decreased HF power in frontal lobe epilepsy patients (Harnod et al., 2009). In our own research, we found that LF power was higher and HF power was lower in drug refractory TLE patients compared to well-controlled patients (Mukherjee et al., 2009). Imaging studies using MIBG-SPECT also provide supporting evidence that sympathetic activity is increased in epilepsy. MIBG, which stands for [¹²³I] metaiodobenzylguanidine, an analog of norepinephrine, allows the quantification of postganglionic cardiac sympathetic innervation. MIBG-SPECT studies performed in TLE patients found an increase in post-ganglionic cardiac sympathetic innervations (Druschky et al., 2001; Kerling et al., 2009).

21.4.3 Measures of Parasympathetic Activity during the Inter-Ictal Period

The HF component of HRV, which is regarded as a marker of the parasympathetic tone, is frequently used to assess parasympathetic tone in epilepsy patients. Most studies using HF show a decrement in parasympathetic function (Massetani et al., 1997; Ansakorpi et al., 2002; Mativo et al., 2010). Toichi et al. used a non-linear measure of HRV, Poincaré plots (which they called Lorenz plots), for the analysis of simultaneous recordings of EEG and ECG during inter-ictal and ictal periods. Their results, although based on only two patients, suggested that parasympathetic activity decreased during the inter-ictal period and increased during the ictal period. Authors concluded that the change in cardiovascular autonomic functions in epilepsy patients was mediated mainly through parasympathetic nervous system (Toichi et al., 1998). However, there are studies that have found an increase in parasympathetic function in the inter-ictal period; one such study used time domain measures of HRV (Druschky et al., 2001) and another study used the decrement of LF and LF/HF ratio during the inter-ictal period (Tomson et al., 1998a).

21.4.4 Measures of HRV during the Post-Ictal Period

Many studies point to a post-ictal change in HRV. A recent study that used simultaneous recordings of EEG and ECG showed that the time domain component of HRV decreased just after the seizure and lasted for 5–6 h post-ictally (Toth et al., 2010). This study indicates how enduring the effects of a single seizure can be on the autonomic nervous system.

21.4.5 Effect of Seizure Laterality on Autonomic Function during the Inter-Ictal Period

Some reports suggest that localization and lateralization of seizure foci may have differential effects on the autonomic nervous system (Massetani et al., 1997; Tomson et al., 1998; Hilz et al., 2001). Massetani and colleagues found that patients with seizure foci in the right temporal lobe have higher impairment of LF/HF ratio during the inter-ictal period than those with contralateral foci and suggested that the right hemisphere had greater control of cardiac autonomic function than the left hemisphere. Tomson and colleagues found that patients with left TLE had higher LF/HF ratio and suggested that such patients had heightened sympathetic tone. In our laboratory, we found that the RMSSD and standard deviation of successive RR intervals in time domain HRV (SDNN) were significantly

higher in left TLE patients than in right TLE patients, which suggests that the parasympathetic tone was higher in left TLE patients, leading to a lower risk of SUDEP in patients with left TLE (Choudhary, 2010). The differential effect of localization and lateralization of seizure activity on HRV emphasizes the importance of recording autonomic function in persons with epilepsy.

21.4.6 Other Factors That Influence HRV in Epilepsy Patients

The impairment of the autonomic function is influenced by many factors, including anti-epileptic drugs (AEDs). It is reported that autonomic dysfunction is slight or absent in patients with new-onset epilepsy but progresses as the epilepsy becomes chronic (Persson et al., 2006; Mukherjee et al., 2009). This may be due to the natural course of the disease. In status epilepticus, structural and functional neural changes are known to occur in various brain regions (Wasterlain et al., 1993). However, there is also the possibility that autonomic dysfunction is exacerbated by the chronic use of AEDs.

AEDs themselves modify autonomic functions, causing arrhythmia, hypotension and respiratory and gastrointestinal tract disturbances. Some of these medications block the sodium channel and, therefore, can affect the cardiac conduction system directly as well as indirectly through central nervous control of the heart (Tomson et al., 1998; Nouri, 2011). The use of AEDs makes the interpretation of results of autonomic assessment in patients taking these drugs rather difficult. Many researchers have specifically studied the effect of AEDs on autonomic functions during the inter-ictal period (Tomson and Kennebäck, 1997, 1998; Ansakorpi et al., 2000; Persson et al., 2003; Massetani et al., 1997; Isojärvi et al., 1998).

Carbamazepine is shown to be associated with sinus bradycardia, sinus pauses, junctional bradycardia and AV block ranging from first degree to complete block at therapeutic doses or plasma concentrations (Stone et al., 1986; Durelli et al., 1985). Bradyarrhythmia predominates at therapeutic doses, while sinus tachycardia is the main arrhythmia in carbamazepine overdose (Kenneback, 1995). Another report demonstrates the depressant effects of carbamazepine on the cardiac conduction system, mainly in the elderly or in otherwise predisposed patients (Tomson et al., 1998). In one study, patients receiving carbamazepine therapy were shown to have arrhythmias and after abrupt withdrawal of carbamazepine therapy, a 10-fold increase in ventricular premature beats was observed with reduced HRV (Kennebäck et al., 1997). Ansakorpi et al. (2000) demonstrated that patients receiving carbamazepine show significant reduction in the heart rate response to deep breathing and tilt table test than controls and suggested that carbamazepine could be associated with autonomic dysfunction. Similarly, HRV during normal breathing and maximum systolic blood pressure increase in isometric work were diminished in patients who had been treated with AEDs for a long time, particularly in those who were receiving carbamazepine, while the heart rate and blood pressure responses were comparable in untreated patients and controls (Isojärvi et al., 1998). Patients receiving carbamazepine had significantly lower total power and LF power compared to controls (Tomson et al., 1998). A study conducted on healthy subjects showed lower HRV with carbamazepine (Quint et al., 1990). Power spectral analysis of HRV showed that carbamazepine may suppress both parasympathetic and sympathetic functions in patients with newly diagnosed epilepsy (Persson et al., 2003).

Phenytoin has been predominantly associated with bradyarrhythmias, asystole and sudden death (Tomson and Kennebäck, 1997). Intravenous phenytoin has resulted in bradyarrhythmia in healthy subjects also (Barron, 1976), while HRV was unaffected in

healthy subjects (Quint et al., 1990). Studies have also shown that the modulation of HR was unaffected by phenytoin and valproate therapy (Isojärvi et al., 1998; Tomson et al., 1998). Similarly, phenobarbital does not seem to have negative effects on the cardiac function and impulse conduction (Massetani et al., 1997).

HRV analysis has shown that children with epilepsy who are not receiving AEDs demonstrate lower HF power than those who do receive AEDs, which suggests that AEDs may be helpful in improving the cardiac autonomic function (Hallioglu et al., 2008). However, another study showed that a slow withdrawal of AEDs in seizure-free patients with epilepsy resulted in an increase in both parasympathetic and sympathetic functions (Lossius et al., 2007).

In summary, these findings indicate that carbamazepine use and its withdrawal can change the autonomic function and suggest that other AEDs may also have similar effects. Further studies are needed to understand the effect of AEDs on autonomic function during the inter-ictal period.

21.5 Discussion

As our review shows, epilepsy patients clearly have an impairment of the cardiovascular autonomic function. Most studies agree that sympathetic tone is increased while parasympathetic tone is decreased. The side and location of seizure foci affect specific manifestation of the autonomic dysfunction. The autonomic dysfunction parallels the severity of epilepsy, that is, patients with well-controlled epilepsy have less autonomic dysfunction than patients with drug refractory epilepsy. Patients with a higher seizure count also have higher autonomic dysfunction (Persson et al., 2006).

The incidence rates of SUDEP range between 0.35 and 2.70 per 1000 person-years in population-based studies (Ficker et al., 1998; Leestma et al., 1989) and between 1.50 and 9.30 per 1000 person-years in selected cohorts (Nilsson et al., 1999; Dasheiff, 1991). The highest SUDEP rate of 9/1000 person-years and the estimated incidence of 1/100 patient-years have been reported in candidates for epilepsy surgery (drug refractory patients) (Dasheiff, 1991). These rates need to be viewed with reference to the background risk of sudden death in the general population of around 0.05 to 0.1/1000 for those <45 years of age and 3/1000 for those older (Annegers, 1997).

Many studies have attempted to identify patients at particular risk of SUDEP. However, mechanisms of SUDEP are still not fully understood. The most frequently cited risk factors of SUDEP are number of seizures, age, GTCS, polytherapy, early onset of epilepsy, duration of seizure disorder, sudden death on bed/floor, alcoholism, congenital neurological deficit, mental retardation, male gender, recent (<1 week) change in AED, right temporal resection and specific antiepileptic medications (Tomson et al., 2005; Hughes, 2009).

In conclusion, epilepsy is associated with altered autonomic cardiac control. Although the impairment varies in extent and type, the most frequent finding is reduced HRV similar to that observed in other patient groups at increased risk of cardiac death. Several factors, for example, seizures, inter-ictal discharges, underlying brain pathology and drugs, may contribute. Most consistently, decreased HRV has been observed in patients at particular risk of SUDEP such as those with refractory epilepsy. This suggests that impaired autonomic cardiac control contributes to the risk of SUDEP (Nashef and Tomson, 2008).

21.6 Future Research

Large cohorts need to be established with uniform evaluation criteria over different institutions. Different variables, such as the location of seizure foci, duration of epilepsy, type of AED used and whether a patient responds or is refractory, need to be considered. Doing so will help us understand the interplay between the autonomic nervous system and epilepsy better and minimize the risk to patients from its dysfunction.

21.7 Conclusion

The analysis of HRV in patients with epilepsy may be helpful in identifying subgroups of patients prone to fatal outcomes and also in understanding pathophysiological functions of the autonomic nervous system.

Abbreviations

AEDs	Antiepileptic drugs
CPS	Complex partial seizure
ECG	Electrocardiogram
ECT	Electroshock therapy
EEG	Electroencephalogram
GTCS	Generalized tonic-clonic seizure
HF	High frequency
HRV	Heart rate variability
LF	Low frequency
LF/HF ratio	Low frequency/high frequency ratio
pNN50	Percent of normal-normal RR intervals whose difference exceeds 50 ms
RMSSD	Root mean of squared successive RR interval difference
SPECT	Single-photon emission computed tomography
SUDEP	Sudden unexplained death in epilepsy patients
TLE	Temporal lobe epilepsy

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22

Classification of Parkinson's Disease Severity Using Heart Rate Variability Analysis

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22.1 Introduction

Parkinson's disease is a neurodegenerative disease that is accompanied by motor symptoms, psychiatric problems and sleep disorders. Four major motor symptoms that accompany Parkinson's disease are tremor, rigidity, bradykinesia and postural instability. Common psychiatric problems observed in Parkinson's disease are memory problems, low cognitive speed, depression and sleep disorders such as disturbances in rapid eye movement (REM) sleep or insomnia. In general, Parkinson's symptoms appear after the age of 50. In addition, Parkinson's disease is also an early warning sign of dementia. A sixfold increased risk of suffering dementia has been reported in patients with Parkinson's disease (Jankovic, 2008).

Clinical diagnosis of Parkinson's disease severity is mainly based on medical history and a neurological examination (Jankovic, 2008). It is believed that the neurodegenerative characteristics of Parkinson's disease are correlated with heart rate variability (HRV) indices. Some of the recent literature in this area has focused on the relationship between HRV, both short term and long term, and the severity of the disease. In this chapter, we

review the literature on how various short- and long-term indices of HRV have provided insights into the degeneration of the nervous system in patients with Parkinson's disease. We also present several methods for classifying Parkinson's disease based on features derived from HRV signals.

In recent years, a number of papers have focused on the correlations between the severity of Parkinson's disease and physiological signals such as HRV, which is regulated by the autonomic nervous system (ANS) (Meco et al., 1991; Mastrocola et al., 1999; Kallio et al., 2000, 2002; Haapaniemi et al., 2001; Devos et al., 2003; Bouhaddi et al., 2004; Pospíšil et al., 2008).

Pospíšil et al. evaluated autonomic cardiovascular regulation in patients with mild and advanced stages of Parkinson's disease using short-term measures of HRV (Pospíšil et al., 2008). Twenty-five patients participated in the study and were asked to undergo a short-term HRV recording of 5 min in the supine position with metronome-controlled breathing at a frequency of 0.33 Hz. The total power, power in the low-frequency (LF) band, power in the high-frequency (HF) band and the LF/HF ratio were evaluated. Their results showed a statistically significant decrease in the total power, power in both LF and HF bands of the HRV of the advanced severity group compared to same parameters computed from HRV of mild severity group. But the LF/HF ratio were not different in these groups.

Kallio et al. compared the differences in HRV parameters between untreated patients with Parkinson's disease ($n = 32$) and healthy controls ($n = 24$) (Kallio et al., 2002). The subjects were asked to perform standard cardiovascular reflex tests followed by a 10 min rest. Standard cardiovascular reflex tests include a rest phase, deep breathing, the Valsalva maneuver and tilt table test. HRV tests were conducted during both the reflex test and the 10 min rest. Kallio et al. concluded that both frequency domain and time domain HRV parameters revealed abnormalities in patients, whereas non-linear and geometrical measures did not. Among time and frequency domain features, the power in the HF band was the strongest independent variable that could discriminate patients from healthy controls ($p = .001$).

Mastrocola et al. performed HRV analysis on 24 h Holter ECG recordings to compare autonomic function between patients with Parkinson's disease and healthy subjects (Mastrocola et al., 1999). The study included 13 subjects with Parkinson's disease and 13 healthy controls. The HRV parameter standard deviation of normal-to-normal intervals (SDNN) and the powers of the LF and HF bands assessed over 24 h and divided into daytime and nighttime, were measured. There was a significant difference ($p < .05$) between the patient and control groups in SDNN and the power in the LF band in all three time periods. The power in the HF band differed significantly only for the nighttime.

Haapaniemi et al. (2001) performed 24 h ambulatory HRV analysis in 54 untreated patients with Parkinson's disease and 47 healthy subjects (Haapaniemi et al., 2001). Conventional (powers in very-low-frequency (VLF), LF and HF bands) and nonlinear HRV analyses (Poincaré plot parameters SD1, which quantifies the instantaneous beat-to-beat variability, and SD2, which quantifies the long-term continuous variability) were used for comparison. The results showed that three spectral components studied ($p < .01$) were significantly reduced in patients with Parkinson's disease compared to those of control subjects (Haapaniemi et al., 2001).

The HRV computed from ambulatory ECG has also been examined for diagnosing the severity of Parkinson's disease. Devos et al. analyzed time and frequency domain HRV during a 24 h period in three groups of subjects (control, mild and advanced Parkinson's disease). They found that diurnal LF power and ratio of LF/HF power decreased in the mild and advanced Parkinson's disease groups. The nocturnal vagal indicators, the HF power and percentage of differences between normal-to-normal intervals larger than 50 ms (pNN50) were decreased only in the advanced Parkinson's disease group (Devos et al., 2003).

In our literature review, we found that many researchers have focused on statistical analysis of HRV parameters obtained in the supine position (short record) or during daily activities (24 h record). Another type of study is concerned with HRV responses to various challenges to the ANS (Meco et al., 1991; Kallio et al., 2000, 2002; Haapaniemi et al., 2001; Devos et al., 2003; Bouhaddi et al., 2004). In this chapter, we will use the term "HRV trends" to represent the time series of HRV parameters obtained from consecutive fixed time intervals during a long-term observation period. We hypothesize that HRV trends may be more suitable for recognizing or classifying severity levels of ANS disease than using a set of HRV parameters measured at one time point only.

Several studies indicate that HRV parameters may discriminate between patients with different levels of Parkinson's disease during challenge tests (Meco et al., 1991; Kallio et al., 2000, 2002; Haapaniemi et al., 2001; Devos et al., 2003; Bouhaddi et al., 2004). In order to investigate and quantify this phenomenon, many researchers examined whether different levels of Parkinson's disease severity revealed varying levels of abnormalities during stimulation of the ANS (Meco et al., 1991; Kallio et al., 2000, 2002; Haapaniemi et al., 2001; Devos et al., 2003; Bouhaddi et al., 2004).

Previous literature focused on statistical comparison of HRV parameters among various Parkinson's disease severity levels. By contrast, we attempt to develop a strategy that can classify Parkinson's disease severity based on HRV parameters. Therefore, in this chapter, we aim to use variations in the HRV time series to classify Parkinson's disease severity by combining HRV analysis and pattern recognition (Lin et al., 2010).

The rest of this chapter is organized as follows. Section 22.2 introduces a detailed description of our experimental design. The proposed hybrid classification approach using the decision tree learning method and hybrid learning method is presented in Section 22.3. The results and discussion are presented in Section 22.4. Conclusions and suggestions for future work are presented in the last section.

22.2 Experimental Design

In order to examine the proposed HRV trends and hybrid approach for the classification of Parkinson's disease severity, a retrospective study with 47 Parkinson's disease subjects from a hospital in southern Taiwan (mean age $68.3 \pm SD 9.4$ years) was conducted. This research was approved by the Institutional Review Board of the hospital. Prior to the study, the experimental procedure was explained to all subjects and informed consent was obtained.

The severity of Parkinson's disease of the subjects in this research is described by Hoehn and Yahr scale (Hoehn and Yahr, 1967), which is presented in Table 22.1. The scale has five stages, but we grouped together some of the stages. These four groups were healthy normal subjects (Group I), stage I and stage II (Group II), stage III and stage IV (Group III) and stage V (Group IV) as described in the Hoehn and Yahr scale. Since all 47 subjects had Parkinson's disease, none belonged to Group I.

All subjects were asked to perform three successive challenge tests, including eyes open, eyes closed and deep breathing. These activities can be considered as stimuli to the ANS. All subjects' ECG signals were recorded throughout the whole procedure. The HRV indices derived from the ECG signals during the challenge test were employed as inputs to the proposed decision tree learning and hybrid learning methods to classify Parkinson's disease severity levels.

TABLE 22.1

Summary of the Hoehn and Yahr Scale

Stage	Description
Stage I	Symptoms are very mild and appear only on one side of the body
Stage II	Symptoms appear on both sides without impairment of balance
Stage III	Symptoms are mild-to-moderate. Some postural instability occurs, but patients are physically independent
Stage IV	Symptoms are severe. Patients are severely debilitated and need some assistance, but they can still walk or stand unassisted
Stage V	Symptoms are very severe. Patients are typically wheelchair-bound or confined to a bed, unless aided

22.3 Classification of Parkinson's Disease Severity Using Hybrid Classification Approach

This section presents the flowchart of the hybrid approach in the classification of Parkinson's disease severity. The proposed approach consists of two parts: (1) feature generation and (2) decision tree learning/hybrid learning. Algorithms employed in our research are presented below (Lin et al., 2010).

22.3.1 Feature Generation Method

The feature generation process results in a statistical feature vector that can represent HRV trends during the challenge tests. The features are generated following the segmentation of long-term ECG signal into consecutive 5 min windows with 50% overlap. All 5 min windows are then subjected to signal analysis to obtain eight HRV parameters, namely, SDNN, RMSSD (root mean square of successive differences of normal-to-normal intervals), NN50 and pNN50 in the time domain and VLF, LF, HF powers and LF-to-HF ratio in the frequency domain. Finally, we adopted the statistical features utilized by Picard et al. (2001) to represent the HRV trend of each parameter. The computing process is as follows: Let X denote the trend from any one of the eight HRV parameters and X_n denote the value of the n th 5 min window of the trend, where $n = 1, \dots, N$.

\tilde{X}_n is defined as the normalized signal:

$$\tilde{X}_n = \frac{X_n - \mu_X}{\sigma_X} \quad (22.1)$$

where μ_X and σ_X are the mean and the standard deviation of X as explained below. We computed the following seven statistics:

1. The mean of each trend,

$$\mu_X = \frac{1}{N} \sum_{n=1}^N X_n \quad (22.2)$$

2. The variance of each trend,

$$\sigma_x^2 = \frac{1}{N-1} \sum_{n=1}^N (X_n - \mu_x)^2 \quad (22.3)$$

- 3. The standard deviation of each trend
- 4. The mean of the absolute values of the first differences of each trend
- 5. The mean of the absolute values of the first differences of each normalized trend
- 6. The mean of the absolute values of the second differences of each trend
- 7. The mean of the absolute values of the second differences of each normalized trend

$$\tilde{\gamma}_x = \frac{1}{N-2} \sum_{n=1}^{N-2} |\tilde{X}_{n+2} - \tilde{X}_n| \quad (22.4)$$

After the feature generation process, HRV trends obtained from the physiological challenge test are transformed into a 56-dimensional (seven statistical features multiplied by eight HRV parameters) feature vector. The 56-dimensional feature vector is used as input to decision tree learning and hybrid learning algorithms to determine which index can be used for the determination of Parkinson's disease severity.

22.3.2 Decision Tree Learning Method

Through the decision tree learning method, one can discover the importance of individual features and identify logical relationships between subjects with different Parkinson's disease severity levels. In this research, a binary decision tree was constructed by repeated splits of the subsets of input data into two descendant subsets. The criterion for choosing a split is based on Gini's diversity index, a measure of node impurity (Breiman et al., 1993).

