

## SPECIAL ISSUE

# Neurocardiology: A Bridge Between the Brain and the Heart

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*Cardiovascular variability in heart rate and blood pressure has been used to quantify the autonomic modulation of cardiovascular function for the past 20–30 years. However, some unresolved questions and controversies remain, some related to methodology. The development of methods to use with heart rate variability and baroreflex sensitivity has prompted a multidisciplinary approach, calling on mathematics, signal processing, physiology, and cardiology. An adequate understanding of certain basic principles is necessary before its clinical potential can be fully exploited. The current overview outlines the physiological background and the fundamental methodology used in the field of neurocardiology by presenting the newer insights and developments from both a fundamental and clinical perspective. The authors also provide an overview of the most important clinical applications of heart rate variability.*

### Introduction

For centuries, popular wisdom described the heart as the source of emotion, courage, happiness or sorrow, and wisdom. This is reflected by numerous popular expressions:

- *In her heart, she knew it wasn't true.*
- *He's a man after my own heart.*
- *It really broke my heart to see him leave.*
- *You'll have to learn phrasal verbs by heart.*
- *At first sight, he seems bad tempered, but he's really got a heart of gold! She is really bad tempered, and she's got a heart of stone!*
- *I'm 65 but I'm young at heart!*
- *and ultimately culminates in the representation of the Holy Heart, the seat of the soul!*

Another, more engineering-oriented approach is to consider the heart from a mechanical point of view as a motor and a pump with a control loop for electronic steering. Just as the driver of a car can modify the number of rotations per minute of the automobile engine according to the needs for speed and acceleration, heart rate adapts to the basic needs of the body. If we perform physical activity or if we are submitted to mental stress, heart rate will increase; during nighttime at rest, heart

rate will decrease (circadian variation). The normal heartbeat varies secondary to respiration (respiratory sinus arrhythmia [RSA]). Throughout all our daily activities, the control mechanism tries to optimize heart rate as a balance between increasing and decreasing. A general term for this behavior is *cardiovascular variability with specific expressions*: heart rate variability (HRV) and blood pressure variability (BPV).

### Neuroanatomy of Cardiovascular Control

Anatomically, the control loop is provided by pathways (sympathetic and parasympathetic) of the autonomic nervous system. Both the basic heart rate and its modulation are determined primarily by alterations in autonomic activity. Increased parasympathetic or vagal activity slows the heart rate and increased sympathetic activity increases the heart rate.

In a healthy individual, the role of the autonomic nervous system in the beat-to-beat adjustment of hemodynamic parameters is essential to adequate cardiovascular functioning. Therefore, cardiovascular control, as expressed by the time-dependence of hemodynamic variables, is a direct reflection of autonomic modulation. It may be used as a probe of autonomic performance and a detector of possible autonomic malfunctioning.

Besides heart rate, the cardiovascular response system involves the orchestration of three other interrelated variables: blood pressure, stroke volume, and total peripheral resistance. A major source of coordination of these variables is the baroreflex control.

The monitoring aspect of the arterial baroreflex consists of stretch receptors located primarily in the walls of the carotid sinus and the aortic arch. Under conditions of increased blood pressure, arterial walls are distended, resulting in increased afferent activity from the baroreceptors. This effect ultimately reduces cardiac performance via increased parasympathetic and decreased sympathetic outflow to the heart, providing reflex cardiac slowing and peripheral vasodilatation in an attempt to bring blood pressure back to normal levels. The reverse sequence of events occurs when blood pressure drops below normal levels.

## Cardiovascular Oscillations

Individual reflex and control mechanisms are interconnected, thereby allowing an optimized regulation of hemodynamics. When more than three parameters interact, the resulting structure becomes extremely complex. If these parameters are nonlinearly coupled in their stimulus response, then solely by treating the entire system more or less as a black box and using methods of nonlinear dynamics is it possible to disentangle the complexity and stability of cardiovascular regulation by addressing the character of the entity: oscillators, noise, stability, complexity, and feedback mechanisms. As a first approximation, however, linear analysis such as power spectral analysis (Fourier analysis) can be used to identify oscillating components.

