Review Article

Heart Rate Variability, Baroreflex Function and Heart Rate Turbulence: Possible Origin and Implications

VASILIOS E. PAPAIOANNOU

Democritus University of Thrace, Alexandroupolis Medical School, Intensive Care Unit, Dragana, Greece

Key words:
Autonomic nervous system, electrocardiogram, monitoring.

Manuscript received:
April 16, 2007;
Accepted:
August 3, 2007.

Address:
Vasilios E. Papaioannou

6-8 Polyviou St.
551 32 Thessaloniki,
Greece
e-mail:
papabil69@panafonet.gr

Risk stratification among patients suffering from cardiovascular diseases is a major field of intense investigation worldwide. The combination of structural indices, such as the left ventricular ejection fraction, with autonomic function indices has recently been proposed as the state-of-the-art method for risk assessment in patients with acute myocardial infarction or severe congestive heart failure. Among indices of autonomic-cardiac coupling heart rate variability, that is, the RR variability on the electrocardiogram, and heart rate turbulence, which describes the change in sinus cycle length after a premature ventricular beat, have been extensively studied in large patient populations and have been proven of significant value for the discrimination between survivors and non-survivors after an acute myocardial infarction. They are both related to the baroreflex arc, whose assessment can ameliorate the discriminating power of different mortality risk stratifiers. In this review article, the basic pathophysiological aspects of the above indices are discussed, along with the major clinical studies where their clinical validity has been tested. It seems that alterations in different autonomic indices can reliably differentiate between normal and pathological responses of the cardiovascular system after an acute (myocardial infarction) or chronic (congestive heart failure) event, whereas continuous individualised patient monitoring may provide the means of determining benefit for a given intervention in a particular patient.

Heart rate variability

Heart rate variability (HRV) describes variations in both instantaneous heart rate and RR intervals. Beat-to-beat fluctuations reflect the dynamic response of the cardiovascular control systems to a host of naturally occurring physiological perturbations. In particular, arterial and venous blood pressures are altered continuously as a result of the cyclic variation in intrathoracic pressure associated with respiratory movements, and also because of the fluctuations in peripheral vascular resistance resulting from regional blood flow autoregulation. The sympathetic and parasympathetic nervous systems maintain cardiovascular homeostasis by responding to beat-to-beat perturbations that are sensed by baroreceptors and chemoreceptors.[1]

Although oscillations in heart rate and blood pressure were identified over 100 years ago, the notion that certain frequencies may be indicative of either sympathetic or parasympathetic tone is considerably newer and has led to great clinical interest in describing changes in a range of physio-

logical and pathological conditions, such as heart failure, diabetes, hypertension, sepsis and brain death.[2-9] The first recorded measurements of oscillations in the cardiovascular system were described by Mayer in 1876. He observed pronounced oscillations in blood pressure in anaesthetised and spontaneously breathing rabbits at 0.1 Hz. A variety of animal and human research has established two clear frequency bands in heart rate and blood pressure signals. These bands include oscillations associated with respiration between 0.2 to 0.4 Hz (high frequency) and bands with a lower frequency range, below 0.15 Hz. The latter has often been subdivided into the low-frequency range below 0.09 Hz as well as a mid-frequency range (0.09-0.15 Hz).[10,11] In 1981 Akselrod introduced power spectrum analysis of heart rate fluctuations in order to quantify beat-to-beat cardiovascular control. Power spectrum density analysis provides the basic information of how power (variance) is distributed as a function of frequency.[1] In 1996, the Task Force of the European Society of Cardiology and the Northern American Society of Pacing and Electrophysiology published guidelines regarding standardisation of nomenclature, specification of methods of measurement, definition of physiological and pathophysiological correlates, description of clinical applications and identification of different areas for future research.[12]

The clinical relevance of heart rate variability was first appreciated in 1965 when Hon and Lee noted that foetal distress was preceded by alterations in inter-beat intervals before any change occurred in the heart rate itself.[13] The association of higher risk of post-infarction mortality with reduced heart rate variability was first shown by Wolf in 1977.[14] The clinical importance of heart rate variability became appreciated in the late 1980s, when it was demonstrated that low heart rate variability was a strong and independent predictor of mortality after an acute myocardial infarction.[6,10]

Measurement of heart rate variability

The RR variations may be evaluated by two methods: time domain and frequency domain.