22.3.3 Hybrid Learning Method

The hybrid learning method employed in this research consists of feature selection, feature extraction and classifier construction processes. Feature selection and feature extraction processes are responsible for reducing the burden of the classifier and increasing the classification accuracy. More specifically, the purpose of feature selection process is to pick p features out of the original d features in order to produce fewer classification errors and ease the burden of computational complexity. The feature extraction process transforms the original m -dimensional feature vector into an n -dimensional subspace to achieve higher class separability. After feature selection and extraction processes, the classifier is responsible for classifying subjects with Parkinson's disease into different levels of severity. Next, technical aspects of these three processes are described.

22.3.3.1 Feature Selection

The feature selection process is comprised of a search strategy and a selection criterion. We adopted the best individual N (BIN) as the search strategy. In the BIN, a selection criterion

is individually applied to each of the features. The given criteria with larger values are selected. As the selection criterion, we adopted the kernel-based class separability (KBCS), which was originally developed by Wang (2008). The KBCS can be computed as follows: Let $(x, y) \in (\mathbb{R}^d Y)$ represent a sample, where \mathbb{R}^d denotes a d -dimensional feature space, Y symbolizes the set of class labels and the size of Y is the number of class c . This method projects samples onto a kernel space. \mathbf{m}_i^ϕ is the mean vector of the i th class in the kernel space, n_i is the number of samples in the i th class, \mathbf{m}^ϕ is the mean vector for all classes in the kernel space, \mathbf{S}_B^ϕ is the between-class scatter matrix in the kernel space and \mathbf{S}_W^ϕ is the within-class scatter matrix in the kernel space. Let $\phi(\cdot)$ be a possible non-linear mapping from the feature space \mathbb{R}^d to a kernel space κ , and let $\text{tr}(\mathbf{A})$ represent the trace of a square matrix \mathbf{A} . The following two equations are used in the class separability measure:

$$\begin{aligned}\text{tr}(\mathbf{S}_B^\phi) &= \text{tr} \left[\sum_{i=1}^c n_i (\mathbf{m}_i^\phi - \mathbf{m}^\phi)(\mathbf{m}_i^\phi - \mathbf{m}^\phi)^T \right] \\ &= \sum_{i=1}^c n_i \left[(\mathbf{m}_i^\phi - \mathbf{m}^\phi)(\mathbf{m}_i^\phi - \mathbf{m}^\phi)^T \right],\end{aligned}\tag{22.5}$$

$$\begin{aligned}\text{tr}(\mathbf{S}_W^\phi) &= \text{tr} \left[\sum_{i=1}^c \sum_{j=1}^{n_i} (\phi(x_{ij}) - \mathbf{m}_i^\phi)(\phi(x_{ij}) - \mathbf{m}_i^\phi)^T \right] \\ &= \sum_{i=1}^c \sum_{j=1}^{n_i} \left[(\phi(x_{ij}) - \mathbf{m}_i^\phi)^T (\phi(x_{ij}) - \mathbf{m}_i^\phi) \right].\end{aligned}\tag{22.6}$$

The KBCS is computed as

$$J^\phi = \frac{\text{tr}(\mathbf{S}_B^\phi)}{\text{tr}(\mathbf{S}_W^\phi)}.\tag{22.7}$$

22.3.3.2 Feature Extraction

The feature extraction process aims to transform a p -dimensional feature space to a t -dimensional subspace in order to achieve higher class separability and ease the burden of computational complexity. Principal component analysis (PCA) (Jackson, 1991) and linear discriminant analysis (LDA) (Martinez and Kak, 2001) were employed in the feature extraction process of the proposed hybrid learning method. Detailed descriptions of PCA and LDA methods are provided in the following sections.

22.3.3.2.1 Principal Component Analysis

PCA is often used to transform one set of variables into a smaller set and has been widely used in statistical data analysis, feature extraction and data compression. The PCA transforms a given set of correlated variables into a new set of uncorrelated variables that are called principal components (PCs). In addition to being uncorrelated, the PCs are

orthogonal and are ordered in terms of the variability they represent. Hence, PCA can be utilized to find a subspace whose basis vectors correspond to the maximum-variance directions in the original space.

Let \mathbf{W} denote the linear transformation mapping a p -dimensional space onto a g -dimensional feature subspace, where g is normally smaller than p . $y_i \in \mathbb{R}^g$ denotes g -dimensional feature vectors, and $x_i \in \mathbb{R}^p$ denotes p -dimensional feature vectors. The algorithm for computing PCA is as follows:

1. Compute the mean μ ,

$$\mu = \frac{1}{N} \sum_{i=1}^N x_i. \quad (22.8)$$

2. Calculate the covariance matrix \mathbf{C} ,

$$\mathbf{C} = \frac{1}{N} \sum_{i=1}^N (x_i - \mu)(x_i - \mu)^T. \quad (22.9)$$

3. Solve the following decomposition, where λ_i is the eigenvalue associated with the eigenvector e_i ,

$$\lambda_i e_i = \mathbf{C} e_i. \quad (22.10)$$

4. Sort the eigenvalues λ_i and their corresponding eigenvectors e_i in a descending order and then select the first g eigenvectors to compose \mathbf{W} ,

$$\mathbf{W} = \{e_i\}_{i=1}^g. \quad (22.11)$$

5. Finally, the PCA transformation is finished by

$$y_i = \mathbf{W}^T x_i. \quad (22.12)$$

22.3.3.2.2 Linear Discriminant Analysis

LDA is an unsupervised dimension reduction method utilized to transform one set of variables into a smaller set. In the feature space of this smaller set, the data distribution can achieve the objectives of maximizing between-class distance and minimizing within-class distance. The following are the equations for computing scatter matrices:

1. Within-class scatter matrix \mathbf{S}_W :

$$\mathbf{S}_W = \sum_{i=1}^N \sum_{j=1}^{n_i} (x_j^i - \mu_i)(x_j^i - \mu_i)^T, \quad (22.13)$$

where N is the number of classes, n_i is the number of samples in the i th class, $\mathbf{x}_j^i \in \mathbb{R}^d$ represents the j th sample of the i th class and $\boldsymbol{\mu}_i$ is the mean of class i .

2. Between-class scatter matrix \mathbf{S}_B :

$$\mathbf{S}_B = \sum_{i=1}^N n_i (\boldsymbol{\mu}_i - \boldsymbol{\mu}_{\text{all}}) (\boldsymbol{\mu}_i - \boldsymbol{\mu}_{\text{all}})^T, \quad (22.14)$$

where $\boldsymbol{\mu}_{\text{all}}$ is the mean of all classes.

The idea of the LDA is to seek a transformation matrix \mathbf{W} that maximizes Fisher's linear discriminant function $J(\mathbf{W})$:

$$J(\mathbf{W}) = \frac{\mathbf{W}^T \mathbf{S}_B \mathbf{W}}{\mathbf{W}^T \mathbf{S}_W \mathbf{W}}. \quad (22.15)$$

The transformation matrix \mathbf{W} is applied to maximize the ratio of the within-class scatter $\mathbf{W}^T \mathbf{S}_W \mathbf{W}$ and the between-class scatter $\mathbf{W}^T \mathbf{S}_B \mathbf{W}$ in the new feature space. Hence, a new feature vector \mathbf{y} can be obtained from the original feature vector \mathbf{x} by $\mathbf{y} = \mathbf{W}^T \mathbf{x}$. In general, the optimal \mathbf{W} satisfies the following equation:

$$\mathbf{S}_B \mathbf{W} = \lambda \mathbf{S}_W \mathbf{W}. \quad (22.16)$$

If \mathbf{S}_W is non-singular (or invertible), the column vectors of \mathbf{W} can be regarded as the eigenvectors of $(\mathbf{S}_W^{-1} \mathbf{S}_B)$. To apply LDA, one should note the following:

1. The maximum number of non-zero generalized eigenvectors is $N-1$, and thus an upper bound on the dimension of \mathbf{y} is $N-1$.
2. The number of samples should be greater than the dimension of samples and the number of classes to guarantee that \mathbf{S}_W does not become singular.

22.3.3.3 Classifier for Recognition

Finally, we used a k -nearest neighbor (k -NN) classifier (Cover and Hart, 1967) to distinguish the feature vectors belonging to various Parkinson's disease severity levels. The k -NN is one of the low-computation-complexity methods for pattern recognition, and the principle of k -NN is based on an intuitive concept that data points of the same class should be closer in the feature space. A given training dataset of n points with their desired class is specified as $\{(\mathbf{x}_1, y_1), (\mathbf{x}_2, y_2), \dots, (\mathbf{x}_n, y_n)\}$, where (\mathbf{x}_i, y_i) represents the data pair i , \mathbf{x}_i is the feature vector and y_i is the corresponding target class. Then for a new data point \mathbf{x} , the most likely class should be determined by k -NN ($k = 1$ in this study>):

$$1-\text{NN}(\mathbf{x}) = y_p, \quad (22.17)$$

where

$$p = \arg \min_i |\mathbf{x} - \mathbf{x}_i|^2. \quad (22.18)$$

Finally, we conduct fivefold cross-validations, tenfold cross-validations and leave-one-out cross-validations to validate the effectiveness and robustness of the classifier. For k -fold cross-validations, we partition the original dataset randomly into k subdatasets, use $k-1$ of the subdatasets to train the classifier and use the remaining subdataset to validate the effectiveness of the classifier. This procedure is repeated k times (k folds), with each of the k subdatasets used exactly once as the validation data. The average of the classification results from the folds represents the accuracy of the classifier.

22.4 Results and Discussion

So far we have described two independent procedures—the decision tree learning method and the hybrid learning method—that we used to classify the severity level of Parkinson's disease. In this section, we present our results. We start with results of the decision tree learning method.

22.4.1 Results of the Decision Tree Learning Method

The decision tree for classifying the subjects with (PD+) and without (PD-) Parkinson's disease is shown in Figure 22.1. The tree classifies various groups at the square nodes based on a series of questions about the features at triangular branching nodes. A "TRUE" answer to any question follows the branch upward, and a "FALSE" answer follows the branch downward. Features utilized in the decision tree learning method were generated from variation trends of the HRV indices computed using time domain and frequency domain parameters of the HRV. The three features utilized to distinguish subjects with and without Parkinson's disease were as follows:

1. The mean of the LF-to-HF ratio trend ($x4$)
2. The standard deviation of the VLF trend ($x9$)
3. The mean of the absolute values of the second differences of the pNN50 trend ($x42$)

The classification accuracy of the decision tree in Figure 22.1 was 91.49%, and Table 22.2 presents the confusion matrix of 47 subjects who were classified by the decision tree.

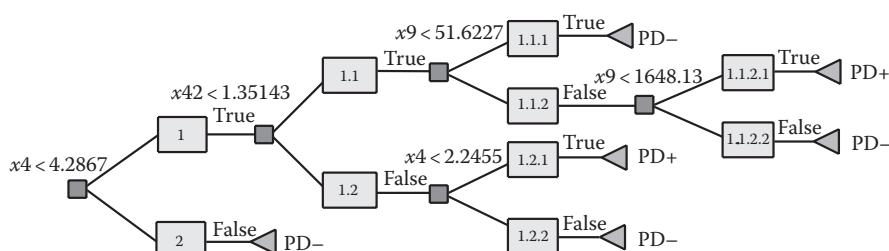


FIGURE 22.1

Decision tree using the HRV trends to distinguish the subjects with and without Parkinson's disease. (Adapted from Lin, C.W., Wang, J.S., and Chung, P.C., *IEEE Comput. Intell. Mag.*, 5, 50–58 © 2010 IEEE.)

TABLE 22.2

Confusion Matrix of 47 Subjects Who Were Classified by the Decision Tree in Figure 22.1

Classification Accuracy: 91.49%		Physician's Diagnosis	
Classified results	PD	PD	PD free
		30	2
PD free	2	13	
	Sensitivity = 93.75%		Specificity = 86.67%

TABLE 22.3

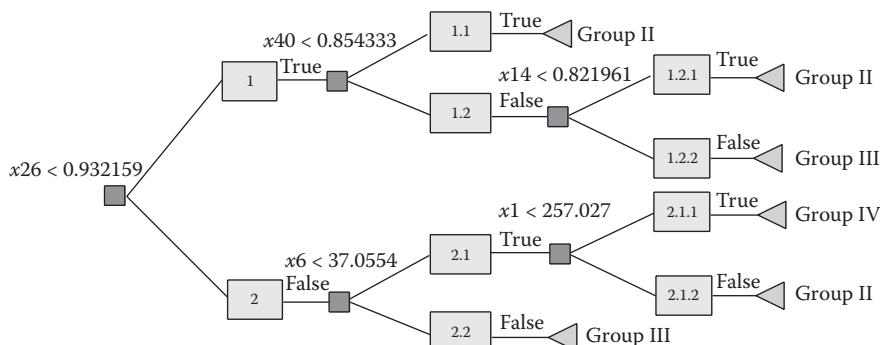
Classification Conditions of Four Misclassified Subjects Who Were Classified by the Decision Tree in Figure 22.1

Misclassified Subjects	Doctor's Judgments	Classified Results by the Decision Tree	Triangular Branching Nodes
1	PD	PD free	$x_4 < 4.2867$
2	PD	PD free	$x_4 < 4.2867$
3	PD free	PD	$x_9 < 51.6227$
4	PD free	PD	$x_9 < 51.6227$

The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the confusion matrix are also shown in Table 22.2. This tree misclassified 4 out of 47 subjects. Table 22.3 summarizes classification conditions of those four misclassified subjects, and the last column specifies triangular branching nodes on which subjects were misclassified by the tree.

The decision tree for classifying subjects with different severity levels of Parkinson's disease (Group II, Group III and Group IV) is shown in Figure 22.2. The five features utilized to distinguish subjects with different severity levels of Parkinson's disease were as follows:

1. The mean of the VLF band power trend (x_1)
2. The mean of the RMSSD trend (x_6)
3. The standard deviation of the RMSSD trend (x_{14})

**FIGURE 22.2**

The decision tree using the HRV trends to distinguish among groups suffering from Parkinson's disease. (Adapted from Lin, C.W., Wang, J.S., and Chung, P.C., *IEEE Comput. Intell. Mag.*, 5, 50–58 © 2010 IEEE.)

4. The mean of the absolute values of the first differences of the normalized LF band power trend (x_{26})
5. The mean of the absolute values of the second differences of the RMSSD trend (x_{40})

The classification accuracy of the constructed tree in Figure 22.2 was 93.75%. Table 22.4 presents the confusion matrix of 32 subjects classified by the decision tree. This tree misclassified 2 out of 32 subjects. Table 22.5 summarizes the classification conditions of these two misclassified subjects, and the last column specifies the triangular branching nodes on which the subjects were misclassified by the tree.

These conditions assigned to the misclassification, as shown in Figures 22.1 and 22.2, are considered reasonable and acceptable to physicians, although there may be some false negatives. In the case of classifying subjects with different severity levels, two misclassified subjects were outliers. Table 22.6 compares the first misclassified subject (Subject ID: TSL) with other subjects in Group II by means of various HRV trends, and Table 22.7 compares the second misclassified subject (Subject ID: CLH) with other subjects in Group IV by means of various HRV trends. The visual presentation of Tables 22.6 and 22.7 and two outliers are shown in Figures 22.3 and 22.4.

TABLE 22.4

Confusion Matrix of 32 Subjects Who Were Classified by the Decision Tree in Figure 22.2

Overall Classification Accuracy: 93.75%		Physician's Diagnosis			Classification accuracy
		Group II	Group III	Group IV	
Classified results	Group II	8	0	1	88.88%
	Group III	0	19	0	100%
	Group IV	1	0	3	75%

Source: Adapted from Lin, C.W., Wang, J.S., and Chung, P.C., *IEEE Comput. Intell. Mag.*, 5, 50–58 © 2010 IEEE.

TABLE 22.5

Classification Conditions of Two Misclassified Subjects Who Were Classified by the Decision Tree in Figure 22.2

Misclassified Subjects	Doctor's Judgments	Classified Results by the Decision Tree	Triangular Branching Nodes
1	Group II	Group IV	$x_1 < 257.027$
2	Group IV	Group II	$x_{40} < 0.854333$

TABLE 22.6

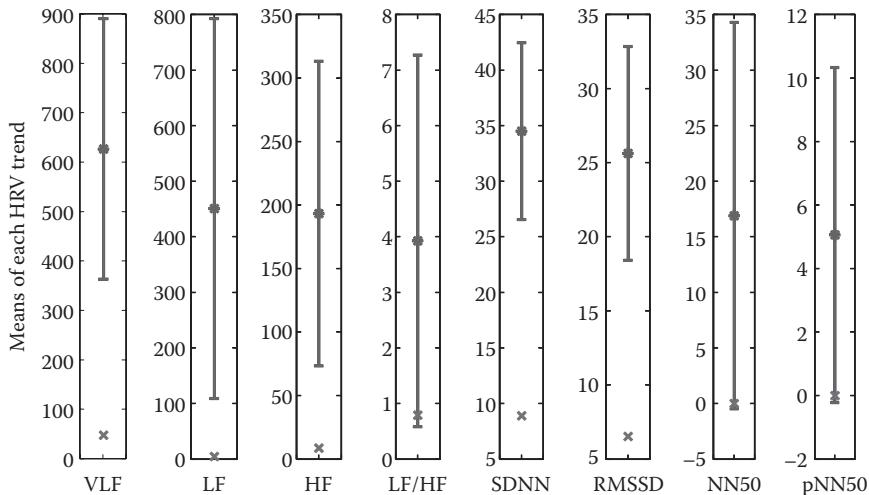
Comparison between a misclassified subject (TSL) and the Other Subjects in Group II

	VLF	LF	HF	LF/HF	SDNN	RMSSD	NN50	pNN50
TSL	49.03	4.96	8.78	0.80	8.92	6.54	0	0
Means (Group II)	628.11	451.01	193.35	3.93	34.51	25.63	16.91	5.06
Standard deviations (Group II)	263.77	341.56	119.89	3.35	7.94	7.21	17.38	5.27

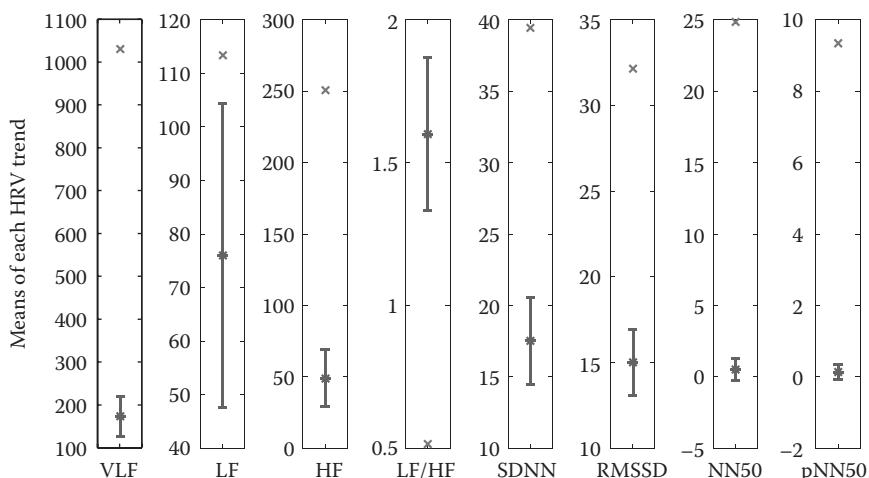
TABLE 22.7

Comparison between a misclassified subject (CLH) and the Other Subjects in Group IV

	VLF	LF	HF	LF/HF	SDNN	RMSSD	NN50	pNN50
CLH	1032.07	113.39	250.74	0.52	39.45	32.17	24.86	9.35
Means (Group IV)	174.83	76.02	49.03	1.60	17.53	15.02	0.52	0.14
Standard deviations (Group IV)	47.02	28.42	19.97	0.27	3.03	1.93	0.74	0.20

**FIGURE 22.3**

Visualized statistical presentation of Table 22.9. Stars and bars: the means and the standard deviations of the parameter excluding the first misclassified subject TSL (denoted by a cross). (Adapted from Lin, C.W., Wang, J.S., and Chung, P.C., *IEEE Comput. Intell. Mag.*, 5, 50–58 © 2010 IEEE.)

**FIGURE 22.4**

Visualized statistical presentation of Table 22.10. Crosses: the second misclassified subject CLH. Stars and bars: the means and the standard deviations of the other subjects in Group IV. (Adapted from Lin, C.W., Wang, J.S., and Chung, P.C., *IEEE Comput. Intell. Mag.*, 5, 50–58 © 2010 IEEE.)