## Physiological Significance

Part of the oscillations in heart rate are linked to respiration via rapid parasympathetic discharge patterns that are passed onto the heart on a beat-to-beat basis. In contrast, the sympathetic nervous system is too sluggish to mediate respiratory oscillations. Therefore, the respiratory oscillations of heart rate (RSA) can be taken as a marker for the vagal control. Being related to respiration, an average RSA is located around .25 Hz.

Another component of HRV is located around .1 Hz. The interpretation of this component has been more controversial and has resulted in a scientific enmity between the groups of Milan and Richmond. The .1-Hz component cannot be ascribed solely to sympathetic modulation. Other factors such as baroreceptor unloading and adrenoreceptor sensitivity are involved also. The .1-Hz oscillation in blood pressure (called Mayer waves) is more clear-cut and provides an index of sympathetic vasomotor control. Spectral peaks in this region are due to resonance of the baroreflex loop mediated through sympathetic efferents.

Finally, the baroreflex sensitivity reflects the relationship between blood pressure and corresponding heart rate.

## Methodology of Cardiovascular Variability Analysis

A first requirement is the recording of a high-quality electrocardiogram tracing under a stationary condition. Duration recordings can vary from 2 minutes to 24 hours (in Holter recordings). Beat-to-beat blood pressure can be obtained noninvasively from a finger cuff. The second step consists of peak detection: recognition of the QRS complex and systolic blood pressure. The result is a discrete, unevenly spaced series of events: the tachogram and the systogram. For spectral analysis, this is usually resampled to obtain an equidistant time series at .5 second if resampling is performed at 2 Hz.

Parameters in the time domain are computed easily. Their main limitation is the lack of discrimination between the different autonomic branches.

In the frequency domain, a steady, stationary, fluctuating time-dependent signal is decomposed into its sinusoidal components: the power spectral density, expressed in  $\text{ms}^2/\text{Hz}$  or  $\text{mm Hg}^2/\text{Hz}$ . Spectral power can then be determined by integrating over a defined frequency region and obtained in  $\text{ms}^2$  or  $\text{mm Hg}^2$ . Power spectral analysis has been performed by Fast Fourier Transform, autoregressive modeling, and wavelet transform. In a typical spectrum, three main frequency bands can be observed: very low (below .04 Hz), low frequency (LF; between .04 and .15 Hz) and high frequency (HF; between .15 and .4 Hz).

Chaotic behavior exhibits a number of characteristics that distinguish it from periodic and random behavior (i.e., HRV spectra show a broadband noise like variability over a large frequency span). This seems to be due to nonlinearity in the cardiovascular control network. The long-term regulation of heart rate contains both short-time periodic modulation and entirely nonperiodic fluctuations. There are indications that a reduction in complexity comes along with a decrease in vagal traffic, suggesting that a considerable amount of nonlinear behavior is provided by this branch of the autonomic nervous system. Methods of nonlinear dynamics define parameters that quantify complicated interactions of independent and interrelated components, which can be described as "complexity measures." Some examples are:

*Fractal dimension.* Nonlinear, deterministic chaos refers to a constrained kind of randomness, which may be associated with fractal geometry. A fractal has an essential characteristic: Its details at a certain scale are similar to those seen at larger or smaller scales.

*Entropy.* This refers to system randomness, regulation, and predictability and allows systems to be classified by rate of information loss or generation.

*Lyapunov exponents.* The trajectories of a chaotic signal in phase space follow typical patterns. Closely spaced trajectories converge and diverge exponentially, relative to each other. Lyapunov exponents measure the average rate of convergence/divergence of these neighboring trajectories. A positive Lyapunov exponent can be considered as a definition of chaos, provided the system is known to be deterministic.