In addition to using both time and frequency domain HRV trends in the classification of Parkinson's disease severity, our research also attempted to construct the tree using only time domain HRV trends. However, the performance was worse than that using the trees constructed using both time and frequency domain HRV trends. Tables 22.8 and 22.9 present results of using the decision tree learning method with time domain HRV trends in the classification of subjects with and without Parkinson's disease and subjects with different severity levels of Parkinson's disease, respectively. The classification accuracy rates in Tables 22.8 and 22.9 are 91.5% and 84.4%, which are equal to/lower than the rates 91.5% and 93.8% shown in Tables 22.2 and 22.4, respectively.

We also tried to construct trees using only frequency domain HRV trends. The confusion matrix of the tree constructed using frequency domain HRV trends for investigating the differences in HRV trends between subjects with and without Parkinson's disease is the same as in Table 22.2. This is because most features shown in Figure 22.1 were from the frequency domain HRV trends, and only one of the features was from the time domain HRV trends. Hence, both sets of results have the same confusion matrix. However, as shown in Table 22.10, the classification accuracy of the tree constructed using the frequency domain parameters was 84.4%. This performance was worse than the 93.8% accuracy of the tree constructed using both time and frequency domain features (Table 22.4).

Overall, the performance of the trees constructed using only time domain features or only frequency domain features did not achieve the same level of performance as that of trees constructed using both time and frequency domain features. We believe these results highlight the importance of using both time and frequency domain features in the classification of the severity levels of Parkinson's disease.

TABLE 22.8

Confusion Matrix of the Constructed Decision Tree by the Time Domain Features for Investigating the Differences in the HRV Trends between the Subjects with and without Parkinson's Disease

Classification Accuracy: 91.5%		Physician's Diagnosis		
Classified results	PD	PD	PD free	PPV = 100%
		32	0	NPV = 73%
	PD free	4	11	
			Sensitivity = 88.9%	Specificity = 100%

TABLE 22.9

Confusion Matrix of the Constructed Decision Tree by the Time Domain Features for Investigating the Differences in the HRV Trends between the Groups That Suffered from Parkinson's Disease

Overall Classification Accuracy: 84.38%		Physician's Diagnosis			Classification accuracy
Classified results	Group II	Group II	Group III	Group IV	
		7	2	0	77.78%
	Group III	0	19	0	100%
	Group IV	0	3	1	25%

TABLE 22.10

Confusion Matrix of the Constructed Decision Tree by Frequency Domain Features for Investigating Differences in HRV Trends between the Groups That Suffered from Parkinson's Disease

		Overall Classification Accuracy: 84.38%			Classification accuracy
		Group II	Group III	Group IV	
Classified results	Group II	8	1	0	88.88%
	Group III	0	19	0	100%
	Group IV	1	3	0	0%

Source: Adapted from Lin, C.W., Wang, J.S., and Chung, P.C., *IEEE Comput. Intell. Mag.*, 5, 50–58 © 2010 IEEE.

The suitability of features selected by the decision tree learning method is supported by other papers in the literature. Three studies (Kallio et al., 2000, 2002; Haapaniemi et al., 2001) have indicated that the VLF band power and pNN50 presented significant differences (i.e., $p < .05$) between subjects free of Parkinson's disease and patients affected by Parkinson's disease. Their results correlate with the decision tree in Figure 22.1 since the standard deviation of the VLF trend (x_9) and the mean of the absolute values of second differences of the pNN50 trend (x_{42}) were utilized in the classification. In addition, the LF-to-HF ratio was nearly significant ($p = .089$ and $p = .0687$) between subjects free of Parkinson's disease and subjects diagnosed with Parkinson's disease (Kallio et al., 2000, 2002). The mean of the LF-to-HF ratio trend (x_4) can be regarded as an extension of the LF-to-HF ratio, which represents the balance between sympathetic and parasympathetic branches of the ANS. This feature was also selected as the criterion to discriminate between healthy subjects and patients with Parkinson's disease. Our research reveals that pNN50, VLF band power and LF-to-HF ratio can be strong indicators for distinguishing between healthy subjects and patients with Parkinson's disease.

It can be noted that during classification of subjects with different severity levels of Parkinson's disease, most of the features from the tree in Figure 22.2 are statistical features that describe RMSSD trend (i.e., x_6 , mean of the RMSSD trend; x_{14} , standard deviation of the RMSSD trend; and x_{40} , mean of the absolute values of the second differences of the RMSSD trend). RMSSD is calculated by a root mean square of the differences between the consecutive RR intervals. Since RMSSD is an estimation of the short-term components of HRV, we conclude that three groups (i.e., Group II, Group III and Group IV) mainly differ due to short-term components of HRV. Other features from the tree in Figure 22.2 denoted as the mean of VLF band power trend (x_1) and the mean of absolute values of first differences of normalized LF band power trend (x_{26}) have a high correlation with VLF band power and LF band power, respectively. In one study (Devos et al., 2003), the LF band power which represents an index of both sympathetic and parasympathetic activities showed a significant difference between different severity levels of Parkinson's disease. Thus, utilizing the x_{26} feature to distinguish different severity levels of Parkinson's disease is reasonable. Although there is no explicit physiological mechanism responsible for the VLF band power, it provides good discriminatory capacity to identify and characterize different severity levels of Parkinson's disease. From these results, one can conclude that

the VLF band power plays a crucial role in classifying the severity of Parkinson's disease. It may be prudent to examine if there is a correlation between the power in the VLF band and the severity of Parkinson's disease in a future study.

22.4.2 Results with the Hybrid Learning Method

We used different combinations of feature selection and extraction methods. Table 22.11 shows the average recognition rates of three different combinations of feature selection and extraction methods by a fivefold cross-validation. The results of Table 22.11 show that the hybrid learning method (KBCS+PCA+LDA+k-NN classifier) outperformed other combinations of feature selection and extraction methods. In order to test the robustness of the proposed hybrid learning method, fivefold cross-validation, tenfold cross-validation and leave-one-out cross-validation were executed (Table 22.12).

Table 22.13 illustrates the effectiveness of feature selection process (KBCS) that we employed. The feature selection process is expected to produce fewer classification errors and reduced computational complexity. KBCS not only reduced the number of features from 56 to 34 but also increased the recognition rates from 76.3% to 91.1%. In conclusion, the results in Tables 22.11 and 22.12 successfully validated the effectiveness of using both PCA and LDA in the feature extraction process and confirmed the efficiency of the feature selection process.

TABLE 22.11

Average Recognition Rates in Different Combinations of Feature Selection and Extraction Methods in a Fivefold Cross-Validation

Feature selection methods	KBCA	KBCS	KBCS
Feature extraction methods	PCA+LDA	LDA	×
Average recognition rate	91.1%	77.1%	74.3%

TABLE 22.12

Average Recognition Rates of HRV-Trend-Based Recognition Strategy for Fivefold Cross-Validation, Tenfold Cross-Validation and Leave-One-Out Cross-Validation

Methods	Fivefold Cross-Validation	Tenfold Cross-Validation	Leave-One-Out Cross-Validation
Average recognition rates of hybrid learning method	91.1%	98%	100%

TABLE 22.13

Number of Utilized Features and the Average Recognition Rates by a Fivefold Cross-Validation between the HRV-Trend-Based Recognition Strategies with and without Using Feature Selection Process

Methods	Hybrid Learning Method	Hybrid Learning Method without Using Feature Selection Process
Number of utilized features	34	56
Average recognition rates	91.1%	76.3%

22.5 Conclusions and Suggestions for Future Work

HRV analysis is an effective non-invasive measure of neuroregulatory control of the cardiac function. It is currently being adopted in studies involving the diagnosis and classification of chronic conditions such as Parkinson's disease. Much of the research reported in the literature has examined the relationship between Parkinson's disease and HRV parameters, especially using statistical analysis of short-term data. Our research found that long-term monitoring of HRV trends helps to identify important features for classifying the severity of Parkinson's disease. In this chapter, we have proposed an effective hybrid classification approach using variations in HRV time series indices for the diagnosis and classification of the severity of Parkinson's disease. In addition, we also adopted specific feature selection techniques (KBCS) and feature extraction procedures (PCA+LDA) to develop a hybrid learning method. Our empirical results have validated the effectiveness and robustness of the proposed hybrid classification approach with a satisfactory classification accuracy. Our team consisting of engineers, computer scientists and neurologists believes that the proposed method has potential clinical applications. We plan to explore these quantitative procedures further for refining the classification and diagnosis of Parkinson's disease.

Abbreviations

ANS	Autonomic nervous system
BIN	Best individual N
ECG	Electrocardiogram
HF	High-frequency
HRV	Heart rate variability
KBCS	Kernel-based class separability
LDA	Linear discriminant analysis
LF	Low-frequency
PCA	Principal component analysis
PCs	Principal components
REM	Rapid eye movement
SDNN	Standard deviation of normal-to-normal intervals
VLF	Very-low-frequency

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23

Heart Rate Variability in Neuropsychiatric Disorders

Brook L. Henry

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23.1 Introduction

Neuropsychiatric disorders represent one of the leading causes of disability in the United States and Canada. One in four American adults suffers from a diagnosable mental disorder in a given year (Kessler et al., 2005). According to a recent study conducted by the World Health Organization, the World Bank and Harvard University, mental illness constitutes over 15% of the disease burden in developed market economies (World Health Organization, 2008). Health-care expenditures for mental disorders have risen dramatically in the United States: between 1996 and 2006, the cost of treating neuropsychiatric disorders increased from \$35.2 to \$57.5 billion, while the number of treated individuals rose from 19.3 to 36.2 million (Soni, 2009).

The widespread prevalence of neuropsychiatric illness is of particular concern, given the significant association between these disorders and elevated levels of morbidity and mortality. In schizophrenia (SCZ) patients, the mortality rate is estimated to be two to four times higher than that of the comparison groups, with a life expectancy reduced by 15–25 years (Brown et al., 2000; Colton and Manderscheid, 2006). Apart from suicide, cardiovascular disease is the most frequent cause of death in this population (Colton and Manderscheid, 2006). Similar to SCZ, a considerable body of evidence demonstrates a strong bidirectional association between mood disorders and cardiovascular diseases (Grippo and Johnson, 2009), suggesting that the presence of cardiac dysfunction influences affective states, while mood-related psychopathology contributes to the probability of detrimental cardiac events. In addition, anxiety disorders may also be implicated in the

development of cardiovascular pathology such as coronary artery disease (Vogelzangs et al., 2010).

While risk factors for adverse cardiac events include metabolic syndrome, sedentary behavior and smoking (Raedler, 2010), a growing body of evidence suggests that the dysfunction of the autonomic nervous system (ANS) may play a significant role in cardiovascular diseases (Lahiri et al., 2008; Thayer et al., 2010). ANS function is regulated by two major branches: (1) the sympathetic nervous system (SNS), which drives the energy mobilization required for a response to a threatening stimulus, including elevated heart rate and blood glucose; and (2) the parasympathetic nervous system (PNS), which promotes vegetative and restorative functions. A substantial literature indicates that a wide array of neuropsychiatric disorders and psychopathological states, including aggression, hostility, depression and anxiety, are characterized by ANS dysregulation marked by PNS suppression and reduced vagal cardiac tone (Beauchaine, 2001). Increased SNS activity and reduced PNS function have also been linked to cardiovascular pathology, including a greater risk of sudden cardiac death (Lahiri et al., 2008). While a variety of measures have been proposed to assess the ANS output, significant emphasis has been placed on the use of heart rate variability (HRV) as an effective, non-invasive and inexpensive method to appraise autonomic activity (Kleiger et al., 2005). Over the past decade, HRV has been increasingly utilized as an indicator of autonomic abnormalities and even proposed as a marker of cognitive impairment in severe mental illness (Thayer and Lane, 2009a).

The objective of this chapter is to review the findings that describe linear and non-linear measures of HRV in psychiatric populations. While the relationship between unipolar depression, autonomic function and cardiovascular disorders has been extensively documented over the past couple of decades, this review focuses on the recent work that details emerging evidence of HRV abnormalities in SCZ, bipolar disorder (BD), anxiety disorders and pathologies such as post-traumatic stress disorder (PTSD).

23.2 ANS Function and HRV

ANS activity represents a critical interface between the central nervous system (CNS) and the body, regulating physiological, cognitive, affective and behavioral responses to external events (Thayer et al., 2009). HRV, the quantification of beat-by-beat variation in cardiac rhythm, constitutes a sensitive measure of ANS function (Low and Pfeifer, 1997) and has been used as a tool to assess the effect of psychopathology on the balance between sympathetic and parasympathetic inputs to the heart.

In many physiological processes, including HRV, healthy activity is characterized by more complex variability, reflecting the interaction of multiple ongoing processes, whereas pathological states are marked by high predictability and reduced flexibility (Friedman, 2007). Healthy individuals exhibit a high degree of HRV, reflecting the ability to adapt quickly to the physical or psychological demands of the environment. By contrast, decreased HRV is hypothesized to reflect a maladaptive response to environmental stressors or indicate explicit myocardial damage that is often characterized by parasympathetic suppression and sympathetic overactivation (Berntson et al., 1997; Carney et al., 2005). While theories of neural control over fluctuations in cardiac activity were proposed during the 1800s (reviewed in Anrep et al., 1936), the relationship between HRV and psychological states was not investigated systematically until the late 1960s, supported by the advent of

the polygraph in academic laboratories (reviewed in Porges, 2007). Early studies tended to treat HRV as (1) a trait-like variable reflecting a “temperament” or consistent behavioral response to external stimuli, (2) an indicator of mental effort or attentional processes and (3) a response controlled by a conditioned stimulus in operant paradigms (Porges, 2007) using distinct experimental approaches.

Over the past 15 years, several groups have attempted to develop comprehensive paradigms that describe the interaction between neural structures and myocardial function to model the effect and role of ANS in psychopathology (Beauchaine, 2001; Porges, 1995; Thayer and Lane, 2000). The polyvagal theory developed by Porges (1995) is predicated on the concept that evolutionary development of the mammalian ANS produced specific neurophysiological substrates that control affective processes mediating social interaction. Porges specifies two sources of vagal input to the heart that terminate on the cardiac sinoatrial (SA) node: one originating in the dorsal motor nucleus (DMN) and the other from the nucleus ambiguus (NA) (Porges, 1995). The DMN vagal branch represents a phylogenetically older system shared with reptiles and acts to reflexively slow the heart rate, representing an immobilization response (freezing when threatened). By contrast, the uniquely mammalian vagal input from the NA mediates attentional and emotional responses that motivate social communication, self-soothing and calming behaviors linked to facial expression and vocalization. Consequently, Porges proposes that dysfunction of the NA vagal branch results in impaired regulation of visceral homeostasis and compromised social behaviors that characterize psychiatric disorders such as SCZ (Porges, 2007).

Beauchaine (2001) outlined a model of ANS functioning in psychopathological states that involves both SNS and PNS, by combining the polyvagal paradigm with Gray's motivational theory. Gray (1982) proposed that behavior is primarily regulated by three distinct, but inter-dependent, brain systems: (1) the fight/flight (F/F) system, including structures such as the amygdala and ventromedial hypothalamus; (2) the behavioral activation system (BAS), delineated by a midbrain dopaminergic pathway that modulates attempts to maximize rewards (approach behaviors) and minimize punishments (avoidance response); and (3) the behavioral inhibition system (BIS), consisting of serotonergic output from the raphe nucleus and noradrenergic output from the locus coeruleus, a network that mediates aversive responses such as passive avoidance and extinction. Beauchaine suggests that both the BIS and BAS systems are regulated by the SNS, as demonstrated by studies describing SNS-mediated skin conductance activity during both punishment avoidance and active reward response (Beauchaine, 2001). By contrast, the F/F system is directly affected by the PNS. In summary, motivational functioning (represented by the BIS and BAS under SNS control) and regulational functioning (represented by the PNS modulation of F/F responses) combine to mediate ANS control over emotional states existing in a broad array of psychiatric disorders.

A third group has developed a model of neurovisceral integration, where a series of neural structures are proposed to regulate autonomic, affective and cognitive functions related to HRV (Thayer et al., 2009). This paradigm emphasizes the importance of inhibitory brain mechanisms that regulate the central autonomic network (CAN), a series of structures that include the prefrontal cortex (PFC), the central nucleus of the amygdala, hypothalamus, the NA and the nucleus of the solitary tract (NTS). The primary output of the CAN is mediated through pre-ganglionic sympathetic and parasympathetic neurons that innervate the heart via stellate ganglia and vagus nerve, respectively. In this model, the PFC is proposed to regulate ANS function by inhibiting the amygdala. The amygdala, which plays a critical role in mediating an individual's response to stress, acts

to suppress parasympathetic activity by inhibiting vagal pathways originating in the NA and DMN (Thayer and Lane, 2009b). Disorders such as depression, SCZ and BD are characterized by a decrease in PFC activity and concomitant deficits in behavioral and cognitive inhibition, as assessed by clinical rating scales and neuropsychological testing (Bora et al., 2009; Thayer and Lane, 2009b). Proponents of the neurovisceral integration model contend that decreases in HRV associated with neuropsychiatric disorders are mediated via the same mechanism, caused by the failure of a damaged frontal cortex to control subcortical structures such as the amygdala, thus resulting in reduced parasympathetic function. It has also been suggested that the activity in this network of neural structures should be assessed from the perspective of nonlinear dynamics (Thayer and Lane, 2000), also known as chaos theory, where ostensibly random variability is actually generated by well-defined non-linear functions.

HRV has traditionally been assessed by quantifying the variance in time domain and frequency domain categories. Common time domain measures include the standard deviation of all RR intervals (SDNN), the root mean square of successive RR differences (RMSSD) and the percentage of adjacent RR intervals that differ by more than 50 ms (pNN50). Frequency domain analysis of the cardiac rhythm can also reveal the relative contribution of the parasympathetic activity as measured by the high-frequency (HF) signal. However, over the past decade, there has been an increasing emphasis on applying non-linear analyses to characterize the variability in cardiovascular processes, including the use of detrended fluctuation analyses, approximate entropy, sample entropy, Poincaré plots and symbolic dynamics (Todder et al., 2005; Voss et al., 2006). Some evidence suggests that non-linear methods may be superior predictors of cardiac dysfunction, including ventricular tachycardia and sudden cardiac death (Baumert et al., 2004; Hoyer et al., 2006), when compared to the traditional time domain and frequency domain analyses. Similar to the traditional time domain HRV measures, higher values of entropy indicate more variability and complexity in the data, while lower values suggest greater regularity in the cardiac rhythm (Richman and Moorman, 2000).

A substantial body of literature demonstrates that the measurement of HRV has significant clinical utility in assessing cardiovascular risk (Kleiger et al., 2005). Lower HRV and impaired vagal tone (as indicated by reduction in SDNN, RMSSD and HF power) have been associated with dilated and hypertrophic cardiomyopathies (Evrangul et al., 2006; Fauchier et al., 1997; Karcz et al., 2003; Piccirillo et al., 2002) as well as elevated mortality following myocardial infarction (Kleiger et al., 2005). Similarly, heartbeat complexity, as quantified by non-linear dynamical measures such as sample entropy, is also decreased in individuals with cardiomyopathy (Batchinsky et al., 2007, 2009; Claria et al., 2008; Lake et al., 2002). In support of the neurovisceral integration theory, several recent reports have also shown that lower HRV is linked to impaired cognitive performance indicative of prefrontal dysfunction in samples of military and police personnel (Thayer et al., 2009). Hansen et al. (2003) observed that male sailors with low HRV (RMSSD values below the sample median) exhibited significantly worse sustained attention and working memory compared to participants with higher HRV. In a similar fashion, subjects who show reduced HRV also demonstrate impaired inhibition on the Stroop and Go/No-Go tasks relative to individuals with higher cardiac variability (Thayer et al., 2009). HRV is also positively correlated with situational awareness (i.e., improved performance in a shooting simulator exercise performed by police cadets) (Saus et al., 2006), suggesting that this measure may be utilized effectively in research studies with strong ecological validity (where the methods and setting of the study are designed to approximate the real-life situation under investigation).

In summary, HRV is a measure of ANS activity modulated by a complex network of brain structures that regulate adaptive responses to the environment. While various models have been proposed to elucidate the intricate interaction between neural factors, autonomic activity and myocardial function, the nature of these relationships requires further study. Previous work has shown that HRV may predict the types of cardiovascular dysfunction and cognitive impairment frequently associated with psychopathological states. The following sections review recent studies that examine time domain, frequency domain and non-linear measures of HRV in a variety of neuropsychiatric disorders.

23.3 HRV and SCZ

SCZ is a chronic disorder that affects approximately 1% of the population (McGrath et al., 2008) and is characterized by profound disruption in emotion and cognition, and by significant social and occupational impairment. The array of symptoms, while wide-ranging and diverse, frequently includes psychotic manifestations such as prominent hallucinations, delusions or disorganized behavior (APA, 1994). Symptoms are typically divided into two categories: positive symptoms (e.g., delusions and hallucinations) are described as an excess or distortion of normal functions, while negative symptoms (avolition and affect flattening) reflect a loss or diminution of normal activity. SCZ has long been associated with abnormal ANS function, classically characterized as a prominent sympathetic hyperarousal marked by dilated pupils, moist palms and elevated blood pressure (Sadock and Sadock, 2000). Over the past several decades, the autonomic function in this population has been quantified with a variety of measures, including galvanic skin responses, heart rate, pupil reactivity and orienting responses to novel stimuli (Zahn et al., 1991). The most common older measures were assessment of electrodermal activity, heart rate and pupil function. Many studies have observed elevated heart rate in drug-free patients with chronic SCZ, acute SCZ and childhood-onset SCZ (Zahn et al., 1975, 1981, 1997) compared to controls. In addition, a substantial number of reports show that SCZ individuals demonstrate elevated basal skin conductance, but reduced conductance responses to orienting stimuli, signifying an elevated but inflexible level of baseline SNS activity (Dawson et al., 1994). Finally, pupillometry studies have reported decreased light reactions and reduced response latencies in SCZ (larger pupil diameter and reduced pupil amplitude alterations following light exposure), indicating both an elevated sympathetic activity and a deficit of parasympathetic input (Bar et al., 2008a; Steinhauer and Hakerem, 1992). It is also relevant to note that many of these findings were conducted in medication-free patients, suggesting that ANS dysregulation can exist independently of drug effects (Zahn and Pickar, 2005).

Data illustrating that HRV may be used as a predictor of mortality in cardiovascular disorders (Kleiger et al., 1987) motivated interest in utilizing this technique as a measure of ANS dysregulation in a variety of diseases (Kleiger et al., 2005). While early studies observed discrepant findings of HRV in SCZ (Malaspina et al., 1997; Rechlin et al., 1994a), a series of reports over the past 10 years have confirmed that this disorder is reliably characterized by impaired cardiac variability (Bar et al., 2005, 2007; Boettger et al., 2006; Chang et al., 2009; Valkonen-Korhonen et al., 2003). Bar et al. (2005) compared the HRV performances of 30 medication-free paranoid SCZ participants with an equal number of matched controls during a 5 min rest period; they observed that the SCZ

patients exhibited significantly reduced HF power and reduced RMSSD, but no difference in LF power, indicating suppression of parasympathetic activity, but no evidence of sympathetic changes. RMSSD values were also lower than that of controls during a deep breathing test (six deep breaths per minute), but the HRV values did not change significantly after 2–3 days of neuroleptic treatment. These findings were replicated by Boettger et al. (2006), who assessed HRV over a 24 h period. Compared to control subjects, 20 unmedicated paranoid SCZ patients demonstrated reduced RMSSD and lower SDANN (reduced variability over time in 5 min mean RR intervals) during the total recording period, as well as decreased nocturnal vagal activity. Additional reports have also confirmed elevated low frequency/high frequency (LF/HF) ratios in SCZ participants compared to healthy controls, providing further evidence of a relative decrease in parasympathetic cardiac tone in SCZ (Chang et al., 2010).

Dysregulation of HRV activity has also been observed in SCZ patients exposed to stressors (Castro et al., 2008; Valkonen-Korhonen et al., 2003). During exposure to a mental arithmetic task (subtracting serial 7s from 700), both SCZ subjects and normal controls demonstrated increased arousal as indicated by reduced HRV and elevated LF signal; however, upon task completion, while healthy subjects quickly returned to a resting state (higher vagal activity), SCZ participants exhibited an extended period of arousal characterized by continued suppression of HF power and higher LF power; these data suggest that SCZ individuals have difficulty “switching off” the cardiovascular autonomic response to a stressor. Valkonen-Korhonen and colleagues (2003) reported that healthy controls, but not individuals with psychosis (including both SCZ and psychotic depression participants), exhibited reduced HRV with tasks that required successively greater mental load (e.g., responding to a tone or performing the Wisconsin Card Sorting Task). They posit that the failure to adapt HRV in response to varying cognitive demands indicates that acute psychosis is marked by a limited autonomic capacity to respond to environmental challenges.

In recognition of the fact that cardiac rhythms are influenced by dynamical systems that are not limited to linear output, a number of reports over the past 5 years have utilized non-linear measures to quantify HRV complexity in SCZ (Bar et al., 2006; Boettger et al., 2006; Chang et al., 2009). Bar et al. (2007) evaluated HRV in a non-medicated SCZ sample using multiple non-linear techniques, including compression entropy, symbolic dynamics, approximate entropy and fractal dimension. They observed that all of these measures indicated reduced complexity and greater predictability in RR interval data in 20 SCZ patients compared to controls, during a 30 min rest period, suggesting again that SCZ individuals are characterized by an inability to adapt to different environmental requirements. Beottger et al. (2006) reported a similar finding, observing decreased RR complexity in an SCZ group using a novel autonomic information flow approach. A subsequent study (Bar et al., 2008a) observed that higher HRV compression entropy (a marker of cardiac parasympathetic activity) negatively correlated with pupil constriction latency (a marker of pupillary parasympathetic activity) in control subjects, while the opposite relationship was observed in SCZ patients. This effect could depend on the differences in the relative SNS–PNS balance between the pupil and cardiac functions. Finally, Chang et al. (2009) conducted a hierarchical cluster analysis between time domain, frequency domain and non-linear HRV measures (sample entropy and corrected Shannon entropy) and observed that LF/HF ratio formed a discrete cluster with sample entropy. These results underscore the utility of assessing both linear and non-linear measures of HRV and support the concept that they may be quantifying the same underlying pathologies.

Some recent work has indicated that HRV abnormalities may extend to relatives of SCZ patients (Bar et al., 2009; Berger et al., 2010; Castro et al., 2009). Bar et al. (2009) assessed HRV in 36 first-degree relatives (18 siblings and 18 offspring) of paranoid SCZ patients. They observed that the SCZ relative group demonstrated an attenuated, yet identical pattern compared to patients, exhibiting significantly reduced RMSSD and decreased compression entropy compared to healthy controls. A subgroup comparison between SCZ siblings and offspring suggested a higher degree of heritability in the children of SCZ patients. Berger et al. (2010) reported that a sample of healthy first-degree SCZ relatives demonstrated significantly reduced approximate entropy compared to normal controls, after accounting for variation in age and smoking. The SCZ patient sample (medication-free) also exhibited decreased HRV compared to their relatives, indicating a potential gene-dose response. Finally, Castro et al. (2009) observed that clinically unaffected first-degree SCZ relatives exhibited a similar HRV response to an arithmetic stressor compared to SCZ patients; both demonstrated parasympathetic suppression during the recovery period. These data suggest that the ANS function in psychotic disorders, as assessed by HRV, may include a strong genetic component. Therefore, decreased HRV measures may be useful as a potential endophenotype to further the identification of genetic abnormalities common to SCZ.

A number of reports indicate that HRV dysregulation in SCZ is associated with the symptomatology of the disorder. Toichi et al. (1999) reported that psychotic symptoms, as assessed by the Positive and Negative Symptom Rating Scale (PANSS), were negatively correlated with the parasympathetic HRV signal, indicating that more severe psychotic symptoms were linked to greater PNS suppression. Kim et al. (2004) observed that the PANSS total score and positive symptoms subscale both showed a negative correlation with the sample entropy in an SCZ group, even when accounting for the medication dose. One recent study indicated that the HF power and LF/HF ratio in paranoid SCZ subjects were negatively correlated with the Brief Psychiatric Rating Scale (BPRS) (Bar et al., 2008b). In addition, SCZ participants with a high BPRS score (above 48, indicating significant current psychopathology) exhibited significantly lower HF power and higher LF/HF ratio compared to patients with lower BPRS scores. A similar study reports that SCZ patients with a high GAF score (above 30, indicating improved overall functioning) exhibited higher HF power relative to a low-GAF group (Fujibayashi et al., 2009). Overall, these data suggest that ANS function in SCZ may be mediated at least to some extent by the state- and symptom-dependent conditions reflected by alterations in HRV parameters.

A variety of psychotropic treatments have detrimental effects on cardiovascular function and ANS regulation. The use of both typical and atypical antipsychotic drugs has been associated with a significant dose-related increase in the risk of sudden cardiac death (Hennessy et al., 2002; Ray et al., 2001). Some of the cases have been associated with drug-induced prolongation of the QT interval (Koponen et al., 2008). Antipsychotic drugs may directly affect HRV via the blockade of muscarinic receptors that mediate vagal parasympathetic control of the heart rate (Chong et al., 2001). Antipsychotic blockade of dopamine D2 receptors may also affect adrenergic activity and increase sympathetic tone (Scigliano et al., 2008). Agelink et al. (2001) compared the effects of amisulpride, olanzapine, sertindole and clozapine on cardiac function in SCZ patients and observed that while all drugs prolonged the QT interval, only clozapine significantly reduced the resting sympathetic tone. The extent of medication effects on HRV parameters may depend on the neurotransmitter systems affected by each agent; olanzapine appears to have a lesser effect on HRV compared to clozapine, due to its balanced anticholinergic and antiadrenergic actions (Hempel et al., 2009). Risperidone, with very little affinity for

muscarinic receptors, is reported to have negligible effects on HRV (Hempel et al., 2009; Silke et al., 2002). A recent paper reports that 6 weeks of risperidone treatment actually improved HRV, leading to a reduced LF/HF ratio; these authors propose that the drug may exert beneficial effects by improving the prefrontal regulation of the autonomic output (Chang et al., 2010).

A substantial number of studies reported HRV abnormalities in medication-free or even medication-naïve first-episode SCZ patients, including those discussed earlier (Bar et al., 2005; Boettger et al., 2006; Chang et al., 2009) and others (Jindal et al., 2009). For example, Mujica-Parodi et al. (2005) observed that unmedicated SCZ patients exhibited significantly decreased vagal tone, as assessed by HRV, although the addition of an antipsychotic treatment has been shown to exacerbate the decrease in vagal tone. In summary, the data indicate that SCZ is a condition associated with ANS dysregulation independent of pharmacological intervention.

23.4 HRV and Bipolar Disorder

Depression is strongly associated with changes in cardiovascular function (Johnson and Grippo, 2006) and decreased HRV (Agelink et al., 2002; Dalack and Roose, 1990; Rechlin et al., 1994b), an effect dependent on the severity of symptoms (Krittayaphong et al., 1997). While alterations in ANS function and HRV have been relatively well characterized for unipolar depression, remarkably little work has been conducted for BD. This disorder is often characterized by extended periods of depression, but the hallmark of BD is the presence of manic episodes that include euphoric or irritable mood, psychomotor agitation, sleep disturbance, grandiosity, racing thoughts and increased goal-directed activity (Goodwin and Jamison, 1990). While the worldwide lifetime incidence of BD Type I is approximately 1%, similar to SCZ, the prevalence of all bipolar spectrum disorders (including cyclothymia and BD Type II illness) is estimated at around 5% of the population (Grunze et al., 2009).

Although ANS dysfunction has been characterized more comprehensively in SCZ and depression, several lines of evidence suggest that autonomic abnormalities also exist in BD. After suicide and accidents, cardiovascular disease and vascular incidents are the leading causes of death in BD patients (Garcia-Portilla et al., 2009). BD individuals experience higher blood pressure during manic episodes and have a higher risk of hypertension and metabolic syndrome (Fagiolini et al., 2008). While the cause of BD remains unknown, one theory posits that mania is driven by a hypocholinergic state and depression by increased cholinergic activity (Janowsky et al., 1972). Previous work shows that manic BD patients exhibit cholinergic insensitivity compared to healthy controls, as demonstrated by reduced pupil constriction upon administration of the cholinergic agonist pilocarpine (Sokolski and DeMet, 2000). These data, while circumstantial, suggest the possibility that the efficacy of cholinergic-mediated cardiac vagal pathways may be impaired in BD, at least in the manic state. In addition, urinary excretion of epinephrine and norepinephrine (NE) was associated with the severity of manic symptoms in BD patients hospitalized for a manic episode (Swann et al., 1991), suggesting elevated sympathetic activity. Finally, the offspring of BD parents demonstrate elevated electrodermal activity during administration of a mild stressor (mental arithmetic task) compared to the controls, implying a genetic predisposition to exaggerated ANS responses to stress (Zahn et al., 1989).

Cohen et al. (2003) assessed HRV in a group of euthymic BD patients compared to a control sample matched for age and sex. Time and frequency domain HRV measures were quantified in a seated resting position. All patients were medicated, with the majority taking lithium. The results indicated that BD patients exhibited lower SDNN, lower LF/HF ratio and higher HF power compared to healthy subjects (Cohen et al., 2003). There was no evidence of any medication effect: HRV did not differ between the subjects on lithium monotherapy, lithium combination therapy and non-lithium treatment. As authors acknowledge, these data are difficult to interpret and somewhat contradictory, as a decrease in SDNN typically indicates a reduction in parasympathetic activity, while higher HF signal is a marker of increased parasympathetic activity. A subsequent study applied non-linear analyses to the same data set, including estimation of the minimum embedding dimension (MED), the largest Lyapunov exponent (LLE), symbolic dynamic measures, Shannon entropy and Poincaré plots (Todder et al., 2005). This report failed to find any significant differences in RR complexity between the control and euthymic BD subjects.

A recent paper examined both linear and non-linear measures of HRV in manic BD and SCZ inpatients compared to healthy control participants matched for age, gender, body mass index and smoking (Henry et al., 2010a). The HRV measures were assessed during a 5 min rest period, and the psychiatric symptoms were quantified with the Young Mania Rating Scale (YMRS) and BPRS. In addition to the traditional time domain and frequency domain measures, RR interval complexity was assessed with sample entropy and dynamical entropy, h , a novel non-linear measure previously used to evaluate the organization of motor activity in psychiatric population (Henry et al., 2010b).

Compared to the control group, manic BD subjects exhibited reduction in SDNN, RMSSD, pNN50, HF power, dynamical entropy (h) and sample entropy, along with an elevated LF/HF ratio, indicating impaired parasympathetic tone and reduced complexity in the RR pattern. Higher levels of both entropy measures were associated with an increased HF power and a diminished LF/HF ratio, confirming that a more unpredictable RR pattern is correlated with greater parasympathetic activity. These results are in contradiction to Cohen et al. (2003), who observed a decrease in SDNN, but an increase in HF power, in euthymic BD individuals. It is possible that a reduction in SDNN (a measure that reflects both sympathetic and parasympathetic tones) could represent a consistent trait exhibited during both the manic and euthymic phases of BD. By contrast, the suppression of parasympathetic vagal function could be state-dependent, observed primarily in the manic phase of the illness (as demonstrated, e.g., by the pupillary cholinergic insensitivity also reported in manic BD individuals) (Sokolski and DeMet, 2000).

Similar to BD subjects, SCZ participants in this study exhibited a strong trend toward lower RMSSD, pNN50, HF power, h and sample entropy compared to healthy controls, but these differences did not reach significance, possibly limited by a relatively small sample size (14 SCZ subjects) and variation in diagnostic subtypes (the group included paranoid, disorganized and undifferentiated patients). No significant effects of antipsychotic treatment were observed in this study. However, BD individuals treated with lithium did exhibit a decrease in the LF/HF ratio compared to BD participants not exposed to the drug. Given that lithium is known to decrease the SA node depolarization rate and, therefore, the heart rate (Chong et al., 2001), it is possible that an administration of this compound may have blunted sympathetic activation of the SA node, thus reducing the relative intensity of LF power.

Manic symptoms, as assessed by the YMRS clinical scale, were significantly correlated with a higher LF/HF ratio in all patients and also in the BD group alone, while they

negatively correlated with HF power in SCZ subjects. Unusual thought content, defined as the expression of bizarre or delusional ideas, was also correlated with decreased HF power and higher LF power in BD subjects. Finally, reduced entropy was significantly related to higher levels of aggression and poor personal hygiene in both patient groups. These results indicate that more severe psychiatric symptoms are associated with sympathovagal dysregulation, supporting previous findings that link vagal suppression to psychotic symptoms in SCZ (Bar et al., 2005; Toichi et al., 1999).

23.5 HRV and Anxiety Disorders

Anxiety disorders are the most common form of psychopathology, encompassing a diverse group of conditions characterized by core symptoms of extreme or pathological anxiety (Regier et al., 1998). The primary emotion associated with clinical anxiety is fear, often expressed as an adaptation to threat involving a flight response (Friedman, 2007). A large body of evidence supports the role of ANS in anxiety disorders, including tonic SNS hyperarousal (Roth et al., 1986), slow SNS habituation (Lader, 1980), excess sympathetic lability (Eysenck, 1970) and cardiovascular events such as tachycardia in panic attacks (Friedman and Thayer, 1998). While the discussion on ANS function in anxiety has traditionally been dominated by models of impaired homeostasis perturbed by sympathetic overreactivity, more recent work has focused on a dynamical framework critically regulated by dysfunction in the parasympathetic tone (Friedman and Thayer, 1998). Studies over the past 20 years have increasingly emphasized the role of vagal function in anxiety, buttressed by recent work utilizing HRV as a measure of cardiac activity (Friedman, 2007). The following section will outline HRV findings in common anxiety disorders, including panic disorder (PD), generalized anxiety disorder (GAD) and phobias.

PD affects between 3% and 5% of the population and has severe behavioral and economic consequences (Wittchen and Jacobi, 2005). This condition was the first anxiety disorder assessed by HRV analysis, beginning with a seminal study reporting reduced RR variability in the time domain in PD patients compared to healthy controls (Yeragani et al., 1990). Subsequent studies replicated these data, observing decreased HF power and greater LF power in PD patients, which suggested reductions in the vagal cardiac signal (Klein et al., 1995; Middleton et al., 1994; Yeragani et al., 1993). Additional reports indicated that PD subjects also exhibited lower HRV complexity compared to controls, as assessed by measures such as MED, LLE and symbolic dynamics (Rao and Yeragani, 2001; Yeragani et al., 2000). HRV complexity in PD was also reduced by the antidepressant nortriptyline (a tricyclic with anticholinergic properties), but increased by paroxetine, a selective serotonin reuptake inhibitor that reduced the LF/HF ratio in PD patients (Yeragani and Rao, 2003). Treatment with cognitive behavioral therapy (CBT) was also successful in improving HRV vagal tone (higher pNN50) and reducing anxiety (Garakani et al., 2009).

Recent reports have demonstrated that time and frequency domain measures of HRV in PD appear to be unrelated to the measures of SNS activity, including NE spillover and NE kinetics dependent on the norepinephrine transporter (NET) (Alvarenga et al., 2006; Baumert et al., 2009). One research paper has suggested that ANS dysregulation in PD may be related to hyperserotonergic function mediated by decreased expression of the serotonin transporter (5-HTT) (Kang et al., 2010). Preclinical studies have shown that decreased 5-HTT function is related to exaggerated sympathoadrenal and neuroendocrine responses

to stress (Murphy and Lesch, 2008; Tjurmina et al., 2002), while 5-HTT function may be altered in PD (Maron and Shlik, 2006). Kang et al. (2010) reported a significant negative correlation between 5-HTT affinity and LF power in PD, suggesting that impaired 5-HT reuptake may be associated with increased sympathetic activity and ANS abnormalities in PD. Although these data should be interpreted cautiously, given that LF power may reflect both parasympathetic and sympathetic tones, they represent an intriguing direction of research in this field.

In contrast to PD, relatively little work has been conducted to examine HRV in GAD (Friedman, 2007), a disorder characterized by persistent tension, anxiety and uncontrollable worry (APA, 1994). Thayer et al. (1996) reported that 34 GAD subjects demonstrated decreased time domain HRV and reduced HF power during periods of baseline measurement, relaxation and worry compared to 32 healthy controls. However, subsequent reports failed to observe evidence of altered cardiac ANS function in GAD (Wilhelm et al., 2001), justifying the removal of autonomic hyperactivity as a GAD diagnostic criterion during the transition from DSM-III to DSM-IV (Conrad et al., 2008).

Over the past decade, a series of reports have observed reduced HRV and diminished vagal tone associated with the concept of worry, a cardinal feature of DSM-IV GAD, including self-reported worry during a 24 h period (Brosschot et al., 2007) and laboratory-evaluated worry (Hofmann et al., 2005). One recent study assessed ANS function in a sample of college students meeting the criteria for GAD during rest and worry conditions (Hammel et al., 2010). They did not observe any HRV differences between the GAD and non-GAD individuals, but noted that all subjects, regardless of group, exhibited decreased parasympathetic tone (lower HF power) during the worry period (when asked to think about an issue of great concern to each individual) compared to rest. Overall, the literature suggests that certain aspects of GAD, such as worry, do appear to be associated with ANS dysfunction, but the effect of GAD on HRV may be more difficult to discern due to diagnostic heterogeneity or variation in illness length (e.g., extended periods of chronic worry may be required to elicit ANS dysregulation in this disorder) (Brosschot et al., 2006).