*Correlation dimension.* This determines an order of the system (i.e., the number of dimensions needed to model the dynamics of the system under consideration).

The use of these new methods may provide a more sensitive way to characterize function or dysfunction of the cardiovascular system. A drawback is that they lack graphic representation to provide a direct link to physiology.

## Applications of Neurocardiology

HRV and BPV analyses have been used extensively in cardiac physiology in both healthy and diseased states. A search in Medline for “Heart rate variability” results in more than 10,000 hits! Moreover, this topic is still very current, for 3,457 papers have been published over the last 5 years in the best clinical and research journals.

The following findings for healthy populations have been published:

*Aging.* Both males and females show a general decrease in HRV parameters with age. Until 40–50 years of age, females show a dominant HF power compared with males. This behavior is possibly favoring an autonomic cardio-protective effect in young and middle-aged women.

*Gender variations.* A difference in HRV parameters between males and females was found (see previous paragraph).

*Circadian variations.* During daytime, more LF modulation has been observed and during nighttime more HF modulation has been observed.

*Physiological correlates.* Several studies have suggested a link among anxiety, hostility, depression, post–myocardial infarction, and reduced HRV. Men reporting higher levels of phobic anxiety had lower HRV values and hence had an increased risk of sudden death. In patients with depression, LF remained significantly lower than in patients without depression.

*Physical training.* Numerous studies reported an increased HF component and a decreased LF value of the power spectrum of HRV in physically trained subjects. The fact that physical training has a distinct impact on HRV in healthy subjects implies that exercising may be of value in cardiac rehabilitation.

*Smoking.* It increases both the HF and LF components. As such, it can enhance arrhythmias.

## Important HRV Findings in Disease

*Myocardial infarction.* There is a strong correlation between time-domain parameters and all-cause mortality after myocardial infarction. Several studies confirmed these results where LF was shown to be the most useful in risk stratification post–myocardial infarction.

*Sudden cardiac death and ventricular arrhythmias.* There is compelling evidence linking sudden cardiac death and ventricular arrhythmias to the autonomic nervous system: Increased sympathetic modulation appears to be proarrhythmic, whereas  $\beta$ -blocker therapy and enhanced parasympathetic modulation counteract this arrhythmogenic insult.

*Hypertension.* Generally a reduction in HRV and BPV parameters have been found.

*Diabetes mellitus.* There is a gradual decline in spectral power in the high and low frequencies with progression of the diabetic neuropathy.

*Heart failure.* Depressed HRV values can be used as a marker of the extent of disease progression. Patients with chronic heart failure demonstrated autonomic dysfunction similar to that seen in myocardial infarction patients, with a withdrawal of parasympathetic tone together with chronic activation of the adrenergic system and impaired arterial baroreflex sensitivity. A worsening New York Heart Association functional class is correlated with a significant progressive decrease in time and frequency domain parameters. These findings suggest that HRV analysis could be used to detect the severity of the disease and evaluate responses to therapeutic interventions.

*Heart transplantation.* A reduced variability was shown with an almost flat power spectrum. HRV analysis was unable to show rejection of the donor heart but could show reinnervation in some cases.

## A Future for Neurocardiology?

The literature in the field of neurocardiology has accrued tremendously over the last decade, and the area has been considered a fertile ground for a collaborative effort in both clinical studies and basic research.

However, there is still a certain disinterest in neurocardiology within the mainstream of cardiologists. This is due, in part, to clinical training that frequently presents a reduced, partial view of the cardiac patient and overlooks a more integrative view that includes the autonomic control system. Another drawback is the need for some understanding of the complex mathematical concepts of signal processing and of computer sciences that are required for a meaningful interpretation of the data. Finally there are still some unresolved issues and controversies in the field of physiological and clinical interpretation of HRV, leading to a “wait and see” attitude.



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