Similar to GAD, HRV studies in phobias have produced varying results (Friedman, 2007). Phobic anxiety, marked by an unreasonable fear during exposure to specific stimuli (closed spaces, heights and crowds), accounts for approximately half of all anxiety disorders and is associated with an increased risk of fatal cardiac events (Watkins et al., 2010). In a large epidemiologic study, higher levels of self-reported phobic anxiety (in reaction to miscellaneous stimuli) were associated with reduced time domain HRV (Kawachi et al., 1995). Similarly, Johnsen et al. (2003) reported that patients with dental phobia exhibited vagal suppression and impaired attention on the Stroop Task relative to controls, when exposed to videos of dental treatment. Individuals with the fear of flying also reported greater anxiety in conjunction with low HRV (decreased RMSSD) (Bornas et al., 2005). By contrast, social phobia may be less distinguished by ANS dysregulation. One report observed that female, but not male, social phobics were characterized by reduced HF power during a speech stressor, when compared to control participants (Grossman et al., 2001). In addition, no ANS differences were found between high- and low-trait socially anxious women during a videotaped speech task (Mauss et al., 2003). While greater subjective anxiety and embarrassment occur in social phobics during public situations, the parasympathetic markers are not affected (Gerlach et al., 2003). A recent study demonstrated a correlation between HF HRV and cerebral blood flow in the anterior cingulate, PFC and striatum of social phobics during a public speaking paradigm (Ahs et al., 2009), but this relationship was similar to that observed in healthy control participants (Lane et al., 2009). Finally, a large study conducted in the Netherlands reported that social phobia was a

significant predictor of lower SDNN and reduced HF power, but this effect was no longer significant after accounting for the consequences of antidepressant use on HRV (Licht et al., 2009). In summary, phobia appears to have significant effects on SNS activation (Friedman, 2007), but a more limited impact on vagal function, perhaps due to situational and experimental factors.

23.6 HRV and PTSD

PTSD is characterized by the development of persistent fear, helplessness or horror following exposure to a traumatic personal event involving threatened or actual death or severe injury (APA, 1994). Symptoms include distressing and intrusive recollection of the event, avoidance of associated stimuli, diminished social responsiveness and increased hyperarousal marked by irritation, anger and impaired sleep. Lifetime rates of prevalence range from 1.9% in North America to 6.8% in Europe, although comprehensive studies have not been conducted in the Middle East, Africa or Asia (Baker et al., 2009). Current conceptual models of PTSD include (1) development of a fear-conditioned response resulting in involuntary event recollection expressed as PTSD symptoms; (2) impaired control or regulation of emotional responses (such as the failure of PFC to regulate the response of amygdala to threat or abnormal neuroendocrine feedback); and (3) dual memory encoding of traumatic experiences as conscious, verbally accessible information and unconscious, situationally accessible knowledge resulting in involuntary emotional reactions triggered by a particular context (Brewin et al., 1996; Charney, 2003; Pitman et al., 1999). Similar to other anxiety-related disorders, PTSD is characterized by ANS hyperarousal, including elevated resting heart rate, greater baseline skin conductance (indicating increased SNS tone) and higher blood pressure (Pole, 2007).

The effect of PTSD on HRV has been assessed by relatively few studies, but results consistently support ANS dysregulation marked by elevated sympathetic activity and reduced vagal tone (Friedman, 2007). An initial study by Cohen et al. (1997), although with a small sample (9 subjects per group), reported that subjects with PTSD expressed a higher LF/HF ratio compared to control participants. Subsequent work comparing patients with PTSD and PD observed that individuals with both disorders exhibited elevated sympathetic HRV activity during rest, but only PD subjects demonstrated an increased LF response during a 15–20 min verbal recall of a negative stressful life event (Cohen et al., 1998, 2000a). These authors suggest that PTSD patients failed to show an autonomic response to mental stress (recollection of the traumatic event) due to decreased flexibility induced by chronic ANS overstimulation (Cohen et al., 1998). A follow-up study also showed that 4 months of fluoxetine treatment normalized the elevated LF/HF signal in PTSD to values observed in the control group (Cohen et al., 2000b).

Others have studied HRV in PTSD individuals during exposure to stress (Keary et al., 2009; Sahar et al., 2001). Sahar et al. (2001) reported that trauma survivors without PTSD exhibited an increase in HF HRV during a mental arithmetic stressor, but this elevation in the parasympathetic tone was not observed in matched PTSD participants, suggesting dysregulation of vagal function during stress. A more recent report indicated that female PTSD participants exhibited significantly greater reductions in HF power during two 4 min speech tasks (trauma recall and mental arithmetic) compared to healthy controls, providing evidence for the impairment of PNS activity (Keary et al., 2009). These authors

suggest that the lack of autonomic effects observed in PTSD during longer speech tasks (15–20 min) (Cohen et al., 1998, 2000) may have occurred due to habituation to the task. A related study examined the threat of shock on HRV and electrodermal activity in PTSD and PD patients (Blechert et al., 2007). PTSD participants exhibited elevated skin conductance and reduced HF power during baseline relative to control subjects, indicating high sympathetic tone and parasympathetic suppression, but none of the groups showed any autonomic response to a 5 min period of potential exposure to shock. Finally, additional evidence suggests that low vagal tone may predict stress responses in PTSD, as PTSD individuals with low HF power exhibited greater heart rate elevation when exposed to trauma-related script-driven imagery (Hopper et al., 2006; Sack et al., 2004).

Recent studies have attempted to utilize HRV as a tool to assess efficacy of therapy in PTSD (Nishith et al., 2003; Zucker et al., 2009). Treatment with CBT was successful in ameliorating PTSD symptoms and reducing the LF/HF ratio during rapid eye movement sleep in a small sample of female rape victims (Nishith et al., 2003). A 4-week regimen of respiratory sinus arrhythmia biofeedback was also successful at reducing symptoms of PTSD, depression and insomnia in a cohort of participants in a substance-use residential treatment facility (Zucker et al., 2009). Subjects in this study also showed a significant improvement (elevation) in SDNN by the end of the treatment period. Yoga treatment has also been reported to improve the HRV in PTSD; eight sessions of hatha yoga reduced PTSD symptoms and significantly increased SDNN values, although movement artifacts during the yoga sessions may have affected the HRV measurements (van der Kolk, 2006).

Exposure to combat or war stressors is associated with a significant risk of developing PTSD (Baker et al., 2009). The prevalence of PTSD in Vietnam and Gulf War veterans is reported to be 30% and 10%, respectively (Kang et al., 2003; Tan et al., 2011). The frequency of the disorder in current active troops, including reservists, has been estimated to be as high as 25% (Milliken et al., 2007). Advances in medical care have improved the survival rates for many soldiers with multiple and massive wounds, increasing the complexity of care and rehabilitation for veterans of recent conflicts, including Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF) (Clark et al., 2009). Chronic pain and severe injuries, such as traumatic brain injury (TBI), are associated with a higher incidence of PTSD; approximately 32% of injured active-duty OIF personnel are estimated to meet the criteria for the disorder, compared to 14% of uninjured soldiers (Hoge et al., 2007).

Tan et al. (2009) examined HRV in a sample of 28 OEF/OIF veterans, 16 of whom met the criteria for PTSD. They report that this group demonstrated reduced SDNN compared to age- and gender-corrected normative data collected over a 24 h period. Furthermore, a composite measure of PTSD, pain and mild TBI was significantly negatively correlated with the SDNN measure. A subsequent pilot study indicated that HRV biofeedback therapy was an effective and feasible treatment for PTSD symptoms (Tan et al., 2011). A sample of 20 PTSD veterans, who demonstrated lower SDNN compared to a matched control group, were exposed to eight weekly sessions of 30 min HRV biofeedback therapy, with the objective of training the participants to practice breathing exercises calculated to maximize the HRV. The results showed that PTSD participants exhibited significant symptom improvement, as assessed by the Clinician Administered PTSD Scale (CAPS) and the PTSD Checklist-Specific (PCL-S), indicating that this paradigm may represent an effective adjunctive treatment. In contrast to these findings, Woodward et al. (2008) did not observe any difference in respiratory sinus arrhythmia between Vietnam and Persian Gulf War veterans with or without PTSD, although respiratory sinus arrhythmia magnitude was correlated with anterior cingulate cortex volume, supporting the importance of

this structure in regulating parasympathetic tone. Finally, a recent study assessed HRV measures in Croatian war veterans with PTSD and myocardial infarction compared to age-matched civilian participants who had also suffered a myocardial infarction (Lakusic et al., 2007). They report no group differences in SDNN, but the PTSD participants did exhibit reduced RMSSD, pNN50, HF power and a higher LF/HF ratio, signifying greater parasympathetic suppression. In summary, while few studies to date have utilized HRV to assess ANS function in combat-related psychological trauma, emerging evidence suggests that this may be a useful tool to quantify the effects and address the consequences of syndromes such as PTSD.

23.7 Assessment of HRV in Animal Models of Psychiatric Disorders

The development and utilization of animal models of human illness constitute an essential research tool for identifying the biological substrates of human disease in many fields of research, including psychiatry. Translational cross-species paradigms that assess common behavioral responses, similar cognitive functions and parallel physiological processes have enabled significant advances in our understanding and treatment of neuropsychiatric disorders (Geyer, 2008). The development of radiotelemetry implants that permit remote long-term monitoring of cardiac function in animals has facilitated the use of HRV to assess ANS function and health in epidemiological and toxicological research (Rowan et al., 2007). Telemetry devices that include pressure gauge sensors may be placed inside the rodent abdominal cavity to assess arterial pressure and quantify blood pressure, heart rate and HRV (Brockway et al., 1991; van den Buuse et al., 2001). While much of the work in this field thus far has focused on environmental toxicology, for example, assessing the effect of particulate exposure on ANS and cardiac functions, a growing number of studies have applied this new technology to quantify changes in sympathovagal balance related to behavioral and emotional pathologies (Rowan et al., 2007; von Borell et al., 2007). Although recent reports have validated HRV as a measure of ANS activity in rodents and indicated that the frequency spectra are analogous to that of humans (e.g., the HF signal represents parasympathetic tone, as demonstrated by sensitivity to cholinergic antagonists) (Cerutti et al., 1991; Rowan et al., 2007), a number of methodological issues warrant consideration. Mice and rats have heart rates that are considerably faster and more variable than that of humans (e.g., 500 beats/min), requiring a higher sampling rate (1000+ Hz) to achieve accurate readings (Mansier et al., 1996; Rowan et al., 2007). Acquisition of stable, stationary measures is also more difficult, given the frequent presence of artifacts due to motor activity, grooming behaviors, etc. Environmental stimuli such as room temperature, circadian cycle and human interaction may exert marked effects on the heart rate and HRV measures. Standardized protocols indicate that a 5 min period is recommended for assessing HRV in human subjects (Task Force, 1996), but similar protocols have not yet been established in rodents. A recent review suggested that HRV should be sampled for at least 70 s in rats, capturing a similar number of cardiac cycles that occur over 5 min in humans (Rowan et al., 2007), but recording periods have differed considerably across studies.

Several reports have measured rodent HRV during exposure to stressors as potential models of anxiety-related responses. Sgoifo et al. (2002) assessed the HRV in adult rats exposed to a novel open-field enclosure for 15 min once a day for 10 days. Data recorded

during the first and last sessions indicated that the animals exhibited consistent decreases in SDNN and RMSSD during open-field exposure compared to baseline homecage periods, indicating that chronic parasympathetic suppression was maintained across repeated stress episodes. Depino and Gross (2007) also quantified HRV in two strains of mice, C57BL/6 and Balb/c, using an open-field paradigm. While C57 mice exhibited less anxiety, spending more time in the center of the enclosure and engaging in greater locomotor activity compared to the Balb/c animals, they also demonstrated lower time domain HRV. In addition, center time and total motor activity were also negatively correlated with cardiac variability. These data suggest that alterations in autonomic function may have been influenced primarily by the level of physical activity, rather than anxiety behavior per se. One intriguing study reported that exposure to a social crowding stressor affected HRV in female prairie voles (Grippo et al., 2010). Compared to pair-housed control subjects, voles exposed to 4 weeks of social isolation demonstrated reduced SDNN and HF power when placed in a container with 5 other voles for 10 min. The results also indicated that increased positive social behaviors during the crowding test were correlated with attenuated heart rate responses to the stressor. This animal model in which social interaction level is varied may be useful in studying human anxiety disorders such as social phobia that affect ANS function and HRV.

In addition to novelty and social stressors, the effect of sleep deprivation on HRV has also been examined in rats (Sgoifo et al., 2006). Male rats bred at the University of Groningen exhibited significant decreases in SDNN and RMSSD when exposed to 48 h of sleep deprivation relative to control animals that were allowed normal sleep (Sgoifo et al., 2006). In addition, sleep-deprived rats also exhibited greater vagal suppression when exposed to a restraint stress following the sleep deprivation period. This finding may be of particular interest as a potential model of BD, which is frequently characterized by extended episodes of reduced sleep (Goodwin and Jamison, 1990). In fact, sleep disturbance is reported to be one of the most common prodromal factors precipitating manic episodes in BD individuals (Jackson et al., 2003). Thus, the effects of rodent sleep deprivation on HRV may have significant relevance to the clinical pathology of this disorder.

HRV abnormalities have also been observed in various animal models of depression (Grippo et al., 2003, 2004; Sgoifo et al., 2002; Vinkers et al., 2009). Repeated 30 min exposures to social defeat in a resident–intruder paradigm (where the animal is attacked by a dominant resident rat) induced significant decreases in SDNN and RMSSD in adult male rats compared to baseline homecage levels (Sgoifo et al., 2002). Treatment with a chronic mild stress paradigm for 4 weeks (involving alternating periods of continuous illumination, noise and water deprivation) induced anhedonia, elevated heart rate and a 45% reduction in SDNN compared to non-stressed control animals (Grippo et al., 2003, 2004). Removal of the olfactory bulb, a putative model of depression, resulted in reduced resting heart rate (contrary to clinical depression) (Carney et al., 2005), but also decreased SDNN during both daytime and nocturnal periods compared to sham-lesioned rats (Vinkers et al., 2009).

Attempts have also been made to approximate PTSD in rodents in conjunction with HRV measurement (Cohen et al., 2004, 2007). According to a model developed by Cohen and Zohar (2004), a proportion of rats (22%) exposed to a predator (cat) for 10 min subsequently demonstrated maladaptive behaviors defined as increased anxiety in the elevated plus maze and an elevated acoustic startle response (observations interpreted as similar to chronic anxiety responses in PTSD). While all stressor-exposed rodents exhibited reduced SDNN compared to non-stress controls, only maladaptive rats showed significant parasympathetic suppression (reduced HF power and elevated LF/HF ratio). In a follow-up

study, a 10 min exposure to the predator scent in juvenile (28 days old) or adult (60 days old) rats induced significant decreases in SDNN and increased anxiety when the animals were tested at post-natal day 60 or 80 (Cohen et al., 2007). The most prominent effects on HRV were observed in rodents exposed to the stressor at both 28 and 60 days.

In summary, while relatively few studies have assessed HRV in animal models of neuropsychiatric disorders when compared to the clinical literature, the existing findings support the use of HRV as a cross-species translational measure. Study limitations include potential confounders such as motor activity, variation in environmental factors and recording periods and the absence of standardized guidelines for animal HRV methodology (as exists for human data) (Task Force, 1996). Nonetheless, this nascent field of research shows considerable promise in facilitating our understanding of the neurobiological factors that underlie psychiatric illness and in contributing to the development of novel treatments for these disorders.

23.8 Conclusions and Future Directions

Dysregulation of the ANS is a common characteristic of a variety of psychiatric disorders, including depression, BD, SCZ and anxiety (Friedman, 2007; Henry et al., 2010a; Valkonen-Korhonen et al., 2003). These disorders are also consistently associated with the medical complications and increased mortality related to cardiovascular abnormalities (Brown et al., 2000; Cohen and Benjamin, 2006; Leung et al., 2010). While there are many variables that may influence cardiac health, including metabolic syndrome and sedentary behavior, autonomic activity represents a critical factor that mediates physical and psychological functioning in these individuals. Over the past two decades, HRV has emerged as an effective, cost-efficient and informative measure of ANS function and cardiac health and, more recently, as a potential indicator of cognitive performance (Thayer et al., 2009). A substantial and growing body of evidence supports the premise that our behavior and interaction with the environment are regulated by a bidirectional relationship between the heart and brain. Thus, HRV, as a measure representing the nexus of neural and cardiac functions, is uniquely positioned to contribute to a comprehensive model of physiological and psychological health.

The same factors that underlie the importance of HRV also present difficulties in interpretation of the measure, especially in the field of psychiatry. As discussed in this chapter, HRV abnormalities, marked by sympathetic overactivity and vagal suppression, are fairly ubiquitous across diagnostic classifications and are reported to occur in SCZ, BD and several different types of anxiety disorders. These findings reflect some of the continuing challenges in determining the classification and differentiation of disorders that contain overlapping characteristics. Individuals with BD may also express psychotic symptoms, while SCZ patients may experience mood swings and depression; anxiety symptoms are often comorbid with depression. In addition, HRV may be influenced by pathology in both the brain and the heart. Cardiac rhythm can be affected by proximal damage to the heart muscle, as well as by impaired cortical function and disinhibition of structures that drive the SNS output, such as amygdala.

Animal models of psychiatric disorders present their own challenges, as it is difficult to produce affective states in rodents that mirror the complete battery of clinical symptoms and cognitive deficits that mark human psychopathology. Thus, recent attempts to model conditions such as BD mania have evolved into more productive rodent experimental

models designed to assess specific individual symptoms rather than the entire syndrome (Einat, 2007). Therefore, it may also be useful to focus on a symptom-based, rather than disorder-based, approach to understanding the significance and causes of HRV in neuropsychiatric illness, focusing on personality traits and individual characteristics independent of DSM-guided classification. Identification of physiological mechanisms underlying HRV measures will also require carefully controlled studies that utilize measures of both cardiac and neural functions. Imaging methods that quantify brain activity, such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), should be administered in combination with tools such as an echocardiogram to test for ventricular dysfunction and cardiomyopathy in HRV studies. Application of such a multifaceted approach will enable clarification of the neural and myocardial factors that may mediate HRV abnormalities in psychiatric disorders.

One limitation common to most assessments of ANS function in psychiatric patients is that these studies are typically conducted in a stationary position, which has the benefit of minimizing the confounding effects of physical activity on cardiac function, but limited applicability to daily functioning in real-world environments. Recent studies have attempted to circumvent these difficulties by using the experience sampling method (ESM), where individuals record their condition throughout the day as prompted randomly by a watch or PDA (Myin-Germeys et al., 2001). A recent study assessed HRV in a sample of 28 individuals with psychosis during a 36 h period of free ambulatory activity, in conjunction with an ESM paradigm requiring subjects to report their stress level and emotional state (Kimhy et al., 2010). Participants wore an ambulatory monitoring vest, which continuously recorded the motor and cardiac activities during the test period (Vivometrics, 2002). Momentary periods of high stress associated with self-reported negative affect negatively correlated with the HF power and positively correlated with the LF/HF ratio. These data support the feasibility and validity of this real-time methodology. Future studies could apply similar methods to assess HRV during a variety of real-world circumstances, enabling elucidation of the temporal relationship between psychopathology and ANS dysfunction. Application of novel techniques such as this will advance our understanding of the relationship between the brain, the heart and the environment that shapes our behavior.

Abbreviations

ANS	Autonomic nervous system
BAS	Behavioral activation system
BD	Bipolar disorder
BIS	Behavioral inhibition system
BPRS	Brief psychiatric rating scale
CAN	Central autonomic network
CBT	Cognitive behavioral therapy
CNS	Central nervous system
DMN	Dorsal motor nucleus
DSM-IV	Diagnostic and statistical manual of mental disorders (4th Ed; DSM-IV) is the book used by qualified mental health professionals to make a diagnosis of generalized anxiety disorder
GAD	

ESM	Experience sampling method
GAD	Generalized anxiety disorder
HF	High-frequency
HRV	Heart rate variability
LF	Low-frequency
LLE	largest lyapunov exponent
MED	Minimum embedding dimension
NA	Nucleus ambiguus
NTS	Nucleus of the solitary tract
OEF	Operation enduring freedom
OIF	Operation Iraqi freedom
PD	Panic disorder
PET	Positron emission tomography
PFC	Prefrontal cortex
PNS	Parasympathetic nervous system
PTSD	Post-traumatic stress disorder
SCZ	Schizophrenia
SNS	Sympathetic nervous system
TBI	Traumatic brain injury

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24

Heart Rate Variability and Depression

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24.1 Introduction

Prevalence of depression is about 10% in the global population (Andrade et al., 2003). This is the second leading cause of disorders that affect the population, after cardiac morbidity (Murray and Lopez, 1997). The situation is more serious when one considers that depression and cardiovascular disorders show a strong comorbidity (Carney et al., 2005).

Heart rate variability (HRV) analysis quantifies the changes in heart rate (HR), or, more precisely, the time between heartbeats. It is not only an important measure of cardiovascular function but also a window into the physiological balance between the sympathetic and the parasympathetic limbs of the autonomic nervous system (ANS) that governs hemodynamic variables. An efficient coordination between the ANS and hypothalamic–pituitary–adrenal (HPA) axis is vital for emotional expression and coping with stress (Bernston et al., 1997; Brown et al., 2009; Ehrenthal, 2010). There is a significant amount of literature that links decreased HRV with emotional stress (Bernston et al., 1997; Ehrenthal, 2010; Licht et al., 2010) and with psychiatric conditions including depression. HRV not only becomes severely reduced secondary to depression but also acts as a good prognostic indicator of depression (Ehrenthal, 2010). A number of antidepressant medications severely compromise ANS function, which is reflected in poor HRV. An investigation into the effects of antidepressant medications on the ANS using the measures of HRV can provide clinically useful information for treating these patients.

24.2 Pathophysiological Implications of HRV and Cardiovascular Integrity

Measuring the HR by counting the arterial pulse for assessing not only the cardiovascular function but also the general well-being is an age-old practice known to almost all cultures across the world (Dimos et al., 2009). Rhythm of the pulse also became more relevant as medical knowledge progressed. Beat-to-beat analysis of HR, however, was not possible until the advent of the electrocardiogram (ECG) and computers. Perhaps, the first documented evidence of variability in HR with other physiological variables such as blood pressure and respiratory rate goes back to the 1700s (Bernston et al., 1997). By the nineteenth and early twentieth centuries, it became known that “sinus arrhythmia” comprising the physiological fluctuations in the HR accompanying respiratory excursions, popularly called “respiratory sinus arrhythmia (RSA),” was regulated by neural feedback from stretch receptors located in the respiratory cage and the oscillatory drive from the cardiorespiratory centers in brainstem through vagus nerve (Bernston et al., 1997). A dysfunction of this reflex circuitry could lead to mild-to-severe cardiorespiratory impairment and, occasionally, severe outcomes such as fetal distress syndrome and sudden cardiac death (Wolf, 1967). This quickly led to pharmacological interventions, including modes of enhancing the parasympathetic activity using HRV as an index of cardiovascular autonomic regulation, and has been recently reviewed (Taylor, 2010).

According to cardiovascular reactivity hypothesis, the most efficient cardiovascular system is not one that merely responds rapidly to an increased demand for cardiac output by increasing HR but one that also quickly returns to resting state once the heightened demand subsides (Krantz and Manuck, 1984; Treiber et al., 2003). Increased cardiovascular demands may be due to a variety of stressors, including physical or emotional states. A poorly reactive cardiovascular system typically manifests itself in the form of poor HRV.

HRV becomes even more relevant in the context of prolonged physical or emotional stress, because it leads to metabolic or biochemical disturbances that cause a disruption of two inter-related major physiological response systems, namely, the ANS and the HPA axis. A derangement in these two pathways will in turn have serious consequences on a plethora of systems, including blood flow to vital organs such as the heart, brain and kidneys and the immunological resilience of the body, and even have a direct impact on brain cells (Licht et al., 2010).

HRV analysis usually uses time intervals between the peaks of electrocardiographic QRS wave (“RR interval”). It can be performed non-invasively to obtain time domain and frequency domain indices as delineated elsewhere in this volume (Bernston et al., 1997; Ehrenthal, 2010). Frequency domain is more useful than the time domain for investigating particular contributing physiological factors to different spectral components of control or regulation (Taylor, 2010). Furthermore, HRV in an individual may be inherited as a trait (Su et al., 2010) and may be modified by biofeedback and behavioral strategies (Taylor, 2010). HRV has been used as a simple bedside tool for assessing the morbidity of a patient, following myocardial damage (Bernston et al., 1997). Decreased HRV is strongly indicative of a very poor prognosis of cardiovascular disease.

24.3 Depression and Its Impact on ANS Function

There is a direct association between depression and cardiovascular disorders (Dimos et al., 2009). Depression may occur secondary to cardiac illness and may contribute to the downhill progression of cardiac pathology, while solitary primary depression is a major independent risk factor leading to heart disease (Phillips et al., 2011; Koschke et al., 2009). HR tends to be higher while HRV tends to be lower in depressed patients (Taylor, 2010). Patients with depression have almost twice the risk of developing cardiovascular diseases in the next 12 years compared to normal population (Carney et al., 2005).

Prolonged depression is known to increase the allostatic load on HPA axis due to constant stress-related “wear and tear” that results in a significant deterioration of ANS responses signaled by a reduction in HRV (McEwen, 1998). HRV component that is most commonly affected by depression is the high-frequency power (Ehrenthal, 2010). In fact, power in the high-frequency band is considered to be a reliable marker of the integrity of ANS and cardiovascular system in depression. A reduction in HRV has also been associated with a decrease in prefrontal lobe function accompanying prolonged depression (Ehrenthal, 2010). Diminished prefrontal lobe activity could result in increased sympathetic activity and decreased parasympathetic activity, which could together result in major cardiovascular sequelae such as myocardial infarction, hypertension and stroke (Thayer and Brosschot, 2005). There is a significantly higher incidence of cardiac mortality in patients with severe depression (Frasure-Smith et al., 2009). While even patients with mild depression are at an increased risk of cardiovascular disease, the relative risk of cardiovascular morbidity increases with severity of depression (Taylor, 2010; Phillips et al., 2011).

Furthermore, patients with long-standing depression not only show a significant reduction in HRV and other cardiac indices during their bouts of depression but also demonstrate reduced HRV when not actively depressed (Ehrenthal et al., 2010). Diminished HRV during intervening states when the patient is not depressed may be explained by “perseverative cognition,” which accompanies chronic depression as proposed by Thayer and Brosschot (2005). Alternately, it may be due to the ensuing anticipation of depression and the consequent decrease in the vagal tone (Ehrenthal et al., 2010). Prospective studies with meta-analysis have indicated that the relative risk of cardiovascular disorders secondary to depression depends on the type of depression. While major depression is associated with a 2.7-fold increased cardiovascular risk, depressive moods are associated with a 1.5-fold increased risk of cardiovascular problems compared to those with no history of depression (Rugulies, 2002).

Patients with depression also show poor cardiovascular regulation, which manifests as reduced recovery of HR to resting baseline levels following physical exercise (Imai et al., 1994). Furthermore, Nishime et al. (2000) have shown that long-term survival following myocardial damage correlates very well with the rate of recovery of HR following an exercise. Moreover, the scores of depression on Beck Depression Inventory (BDI, a widely used instrument for measuring the severity of depression) negatively correlate with rate of recovery of HR following a treadmill exercise (Hughes et al., 2008). A similar correlation was established by Phillips et al. (2011) using bivariate analysis during different “waves” of depression over a 5-year time period using the Hospital Anxiety and Depression Scale.

According to some reports, a decreased HRV and not an increased HR per se in depressed patients is a reliable predictor of ensuing cardiovascular disorder (Kamphuis et al., 2007). However, there is no consistent correlation between subtypes of depression and HRV patterns (Glassman et al., 2009; de Jonge et al., 2007). In patients with depression, Ehrenthal et al. (2010) found a decrease in the high-frequency power of HRV and cardiac adaptability with regard to HR, blood pressure and cardiac output.

Dysfunction in the ANS caused by depression leads to a decrease in HRV and an increase in HR (Carney et al., 2005). However, the biochemical mechanism underlying this observation is not clearly defined (Taylor, 2010). Increased levels of catecholamines have been suggested to play an important role in this (Taylor, 2010; Carney et al., 2005). In support of this hypothesis, studies show that long-term administration of β -adrenergic receptor blockers (which block the effects of catecholamines) significantly increases HRV and reduce cardiac morbidity and mortality in patients with depression (Freemantle et al., 1999). Based on such studies, β -adrenergic receptor blockers have been recommended as adjuvant therapy together with antidepressants (Taylor, 2010).

Currently, we do not yet have a definite understanding of the biochemical link between depression, reduced HRV and cardiovascular pathology. Studies in patients with depression seem to show that the levels of serum fibrinogen, a protein important for blood clotting, and interleukin-6, a factor involved in blood vessel inflammation, negatively correlate with HRV (Carney et al., 2005, 2009; Frasure-Smith et al., 2009). However, HRV is known to correlate negatively with most of the major biochemical markers associated with cardiovascular pathology such as C-reactive proteins and interleukin-6 (Frasure-Smith et al., 2009) independent of coexisting depression. Parissis et al. (2005) have shown a correlation between levels of depression and endothelial-inflammation-related factors such as tumor necrosis factor (TNF)- α and soluble Fas ligand.

Vagal modulation of HR is significantly suppressed in patients with depression. Recent studies indicate that vagus nerve stimulation suppresses the synthesis of inflammatory cytokines such as TNF. Acetylcholine released by vagus nerve binds to nicotinic acetylcholine receptors on macrophages and inhibits the release of TNF and interleukins (Tracey, 2002). Reduction in vagal activity that is likely to occur in depressed patients may predispose them to vascular inflammatory responses, leading to various pathologies including hypertension and stroke as well as diabetes (Tracey, 2002; Heffernan et al., 2009; Benarroch, 2009). Thus, we seem to be getting closer to an understanding of the biochemical link between depression and cardiovascular morbidity, which may help us develop more targeted, effective therapeutic interventions for treating patients with depression in the future. For example, physical exercise, which is known to increase HRV, may improve the prognosis of patients with severe depression with respect to cardiovascular morbidity. Other therapies such as relaxation therapy (Rees et al., 2004) and cognitive behavioral therapy (Taylor et al., 2010) may be similarly helpful. Although the roles of the sympathetic nervous system (which is thought to be reflected in the low-frequency band of the HRV spectrum) and of the parasympathetic system (which is thought to be reflected in the high-frequency band) are well documented, interestingly, it is the very-low-frequency band (0.0033 to <0.04 Hz) that has been shown in some studies to have highest correlation with cardiovascular morbidity and mortality due to arrhythmias and myocardial infarction among depressed patients (Carney and Freedland, 2009; Bigger et al., 1993; Stein et al., 2000). Patients with a reduction in very-low-frequency power have a 2-year mortality rate that is 4.4 times that of patients with normal very-low-frequency power. Thus, HRV may account for a substantial part of the risk associated with depression in cardiovascular morbidity.

Depression is also strongly associated with "metabolic syndrome," a syndrome consisting of central obesity and a minimum of two of the following: increased triglycerides, reduced HDL cholesterol, hypertension and diabetes. Downregulated parasympathetic tone and increased sympathetic tone were shown to be involved in metabolic syndrome by Licht et al. (2010). They found RSA (a marker of parasympathetic tone) and pre-ejection period (PEP) to be negatively correlated with metabolic syndrome and its individual components with the exception of HDL cholesterol (Licht et al., 2010). Perhaps, it may be possible to link such autonomic disturbances seen in metabolic syndromes with depression.

24.4 Independent Comorbidity of Depression with Poor HRV and the Genetic Link

Depression and cardiac diseases follow a common "downhill" pathophysiological course (Dimos et al., 2009). Both diseases seem to share a common etiology from gene polymorphism to psychosocial predisposition (Dimos et al., 2009). More specifically, depression, reduced HRV and genetics seem to be forming part of the triad. Is this triad an occurrence by chance? These links are being investigated by Su et al. (2010) and Vaccarino et al. (2008).

Su et al. (2010) studied depression in monozygotic- and dizygotic-twin population and investigated the correlation between depression and powers in high-frequency, low-frequency, very-low-frequency and ultralow-frequency bands. They used middle-aged, male, monozygotic and dizygotic twins in their study. Depression was assessed with the BDI, and the HRV was determined using a 24 h ECG. They found that while depression correlated with reduction of powers in ultralow-frequency (<0.0033 Hz) and very-low-frequency bands within twin pairs, powers in low-frequency and high-frequency bands did not show the same association.

Further, another related study conducted by Vaccarino et al. (2008) showed a graded response pattern of decrease in different spectra of HRV with severity of depressive symptoms as determined by the BDI. In their study, they found that the existing state of depression had a greater influence on reducing the HRV compared to a past history of depression. Thus, both active depression and its severity of symptoms were important contributors to a decreased HRV.

Although a strong genetic link has been clearly shown between cardiac derangement in the form of low HRV and depression, there is no current definite explanation as to why specific frequencies of HRV are affected. Vaccarino et al. (2008) did not see a correlation between high-frequency power and inheritability. Other components of the power spectra of HRV were, however, genetically paired between the twins. They suggested that this was responsible for the lack of correlation between high-frequency power and depression. In related studies, increased levels of corticotropin-releasing hormone (CRH) have been associated with reduced HRV (Grippo and Johnson, 2002). Furthermore, certain alleles of haplotypes for CRH receptor gene and glucocorticoid receptor gene are related to depression (Liu et al., 2006). There are reports that depression, low HRV, HPA axis compromise and ANS dysfunction occur on the platform of a common single-nucleotide polymorphism (Levinson, 2006; Neumann et al., 2005, 2006).

Thus, certain phenotypic or biochemical characteristics and autonomic functions are shared between depression and low-frequency power or ultralow-frequency power, which

seem to be mediated through a common gene. This is responsible for a reduction in the low-frequency or ultralow-frequency power in twins with severe depression (Vaccarino et al., 2008). However, this warrants further investigation in larger cohorts. Differences in results documented by various studies may be related to variables such as the technique of HRV quantification, the measurement of depression or differences in antidepressant medications used by patients.

24.5 Antidepressants and HRV

Depression and severity of symptoms independently reduce cardiac regulation as measured by HRV. This is caused by an imbalance between the parasympathetic activity and sympathetic activity. Such an imbalance, in turn, leads to a high incidence of coronary heart disease and mortality rates (Lett et al., 2004).

The problem of cardiovascular dysfunction can become worse when we treat depression pharmacologically, since some antidepressant medications themselves reduce cardiac regulation and HRV, probably secondary to the effects on the ANS (van Zyl et al., 2008). In fact, some antidepressants can independently lead to significant lowering of HRV in depressed patients who had a normal cardiac function to begin with (Sala et al., 2009; Fraguas et al., 2007; Glassman et al., 2007). The class of drugs that is particularly problematic is that of tricyclic antidepressants (TCAs). Selective serotonin reuptake inhibitors (SSRIs) are relatively less harmful in that regard (McFarlane et al., 2001; van Zyl et al., 2008). TCAs are notorious for their anticholinergic and α -adrenergic effects that cause HRV to decrease (Kemp et al., 2010).

In order to reduce mortality in depressed patients with coronary heart disease, the International Consensus Group on Depression strongly recommends the use of SSRIs instead of TCAs in patients who have cardiovascular comorbidities (Ballenger et al., 2001). Furthermore, clinical reports indicate that SSRIs, in fact, normalize the HRV in patients with depression or panic disorder and cardiac disease (Sala et al., 2009). An additional potential benefit of using SSRIs is a decrease in platelet aggregation that enables the blood to flow more smoothly (Bruce and Musselman, 2005). One group, however, warns against the indiscriminate use of antidepressants (Licht et al., 2009). They hypothesize that it is the antidepressant medication and not underlying depression that causes the decreased cardiovascular reflexes and reduced HRV. Perhaps, patients with longer treatment histories and larger patient populations should be investigated with sensitive techniques for assessing HRV along with the biochemical markers to address these questions.

24.6 Future Directions

An early diagnosis of cardiovascular disease in patients with major depression using HRV may turn out to be an important clinical practice, pending confirmation by more extensive, large population-based studies. Judicious choice of antidepressant medications, especially in patients with associated cardiovascular dysfunction, requires careful monitoring and follow-up of HRV.

24.7 Conclusion

Depression is independently associated with cardiovascular dysfunction that is manifested in the form of decreased HRV. The degree of this effect is often proportionate to the level and phase of depression. Thus, HRV serves as an excellent marker to signal the ensuing cardiovascular morbidity and may potentially provide time for adequate therapeutic interventions.

An imbalance between parasympathetic and sympathetic limbs of the ANS, excessive allostatic load on the HPA, biochemical mediators such as interleukins, cholesterol, triglycerides and low-density lipoproteins, and platelet aggregation factors are some of the features associated with cardiovascular diseases in depression. Furthermore, genetic differences appear to be an important link between depression and reduced HRV. Specific antidepressant medications, such as the tricyclics, should be used with caution.

Abbreviations

ANS	Autonomic nervous system
BDI	Beck depression inventory
CRH	Corticotropin-releasing hormone
HPA	Hypothalamic–pituitary–adrenal axis
HRV	Heart rate variability
PEP	Pre-ejection period
RSA	Respiratory sinus arrhythmia
SSRIs	Selective serotonin reuptake inhibitors
TCA	Tricyclic antidepressants

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25

Heart Rate Variability as a Measure of Depression and Anxiety during Pregnancy

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25.1 Introduction

Pregnancy is a time when women are busy preparing for the future and for their new addition to the family unit. However, this exciting time may be darkened with new or pre-existing depression. Numerous studies over the past decade have demonstrated that prenatal depression is much more common than previously thought, with incidence rates ranging from 13% to 20% of pregnant women (Andersson et al., 2006; Evans et al., 2001; Faisal-Cury and Rossi Menezes, 2007). Maternal depression and anxiety during pregnancy have been associated with preeclampsia (PE), premature delivery, fetal growth restriction, newborn irritability and increased infant/child behavioral problems (Gutteling et al., 2005; Kurki et al., 2000; Huizink et al., 2003; Alder et al., 2007; Zuckerman et al., 1990; Huot et al., 2004). Furthermore, the number of women using antidepressants (AD) during pregnancy has increased (Cooper et al., 2007). However, physiological changes related to both gestational depression and the medications used to treat it are poorly understood. Changes in affect (depression and anxiety) are associated with deleterious changes in the autonomic nervous system (ANS) function during pregnancy that may have serious consequences to the mother and the developing fetus (Bleil et al., 2008). Investigation of such physiological correlates of depression during pregnancy may help explain the negative sequelae and may lead to better treatment options. The measurement of heart rate variability (HRV) provides a non-invasive window into the role of the ANS in prenatal pathophysiology. This chapter outlines the effect of prenatal depression and anxiety on the ANS as measured by HRV indices. Section 25.2 identifies factors that

describe the importance of a healthy expectant mother. Sections 25.3 and 25.4 deal with the physiological changes associated with both depression and anxiety. Sections 25.5 and 25.6 discuss HRV measurement in pregnant women and children. The latter part of this chapter presents some of our work.

25.2 Importance of Prenatal Maternal Well-Being

Depression is often under-reported and has not been well recognized in clinical practice during the perinatal period (Austin et al., 2007; Kelly et al., 2001; Spitzer et al., 2000). In addition, there may be a significant amount of stress associated with the transition to motherhood, which can increase the vulnerability for the development of depressive and anxiety disorders (Shear and Mammen, 1995; Steinberg and Bellavance, 1999). Furthermore, maternal anxiety during pregnancy has often been identified as "maternal stress" (Saunders et al., 2006). Since depression and anxiety disorders exist with high comorbidity in the general population as well as in pregnant women, it can be difficult to study each type of disorder independently (Kendler et al., 2007; Faisal-Cury and Rossi Menezes, 2007; Sutter-Dallay et al., 2004; Ross and McLean, 2006).

The symptoms of depression include negative mood, disordered sleep, decreased interest in activities, feelings of guilt/hopelessness, decreased energy, concentration difficulties, appetite changes, psychomotor agitation or retardation and suicidal ideation. Clinical depression often develops following chronic or recent stressful life events (You and Conner, 2009). On the other hand, anxiety is a normal reaction to stress but can become clinically relevant when it becomes excessive or when the symptoms of anxiety are out of proportion to the situation. Symptoms of anxiety that may affect everyday well-being include difficulty in concentrating, disordered sleep, irritability, psychomotor agitation, feelings of guilt/hopelessness, appetite changes, decreased energy, as well as physical symptoms (sweating, gastrointestinal upset, shortness of breath, tremors, muscle tension, headaches and palpitations). Depression and anxiety disorders not only share symptoms but also respond to comparable treatment strategies (Morilak and Frazer, 2004). Furthermore, similar genes have been implicated in both (Kendler, 1996). These overlapping features suggest common neurophysiological substrates.

Based on the inter-relations between maternal stress, depression and anxiety, as well as the adverse developmental outcomes reported in infants and children, we suggest that pathophysiological mechanisms that are deleterious to maternal and fetal health exist. However, it is important to note that not all studies support the associations reported between maternal depression and anxiety and negative infant sequelae (Andersson et al., 2004; Berle et al., 2005), and the explanation as to why some infants born to women experiencing adversity remain resilient is not clear. Challenges of the existing literature include reliance on self-report measures, retrospective data collection and a lack of physiological measures to explain possible mechanisms. Comprehensive examination of stress/depression/anxiety during the prenatal period is, therefore, justified. To identify and quantify symptoms of depression during pregnancy, tools such as the Edinburgh Postnatal Depression Scale (EPDS) can be easily administered (Cox et al., 1987). This 10-item self-report scale was designed to screen for post-partum depression but has been used also during pregnancy (Murray and Cox, 1990; Adouard et al., 2005). Anxiety can be measured using the Spielberger State-Trait Anxiety Inventory (STAI) (Spielberger et al., 1970),

which is a self-report scale with two forms of 20 items that measure various components of state anxiety and trait anxiety. The scale has good reliability and sensitivity to change, has been well documented and has been used in several perinatal populations (McDowell and Newell, 1996; Faisal-Cury and Rossi Menezes, 2007; Austin et al., 2005). The early-life chronic stress of childhood maltreatment can be measured using the Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 2003), while recent life stressful events may be quantified using the Interview for Recent Life Events (IRLE) (Paykel, 1997).

Prospective examination of maternal physiology during pregnancy and of her infant post-partum, in addition to psychosocial measures, may help clarify associations between prenatal depression, anxiety and stress and infant physiological and temperamental outcomes.

25.3 Physiological Changes Associated with Depression and Anxiety

Comprehensive investigation of the physiological state of the mother during pregnancy will help clarify the relationship between maternal affect/stress and development. Both the sympathetic branch of the ANS and the hypothalamic–pituitary–adrenal (HPA) axis are activated during acute stress (Miller and O'Callaghan, 2002). Chronic and/or unpredictable activation of these stress response systems can lead to a diminished capability to respond appropriately, which has been described by the allostatic load theory (McEwen and Stellar, 1993). The concept of allostatic load suggests that there is a cumulative physiological risk associated with exposure to psychosocial stressors over the course of life. The resulting dysregulation or "wear and tear" of physiological systems, including neuroendocrine, immune, metabolic and cardiovascular systems, is thought to predict poor health outcomes (Juster et al., 2009). This model has previously been used to describe the relationship between maternal stress and adverse perinatal outcomes (Shannon et al., 2007).

The HPA axis hormone, cortisol and ANS system neurotransmitters, norepinephrine (NE) and epinephrine (Epi), have been described as mediators of the allostatic load (Seeman et al., 1997). Increased activation of the HPA axis and that of the sympathetic nervous system (SNS) are frequently reported in depressed and anxious patients (Sevy et al., 1989; Gillespie and Nemeroff, 2005; Hughes et al., 2004; Takase et al., 2004; James et al., 2004; Lechin et al., 1995). Also, dramatic changes along the HPA axis and the ANS occur during normal pregnancy to accommodate maternal–fetal metabolic requirements (Lindsay and Nieman, 2005; Voss et al., 2000). A dysregulation of these systems (HPA axis and the ANS) may be the basis for an important etiological link between maternal adversity and negative infant neurodevelopmental outcomes.

25.4 HPA Axis

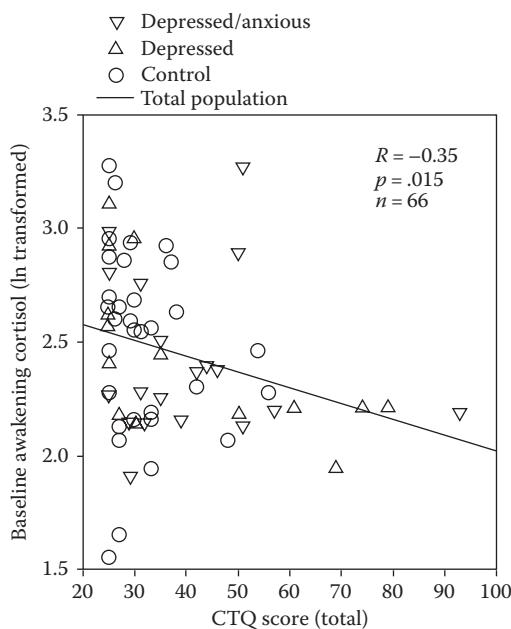
The HPA axis activates and coordinates the stress response by receiving and interpreting the information from other areas of the brain (primarily the amygdala and the hippocampus), as well as from the ANS and from the environment. The steroid hormone cortisol

is released from the adrenal gland to prepare the body for stress, and it self-regulates by a negative feedback system. The HPA axis provides the adaptive mechanisms needed to maintain allostasis in times of increased stress. Findings suggest a stimulatory role of the brain NE on the activity of the HPA axis, via corticotropin-releasing hormone release from the hypothalamus (Al-Damluji, 1988, 1993; Plotsky et al., 1989; Whitnall, 1993). Thus, an examination of both SNS and HPA axis systems can provide valuable information about an individual's stress physiology.

In numerous studies, depressed patients have exhibited a disrupted circadian rhythm of cortisol and an increased cortisol response to psychosocial stress (Sachar et al., 1973; Young et al., 2004; Deuschele et al., 1998). Fetal cortisol concentrations were found to be linearly related to maternal cortisol concentrations, and it was suggested that maternal cortisol may account for 40% of the variance in fetal cortisol (Gitau et al., 1998, 2001). Increased cortisol levels during pregnancy can be harmful during development, but high levels of the placental enzyme 11 β -hydroxysteroid-dehydrogenase-type 2 (11 β -HSD2) protect the developing fetus by converting cortisol to its inactive form, cortisone (Benediktsson et al., 1997; Sun et al., 1999). The placentas of women who demonstrated intrauterine growth restriction showed decreased 11 β -HSD2 gene expression, indicating the importance of this enzyme for healthy growth *in utero* (McTernan et al., 2001). The activity of 11 β -HSD2 is influenced by ANS activation: increased levels of catecholamines, NE and Epi, were found to downregulate 11 β -HSD2 gene expression in the human placental cells (Sarkar et al., 2001). This suggests further interplay between the two main stress response systems during the highly vulnerable time of fetal development.

Maternal HPA axis function during pregnancy has also been linked to infant development. Women with morning cortisol levels that fell in the upper quartile of the distribution in late pregnancy (weeks 37–38) gave birth to infants who scored lower on the Bayley Infant Mental Development Index at 3 months of age (Huizink et al., 2003). Women who were depressed in the third trimester of pregnancy had higher levels of urinary cortisol, which predicted more abnormal reflexes in their newborns, as scored using the Brazelton Neonatal Assessment, but there were no significant associations with other factors that were scored (Lundy et al., 1999).

We previously examined the HPA axis function in depressed pregnant women during late pregnancy (25–33 weeks of gestational age) in comparison with healthy control pregnant women (33 in each group), by measuring the cortisol awakening response (CAR). The CAR is a non-invasive and reliable measure that can detect subtle changes in the HPA axis function (Pruessner et al., 1997). Although the cortisol levels were lower in depressed women, we found no significant difference between the two groups, as measured by the CAR. However, we did find that depressed pregnant women with a history of childhood maltreatment (as measured with the CTQ) had a lower baseline cortisol concentration, explaining 12% of the variance (Shea et al., 2007). This suggests that the maternal "allostatic load" accumulated during early life persists into adulthood and affects HPA axis function during pregnancy. Glucocorticoids, such as cortisol, stimulate the development of fetal tissues and organs such as the liver, lungs, gut, skeletal muscle and adipose tissue (Fowden et al., 1998). Animal studies have found that glucocorticoids regulate fetal organ development and that a deficiency can affect normal development of the adrenals, kidneys, liver, lungs and gut (Fowden and Forhead, 2009). Effects of the allostatic load on cortisol regulation evident during pregnancy may negatively affect healthy fetal development. The involvement of the maternal HPA axis, as well as the maternal ANS, with respect to infant developmental outcomes is unclear and requires further investigation (Figure 25.1).

**FIGURE 25.1**

The relationship between early-life trauma (CTQ) and the baseline awakening cortisol level in pregnant women. Linear regression analyses indicated that the CTQ was negatively related to the baseline morning cortisol level, controlling for wake-up time and AD medication. (Adapted from Shea, A.K., Streiner, D.L., Fleming, A., Kamath, M.V., Broad, K. and Steiner, M., *Psychoneuroendocrinology*, 32, 1013–1020, 2007.)

25.5 Measurement of the ANS in Pregnancy Using HRV

Evaluation of the ANS in relation to prenatal maternal affect can be completed by measuring the HRV from an electrocardiogram (ECG) recording. The HRV is modulated primarily through sympathetic and parasympathetic (vagal) cardiac nerve innervations of the sinoatrial node (Malik, 1996; Malik and Camm, 2004). Vagal fibers reduce the heart rate (HR) and actively inhibit sympathetic influences on the heart to maintain allostasis and promote calm behavioral states (Vanhoutte and Levy, 1979; Porges, 1995). Measures derived from HRV analyses during pregnancy can demonstrate centrally mediated changes in the autonomic modulation of cardiac function and represent a reliable marker of ANS (Kamath and Fallen, 1993). Decreased HRV may indicate higher sympathetic control of the ANS and a lack of the systems' ability to respond in an appropriate manner. A common finding in depression and anxiety is the loss of normal ANS control of HR and its rhythm, as reflected in decreased HRV (Davydov et al., 2007; Agelink et al., 2002; Kim et al., 2005; Yeragani et al., 1993; Hughes and Stoney, 2000; Rechlin et al., 1994). Similarly, both acute stress and chronic work stress have been associated with decreased HRV (Lucini et al., 2005; Lin et al., 2001; van Amelsvoort et al., 2000; Sloan et al., 1994; Pagani et al., 1991). Considering the reported negative associations between maternal adversity and infant development, measurement of HRV may provide an important index that can quantify the psychophysiological mechanisms involved.

The ANS is dramatically different in pregnant women, compared to the non-pregnant state, to accommodate the developing fetus (see Chapter 8). Extreme hemodynamic changes occur during pregnancy, including increased cardiac output and decreased systemic vascular resistance, together with expanded blood volume (Cunningham et al., 2001; Desai et al., 2004). A decreased parasympathetic influence during pregnancy and attenuation of the baroreceptor sensitivity in late pregnancy (third trimester) have been suggested (Ekholm and Erkkola, 1996; Blake et al., 2000; Moertl et al., 2009). In healthy pregnant women, HRV is reduced (but stable), while the mean 24 h HR increases with gestational age (significantly higher in the third trimester vs. the first) to adapt to the changing metabolic requirements (Ekholm et al., 1993; Moertl et al., 2009). Healthy ANS function is essential to accommodate changes in blood volume and circulation that take place during normal pregnancy.

Poor adaptation of maternal hemodynamics may alter uteroplacental circulation and subsequent fetal development. In particular, changes in the umbilical blood flow velocity are purported to be determined mainly by maternal hemodynamics, including the vascular pressure changes associated with maternal HR (Struijk et al., 2001). HRV was found to be reduced in pregnant women with abnormal uterine perfusion compared to healthy women and was suggested to predict PE (Walther et al., 2006). Women with abnormal uterine perfusion gave birth to infants of smaller birth weight earlier: a similar outcome was reported in women experiencing stress/depressed mood/anxiety during pregnancy (Warren et al., 2006; Paarlberg et al., 1999). Pal and colleagues (2009) measured the HRV in 211 pregnant women during each trimester, in an attempt to find differences among those who developed pregnancy-induced hypertension (PIH) compared to those who did not (Pal et al., 2009). They compared women with PIH risk factors (family history of PE, PE in previous pregnancy, extremes of reproductive age, BMI > 35, DBP > 80 mm Hg at the first visit, first pregnancy, multiple pregnancy, underlying medical conditions [diabetes mellitus, renal disease pre-existing hypertension]) with those without such risks and found that the sympathetic tone (low-frequency [LF] band power) in the women who did develop PIH ($n = 27$) was significantly higher than that in women without any risks during all three trimesters. Also, the women who developed PIH had higher low frequency: high frequency (LF:HF) ratios (which indicate sympathovagal balance) compared to both groups during the first trimester. These results suggest that women who go on to develop PIH during gestation have an increased sympathetic drive, which may affect fetal well-being. Since adrenergic receptors, involved in the regulation of the SNS, are found in human placental blood vessels (Resch et al., 2003), further investigation of the maternal ANS is warranted.

Although reports on perinatal HRV with respect to psychological stress and negative affect are lacking, changes in NE have been described. Depressed pregnant women had elevated urinary NE levels during the second and early third trimesters compared to non-depressed women (Diego et al., 2004; Lundy et al., 1999). Higher NE levels were also positively correlated with depression and anxiety scores during pregnancy and negatively correlated with fetal abdominal and head circumferences (Diego et al., 2006). Neonatal catecholamine levels have been reported as predicted by maternal prenatal levels and also by maternal prenatal trait anxiety and depression (Lundy et al., 1999; Field et al., 2004). Synchrony of maternal–fetal physiology may explain how maternal adversity affects the development of the infant.

DiPietro and colleagues reported an association between maternal and fetal HRs: higher fetal HR was associated with lower HRV at 1 year of age (DiPietro et al., 2000). If changes in the maternal ANS function during pregnancy translate to similar changes in the fetus, the development of the ANS may be compromised. Also, increased maternal sympathetic

influence during pregnancy has been suggested to be involved in vasoconstriction of placental vessels. Animal studies have shown that increased NE levels result in decreased blood flow to the placenta as well as vasoconstriction (Birnbaum et al., 1994; Rankin et al., 1982). Increased fetal activity at 15 weeks of gestation in humans was associated with higher levels of amniotic fluid NE during amniocentesis, but maternal anxiety scores were not, with the exception of fetal hiccups (Bartha et al., 2003). This study demonstrates that maternal physiological changes may be a better predictor of fetal activity than maternal report of affect. Another recent study found that the maternal depression scores did not influence fetal activity at 20–22 weeks of gestation, but that both higher anxiety scores and caffeine intake were associated with increased fetal single limb movement (Conde et al., 2010). Not all women who report negative affect and stress have associated pathophysiology, and some women reporting normal mood may also show changes consistent with the allostatic load. The SNS activity of a pregnant woman experiencing adversity in relation to her developing fetus remains unclear. Measurement of the ANS via the HRV in both the mother during pregnancy and the infant post-partum will help clarify if the maternal allostatic load affects the infant physiological outcomes relevant to neurodevelopment. Furthermore, the measurement of the infant stress physiology may help determine whether the maternal prenatal pathophysiology has transgenerational effects.

25.6 Assessment of Infants Exposed to Prenatal Depression and Anxiety

Assessment of the allostatic load markers in infants exposed to maternal adversity *in utero* may provide information about stress vulnerability. The ANS can also be measured non-invasively in infants, using HRV. Measures of HRV have been commonly used for the investigation of psychobiological processes in infants. Studies have measured the vagal tone and other components of HRV as early as post-natal day 1 (Fox and Porges, 1985; Clairambault et al., 1992; Mehta et al., 2002). A child's physiological capacity to self-regulate can be measured using the vagal tone: higher vagal tone was associated with improved performance on executive function tasks in 3.5-year-olds (Marcovitch et al., 2010). Infant vagal tone has been associated with individual differences in behavioral regulation, emotional arousal and temperament (Hastings et al., 2008; Huffman et al., 1998; Calkins et al., 2007), indicating a valuable measure for infant developmental research. For example, using a laboratory-based measure of temperament, infants with higher vagal tone at 12 weeks of age showed fewer negative behaviors (Huffman et al., 1998). Infants who showed a greater change in the vagal tone (i.e., ANS response to the changing environment) were rated by their mothers, using the Infant Behavior Questionnaire (IBQ) (Garstein and Rothbart, 2003), as easier to soothe and having longer durations of orientation. However, infants who were identified as having colic did not differ from control infants in the vagal tone at both baseline and during a physical exam (White et al., 2000). Since HRV measurement provides an indirect measure of infant ANS, it presents an important and non-invasive tool to explore the effects of *in utero* exposure to maternal adversity.

Infants exposed *in utero* to maternal smoking and cocaine have lower HRV compared to non-exposed infants (Schuetze and Zeskind, 2001; Mehta et al., 2001), but investigations focused on prenatal stress are lacking. Lower HRV values suggest ANS dysfunction and a decreased ability of the sinus node of the heart to respond to extrinsic signals, thereby indicating a reduced ability to adapt. A few groups have examined

the vagal tone in infants in relation to maternal depression and anxiety and have suggested an association between negative affect (depression) and a reduced infant HRV (Field et al., 2003; Jones et al., 1998). In particular, higher maternal trait emotionality (trait anxiety, depression, hostility), but not maternal state emotionality, in early pregnancy (before 16 weeks of gestation), was associated with decreased vagal tone in 4-week-old infants (Ponirakis et al., 1998). However, two recent studies have found no influence of maternal prenatal depression (measured during the second trimester only) on infant HRV (Dierckx et al., 2009; Kaplan et al., 2008). However, ANS development continues into the third trimester (Pillai and James, 1990) and the maternal psychiatric symptoms were not measured during this time; the study done by Jones and colleagues (1998) suggested that maternal affect in the third trimester influences infant vagal tone. Of interest, regular maternal exercise (3 times/week) during pregnancy was associated with increased fetal HRV and lower HR in the third trimester, suggesting that women who are more cardiovascularly fit positively influence fetal ANS development (May et al., 2010).

A recent study from Yoga University at Bangalore, India, investigated the effects of yoga on perceived stress and HRV during pregnancy (Satyapriya et al., 2009). Authors randomly assigned 90 pregnant women to either a yoga practice routine (including postures and meditation) or a standard prenatal exercise routine (both 1 h daily) from study recruitment (18–20 weeks of gestational age) to delivery. They found that women who completed the yoga practice had significantly lower perceived stress scores at 36 weeks of gestation compared to scores at 20 weeks. The other group (exercise) had scores that were both significantly higher versus their own scores in mid-pregnancy and, also, compared to the yoga group. Further, they also measured HRV before, during and after a relaxation session for both groups at 20 and 36 weeks of gestation and found that the yoga group had a greater reduction in sympathetic tone (LF band) after the session compared to their changes at week 20 but that the reductions in sympathetic tone in the regular exercise group were dampened. The authors suggest that yoga was superior to standard prenatal exercises in improving ANS responses.

HRV measurement in newborns and infants has been studied in relation to later behavioral and emotional development. Higher neonatal vagal tone and lower HR were related to a more positive intellectual outcome, as assessed by the Bayley Mental Development Scale at 8 and 12 months of age (Fox and Porges, 1985). A greater HRV in very low birth weight preterm neonates was associated with better mental processing, social skills and fine motor skills and with fewer behavioral problems 3 years later (Doussard-Roosevelt et al., 1996). Similarly, a greater RR interval in the recovery period post-stress (heel stick) in newborns was associated with higher maternal-rated activity on the IBQ at 6 months of age; the RR interval and vagal tone were not related to any other behavioral scales of the IBQ (Gunnar et al., 1995). Also, the RR interval and vagal tone were not related to cortisol levels measured at the same time, and authors suggest that both the HPA axis and ANS should be measured before an infant may be identified as "stress-reactive." However, increased vagal tone during the Bayley test was associated with higher levels of maternal-rated difficult behavior at the time (Porges et al., 1994). When the infants were tested again at 3 years of age, stability of their vagal tone was observed, suggesting that early measures are appropriate with respect to later behavioral outcomes. Results from the same study indicated that 9-month-old infants who showed less change in their vagal tone during a social/attention task had significantly more behavioral problems at 3 years of age (Porges et al., 1996). Specifically, a smaller change in the vagal tone during the tasks was associated with more aggressive behavior and social withdrawal in 3-year-olds. These studies

indicate a continuity of the relationship between HRV and self-regulation over time. HRV measurement, in addition to HPA axis measures, may help identify the infants that may be at risk for negative developmental outcomes.

There is evidence that both high and low birth weights are associated with cardiovascular disease (CVD) in adulthood, that is, the "Barker hypothesis" (Barker et al., 1990), suggesting *in utero* programming of disease. Considering the reports on negative birth outcomes following prenatal exposure to maternal adversity, this may present an important parallel that merits investigation of underlying physiological mechanisms. It is well documented that lowered HRV strongly correlates with negative CVD outcome in adults (Singh et al., 2003). It might, therefore, be prudent to assess HRV measures in infants exposed to prenatal stress, in order to examine whether cardiovascular programming of the ANS occurs.

While the relationship between maternal stress, anxiety and depression in relation to pregnancy outcomes has been studied, specific mechanisms and effects on infant development remain largely unknown. The maternal allostatic load may be the important mediating factor. Prospective investigation of pregnant women experiencing adversity from early pregnancy and of their infants post-partum, using both psychosocial measures and comprehensive physiological stress measures, may provide valuable information. In particular, infant HRV measurement is required, as neural regulation of the heart has been implicated in emotional and behavioral regulations in infants and children. By doing so, it may be possible to establish a measure, which may predict either resiliency to the effects of stress or, conversely, impaired fetal growth development. This information is essential for the understanding of maternal stress and infant developmental outcomes and may contribute to early intervention strategies.

25.7 Our Work

We have published the analyses of the HRV data recorded from depressed and healthy pregnant women (Shea et al., 2008a). We have also completed the HRV analyses for the infants of those women (6–8 weeks of age), which have been presented elsewhere (Shea et al., 2008b). The work is summarized below.

12–25 weeks of gestation
25–31 weeks of gestation
Parturition
6–8 weeks post-partum
3 months post-partum

Study Design

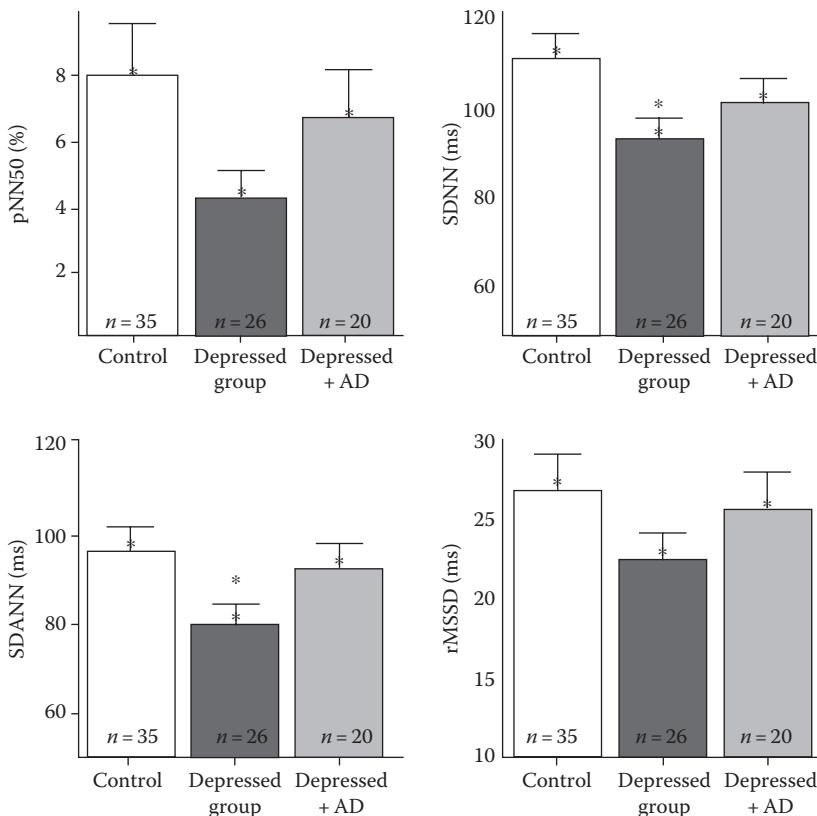
- *Study Intake:* clinical interview; depression/anxiety rating scales; stressful life event inventory; salivary samples
- *Follow-up:* mood/anxiety reassessed; 24 h ECG; salivary samples
- Birth outcomes
- 20–30 min infant ambulatory ECG (lead II)
- Infant Behavior Questionnaire—revised version (IBQ-R); infant salivary samples; maternal mood/anxiety reassessed

Pregnant women presenting with depressed symptoms at 12–25 weeks of gestation to the Women's Health Concerns Clinic (WHCC) were recruited and offered a choice regarding treatments/interventions (*Depressed Group, n = 46*). Healthy control subjects were recruited from the community and from our ultrasound department, Hamilton (*Control Group, n = 35*). Inclusion criteria were: age of 18 years; pregnant (up to 25 weeks of gestation); and able to communicate in English. Further inclusion criteria for the *Depressed Group* were to score as "depressed" using one of the following cutoffs: EPDS score of ≥ 13 (Cox et al., 1987; Matthey et al., 2006) and the Montgomery–Asberg Depression Rating Scale score of ≥ 9 (Mittmann et al., 1997). Prenatal anxiety was measured using the STAI (Spielberger et al., 1970). Of the 46 women in the *Depressed Group*, 26 were treated using psychotherapy only and 20 were treated using psychotherapy in combination with AD. A variety of selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs) were used; the specific kind selected on a case-by-case basis by the attending psychiatrist.

Women with a recent diagnosis or history of psychotic disorder, as well as those with serious medical conditions, were excluded. Potential control subjects were excluded if they had a recent or past diagnosis of psychiatric illness, as assessed by the Mini International Neuropsychiatric Interview (Sheehan et al., 1997), and/or at least two stressful life events in the last 6 months (including relationship stress), as measured using the Interview for Stressful Life Events (Paykel, 1997).

The women wore a Holter monitor for 24 h between 25 and 31 weeks of gestation. The 24 h Holter ECG recordings were analyzed by an experienced technologist blinded to group membership at the McMaster University electrocardiography laboratory. The data was first annotated with Delmar Avionics scan software and a beat-to-beat recognition software assigned a class (normal or ectopic) to each beat. All the interbeat intervals were downloaded for off-line computational analyses. The following time domain variables were obtained: the mean values for the standard deviation of all 24 h N-N intervals (SDNN), the SD of the averages of N-N intervals in all 5 min segments of the entire recording (SDANN), the percentage of N-N intervals differing by more than 50 ms (pNN50) and the root mean square of the SD of successive N-N intervals (rMSSD). The SDNN and the SDANN values are influenced by short-term (i.e., respiration) and long-term (circadian) factors. The pNN50 and the rMSSD reflect vagal cardiac modulation under normal conditions (Stein et al., 1994). Spectral analyses of the data were also completed (Shea et al., 2008).

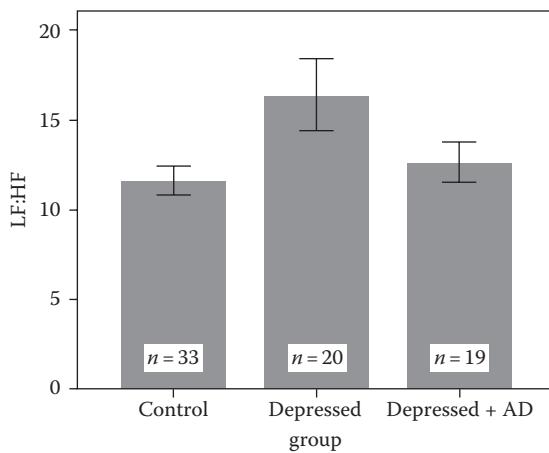
As prematurity can influence the development of ANS, only infants born at a minimum of 36.5 weeks of gestation were followed (Haley et al., 2009). The infants were tested at approximately 6 weeks of age. A 20 min lead II ECG recording from each of the infants was obtained using three surface electrodes. The visit occurred either at the WHCC or at the home. The ECG was digitized at a rate of 1000 samples/second using a 12-bit A/D converter connected to a personal computer and stored on a hard drive for off-line analysis. The power spectral analyses were completed using the MATLAB® software (The MathWorks Inc., Natick, MA, USA). A QRS detection algorithm was implemented and a series of RR intervals were obtained from the raw ECG signal. If there were occasional ectopic beats, the RR interval data at the instant when the ectopic appeared were averaged using previous five and subsequent five beats. The instantaneous HR was computed from RR interval time series. The HR data then were resampled at 6 times/second to obtain an equally sampled HRV signal. Sequential segments of data lasting 128 s were subjected to power spectral analysis as follows: Hanning window was applied to reduce leakage in the neighboring bands and the Blackman–Tukey power spectra were computed. Based on

**FIGURE 25.2**

Mean (+/– SE) HRV time domain variables in healthy pregnant women (controls) and women who had experienced depression during pregnancy, stratified according to whether they took antidepressants (AD) or not. The groups were compared using MANCOVA, controlling for age, the number of cigarettes smoked per day while pregnant; * $p < .05$, significantly depressed than the controls. (Adapted from Shea, A.K., Kamath, M.V., Fleming, A., Streiner, D.L., Redmond, K. and Steiner, M., *Clin. Auton. Res.*, 18, 203–212, 2008a.)

a review of the literature, the LF band (0.015–0.15 Hz) and the HF band (0.16–1 Hz) were identified (Longin et al., 2005; Ariagno et al., 2003) and power in each band was integrated and the LF:HF ratio was computed. The averaged power in each band for a recording session, ratio of powers (LF:HF) and percentage power in each band were computed and used for subsequent statistical analysis. In general, the variability of the HR as a measure of the autonomic regulation of the sinus node was assessed through a power spectral analysis of the beat-to-beat HR time series. While the HF area (0.16–1 Hz) in the neonatal HRV power spectra is highly correlated with vagal modulation of the sinus node, the LF area (0.015–0.15Hz) is associated with predominantly sympathetic and to a lesser extent, vagal influences mediated through the SA node. The results are presented in Figures 25.2 and 25.3 and Tables 25.1 and 25.2).

These data suggest that maternal depression during pregnancy is associated with decreased HRV both in mothers and their infants and that AD medication may have a positive effect on these parameters. The SDNN, a time domain measure reflects the balance between sympathetic and parasympathetic inputs on the pacemaker of the heart,

**FIGURE 25.3**

Infants born to women in the Depressed group had higher LF:HF ratios (measure of sympathovagal balance) at 6–8 weeks of age than those born to the Controls, but not when the mothers took ADs while pregnant, controlling for infant sex and maternal smoking. (Adapted from Shea, A.K., Streiner, D.L., Fleming, A., Kamath, M.V. and Steiner, M., Maternal depression, antidepressant use during pregnancy and infant autonomic and endocrine outcomes. Paper presented at International Society of Psychoneuroendocrinology, Dresden, Germany, 2008b.)

but more specifically, the lower SDNN values found in the depressed pregnant women indicate less parasympathetic (vagal) influence. This reduced maternal HRV suggests ANS dysfunction, which may have consequences for healthy fetal development.

Lowered HRV, in general, may be involved in the hemodynamic accommodation during normal pregnancy. However, further reductions in HRV were found in women with complications of pregnancy, such as PE and PIH (Metsaars et al., 2006; Yang et al., 2000). Increased sympathetic activity has been associated with negative outcomes in PE, such as reduced birth weight (Ophir et al. 2006; Jerath et al., 2009). Likewise, a sympathetic dominance in depressed and anxious pregnant women may affect fetal development. Women with high trait anxiety scores were found to have a higher pulsatility index (PI) (which increases with increasing vascular resistance) in their umbilical arteries, as measured using Doppler ultrasound velocimetry (Sjostrom et al., 1997). Also, an increased

TABLE 25.1

Unadjusted Means (SD) for the 24 h HRV Time Domain Measures in Pregnant Women

Group	Depressed n = 46	Control n = 35	p
pNN50 (%)	5.4 (5.4)	8.0 (9.6)	.09
SDNN (ms)	97.9 (21.8)	112.4 (31.7)	.01
SDANN (ms)	85.4 (23.6)	96.6 (30.0)	.02
rMSSD (ms)	23.9 (9.0)	26.6 (13.0)	.18

Source: Shea, A.K., Kamath, M.V., Fleming, A., Streiner, D.L., Redmond, K. and Steiner, M., *Clin. Auton. Res.*, 18, 203–212, 2008a.

p-values represent MANCOVA analyses, controlling for age, smoking and antidepressant use. When the Depressed group was stratified according to antidepressant use, the differences in the SDNN and SDANN were only significant when comparing those not taking ADs and the controls.

TABLE 25.2

Infant HRV Measures at 6–8 Weeks of Age

Group	Depressed <i>n</i> = 20	Depressed + AD <i>n</i> = 19	Control <i>n</i> = 33	<i>p</i> (vs. Controls)
HR	149.7 (13.4)	151.2 (14.7)	149.8 (11.5)	NS
LF area	470.2 (33.9)	468.5 (24.6)	467.4 (22.7)	NS
HF area	43.3 (32.4)	44.7 (23.8)	46.1 (20.4)	NS
LF:HF ratio	16.4 (8.9)*	12.7 (4.9)	11.6 (4.5)	.013*

Source: Shea, A.K., Streiner, D.L., Fleming, A., Kamath, M.V. and Steiner, M., Maternal depression, antidepressant use during pregnancy and infant autonomic and endocrine outcomes. Paper presented at International Society of Psychoneuroendocrinology, Dresden, Germany, 2008b. *p*-values represent MANCOVA analyses, controlling for maternal smoking, infant sex and infant state (awake; asleep). *The Depressed group had significantly higher LF:HF ratios compared to the Control group.

mean uterine artery resistance index was found in women with high anxiety scores, as compared to those with low trait anxiety (Teixeira et al., 1999). It was suggested that these changes may explain the finding of low birth weight in infants born to mothers experiencing depression, stress and anxiety. Only one other study examining uterine artery Doppler ultrasound velocimetry in pregnant women suffering from psychiatric disturbance could be located to date. That study found no difference among women suffering from a psychiatric disorder (mixed group of depressed and anxious patients, *n* = 20), when compared to healthy pregnant women (Maina et al., 2008). However, since women included were from a group of mixed disorders, it is difficult to draw any conclusions specifically about depression or anxiety.

If there is a sympathetic overdrive in depressed pregnant women, it may be possible to overcome it with effective treatment strategies. When the *Depressed Group* was stratified according to whether they took AD, the results were significant only when comparing the depressed women not taking AD with the controls. This suggests an improved sympathovagal balance with AD medication. A linear increase in the SDNN was found after a 6-month course of the SSRI sertraline in depressed patients (McFarlane et al., 2001). Improved HRV measures were also found after 16 weeks of sertraline treatment (Glassman et al., 2007). However, the decision for pregnant women to take AD medication needs to be assessed on a case-by-case basis, weighing both the risks and benefits. When AD use is not appropriate, there may be other ways to improve vagal modulation. In particular, cognitive behavioral therapy was found to be associated with a reduced HR and an increased HRV among severely depressed patients with heart diseases (Carney et al., 2000). Also, regular yoga practice was associated with a greater reduction in the sympathetic tone (LF band) in pregnant women after a meditation session, as compared to standard prenatal exercise (Satyapriya et al., 2009).

Furthermore, we found that infants born to women experiencing depression during pregnancy had a significantly higher LF:HF ratio compared to the control infants, suggesting that the maternal state and/or physiological changes associated with depression negatively affected the development of fetal ANS.

Infants who were exposed to maternal AD medication *in utero* did not differ from the controls. Although women still reported depression (and anxiety), the AD treatment appeared to decrease some of the negative effects of maternal depression on infant ANS development, a similar pattern as we observed in their mothers' ANS function.

It is likely that depression during pregnancy is associated with ANS dysfunction, which may then have transgenerational effects on the ANS of the fetus.

The concept of fetal “programming” effects on ANS development has been studied in rats. Decreased blood flow to the uterine arteries (by ligation) during pregnancy resulted in rat offspring that showed increased adrenergic responsiveness (Sanders et al., 2004). Also, prenatally stressed rats showed increased systolic blood pressure responses to restraint stress in adulthood, suggesting a programming effect (Igosheva et al., 2007). Increased maternal anxiety in humans was associated with increased uterine artery resistance, which may due to a similar mechanism to that demonstrated in animal studies on decreased uterine artery hemodynamics (Teixeira et al., 1999). Maternal-fetal HR synchrony has been reported, and higher fetal HR was related to lower infant HRV 1 year post-partum (DiPietro et al., 2000). It appears that the intrauterine stress of maternal adversity, possibly mediated by increased maternal SNS activity and/or decreased parasympathetic tone, may have influenced the infant’s ANS development, demonstrated by reduced infant HRV at 6 weeks of age. Another recent study showed that maternal behavior during pregnancy (impulsive and aggressive outbursts) was associated with a decreased HRV in the infants at 6 weeks of age (Koelsch et al., 2009). Since previous studies have demonstrated that the intrauterine environment can affect the cardiac development as well as influence CVD later, these findings together help highlight the possible mechanisms involved (Louey and Thornburg, 2005). Physiological measures of both the mother during pregnancy and the infant post-partum are required to examine how maternal depression affects the infant.

Our results of the LF:HF ratio in healthy infants recorded at 6 weeks following birth were compared to those of Ariagno et al. (2003) taken at 1 month and 3 months following birth (Ariagno et al., 2003). They report values of 21.4 (28.3) and 7.8 (9.2) (mean \pm SD) for LF:HF ratio for infants at 1 month and 3 month following birth, respectively. Stability of the HRV measures was reported from infancy to childhood, suggesting that early assessment is appropriate. Bornstein and Suess tested infants at 2 months of age and again when they had reached the age of 5 years and found that the parasympathetic influence on the HR (vagal tone) did increase with age, but the value at 2 months of age was related to that at 5 years ($p = .07$) (Bornstein and Suess, 2000). Although this was only marginally significant, they may have been limited with only 38 infants repeating the test at 3 years.

We found that the LF:HF ratio differed between infants born to women in the Depressed Group not taking AD versus those in the Control Group. The LF:HF ratios in the infants born to women in the Depressed Group who did take AD were similar to those in the Control Group, suggesting an improvement with *in utero* AD exposure. This may occur indirectly through the AD effect on the maternal ANS, by improving the parasympathetic tone and maternal hemodynamics. Alternately, AD medications may mediate changes in the ANS function directly, since they have been found to readily cross the placenta (Hendrick et al., 2003; Rampono et al., 2009). Six-month-old infants that were exposed to maternal psychotropic medication had an attenuated cortisol reactivity to stressful laboratory tasks compared to infants whose mothers were depressed (but did not take medication), indicating a possible modulatory effect during fetal development (Brennan et al., 2008). Likewise, Oberlander and colleagues found lower evening cortisol levels in SSRI-exposed 3-month-old infants and suggested that prenatal SSRI exposure may “buffer” the HPA axis effects related to the disturbed maternal mood (Oberlander et al., 2008). If, in fact, the SSRI/SNRI medication in the current study exerted similar effects on improved fetal hemodynamics, the AD medication may be serving to “buffer” the effect of maternal depression on fetal ANS development. However, these preliminary data require much further investigation.

Other groups have examined the effects of AD exposure on infant HRV measures. One study investigated the response to a heel lance for biological testing in neonates (within the first 5 days of life) exposed to SSRI medication during pregnancy and found no differences at baseline or post-lance when compared to non-exposed infants (Oberlander et al., 2002). However, during the recovery period, infants exposed to SSRIs showed lower HR and increased parasympathetic (HF) modulation; there were no differences at any time point in the LF:HF ratio. Conversely, Zeskind and Stephens found no differences in the HR or HRV measures between SSRI-exposed and non-exposed newborns (1–2 days), but reported that SSRI exposure was associated with fewer reliable peaks in the HRV power spectrum (Zeskind and Stephens, 2004). However, this effect disappeared when gestational age was controlled. Results from testing within the first few days following birth may not be useful for examining the effects of maternal AD medication because there have been reports of a withdrawal syndrome that resolves with time (Nordeng et al., 2001; Sanz et al., 2005).

Another investigation by Oberlander and colleagues examined SSRI-exposed infants at 2 months of age (Oberlander et al., 2005). The infants who had been exposed to SSRIs during pregnancy showed lower HR in the recovery period post-heel lance, compared to non-exposed infants, which is similar to their findings in infants tested during the immediate neonatal period. The LF:HF ratio was lower in infants who were exposed both prenatally and post-natally to maternal SSRIs, compared to non-exposed infants, and the authors suggested that this demonstrated an attenuated biobehavioral pain response. The difference between the groups was unrelated to the maternal SSRI dose level during the third trimester. The work of Oberlander and colleagues suggests that AD medication exposure *in utero* is associated with increased infant parasympathetic function. The AD medication in our studies appears to have “corrected” the ANS dysfunction both in women during pregnancy and their infants at 6 weeks of age.

Decreased HRV, as measured using the vagal tone (PNS influence on HR), was found in infants born to women with higher depression and anxiety scores during pregnancy and also with lower socioeconomic status (Ponirakis et al., 1998; Field et al., 2003; Jones et al., 1998; Porges et al., 1994; Allen et al., 2000; Jacob et al., 2009). Infant HRV measurement presents an important window into ANS, and individual differences in such measures are related to behavioral regulation and impulse control in children (Calkins et al., 2007). Long-term follow-up of this cohort will help determine how these changes in ANS function may relate to development.

25.8 Conclusions

Evidence is mounting that a dysfunction of the ANS may occur in depressed pregnant women. Deleterious effects of such dysfunction can be modified by antidepressant medications. However, such compounds also affect the babies born to depressed mothers. Careful clinical considerations must be made before prescribing AD medication during pregnancy. Experts from psychiatry and obstetrics and gynecology, as well as a panel of consultants, recently put together a review paper about the management of depression during pregnancy (Yonkers et al., 2009). They suggested that most studies examining the effects of AD were unable to control the effects of depression. Also, the authors created several algorithms for evaluating the need for either continuation or commencement of

AD medication during pregnancy. Further prospective and long-term studies about the physiological influences of antidepressant use during pregnancy are required, so as to optimally treat depression during this vulnerable time for fetal development.

Abbreviations

AD	Antidepressant
ANS	Autonomic nervous system
11 β -HSD2	11 β -hydroxysteroid-dehydrogenase-type 2
CAR	Cortisol awakening response
CTQ	Childhood trauma questionnaire
CVD	Cardiovascular disease
ECG	Electrocardiogram
Epi	Epinephrine
EPDS	Edinburgh post-natal depression scale
HPA	Hypothalamic–pituitary–adrenal
HR	Heart rate
HRV	Heart rate variability
IBQ	Infant behavior questionnaire
IRLE	Interview for recent life events
LF	Low-frequency
NE	Norepinephrine
PE	Preeclampsia
PIH	Pregnancy-induced hypertension
SNS	Sympathetic nervous system
SNRIs	Serotonin–norepinephrine reuptake inhibitors
SSRIs	Selective serotonin reuptake inhibitors
STAI	Spielberger state–trait anxiety inventory
WHCC	Women's health concerns clinic

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