Time domain methods

Time domain methods determine heart rate or RR intervals in continuous electrocardiographic recordings. Each QRS complex is detected and the normal-to-normal intervals (all intervals between adjacent QRS complexes) are calculated. Other time domain variables include the mean normal-to-normal interval, the mean heart rate, and the difference between the longest and the shortest interval. More complex statistical methods are also used, especially in the case of heart rate signals that are recorded over 24 hours or more. The simplest of these metrics is the standard deviation of the normal-to-normal intervals (SDNN), which is the square root of the variance. However, it should be emphasized that the shorter the monitoring period the less accurate the SDNN variable becomes. The most commonly used time domain methods are the square root of the mean squared differences of successive intervals (RMSSD), the number of differences between successive intervals greater than 50 ms (NN50), and the proportion derived from dividing NN50 by the total NN intervals (pNN50).[12]

Frequency domain methods

Spectral analysis of heart rate signals provides their power spectrum density and displays in a plot the relative contribution (amplitude) of each frequency. This plot includes at least three peaks. Fast periodicities in the range 0.15-0.4 Hz (HF) are largely due to the influence of the respiratory phase on vagal tone. Low frequency periodicities (LF), in the region of 0.04-0.15 Hz, are produced by baroreflex feedback loops, affected by both sympathetic and parasympathetic modulation of the heart, and very low frequency periodicities, in the frequency range less than 0.04 Hz, have been variously ascribed to modulation by chemoreception, thermoregulation and the influence of vasomotor activity (Table 1). The area under the power spectral curve in a particular frequency band is considered to be a measure of heart rate variability at that frequency. According to the report of the Task Force, the ECG signals analysed must satisfy several technical requirements in order that reliable information may be obtained. Ectopic beats, arrhythmic events, missing data and noise effects should be properly filtered and omitted. Frequency domain methods must be preferred in short term investigations. The recordings should last for at least 10 times the wavelength of the lower frequency bound, thus recordings of approximately 1 minute can assess the HF component of heart rate variability while 2 minutes are needed for the LF component. In conclusion, 5-minute recordings are preferred, unless the aim of the study dictates a different design.[1,10-12]

Table 1. Heart rate variability metrics in the frequency domain.

Frequency components	Units	Characteristics
ULF (ultra low frequency)	ms^2	24-hour recordings: <0.003 Hz
VLF (very low frequency)	ms^2	24-hour and 5-minute recordings: 0.003-0.04 Hz
LF (low frequency)	ms^2	24-hour and 5-minute recordings: 0.04-0.15 Hz
HF (high frequency)	ms^2	24-hour and 5-minute recordings: 0.15-0.4 Hz

Origin of heart rate variability components

Respiratory oscillations

The cyclic variation in intrathoracic pressure perturbs venous return, cardiac output, and thus blood pressure. These changes are sensed by baroreceptors and result in changes in autonomic activity in the heart. The important point is that such perturbations are mediated via the vagus nerve, since atropine administration eliminates high frequency oscillations in heart rate. It seems that a major cause of respiratory arrhythmia is a central coupling of respiratory drive to cardiac vagal motor neurons. However, the changes in vagal activity are partly induced by baroreceptor sensing of respiratory oscillations in blood pressure and reflect all components of the baroreflex loop. In addition, factors such as reduced respiratory capacity and body position may alter the amplitude of high frequency oscillations in blood pressure and subsequently the HF component of heart rate oscillations as well. Thus, heart rate variability analysis concerning slow frequencies cannot be used for comparisons between different patient groups, since there is a need for control of ventilation for both rate and depth. A more longitudinal study, involving patients whose respiratory variables remain stable, seems of greater importance and deserves further investigation.[15,16]

Slow oscillations

The low frequency component of heart rate variability is probably the most contentious aspect with respect to cardiovascular variability. There are two opposing theories in the literature proposing different potential origins: the central oscillator theory and the baroreflex feedback loop theory. According to the first viewpoint, LF oscillations reflect sympathetic tone and are generated by the brain stem circuits. Montano analysed the discharges of single neurons, which were classified as sympathetic and were located in the rostral ventrolateral medulla and caudal ventrolateral medulla in cats, and observed activity at 0.12 Hz that was positively correlated with heart rate and blood pressure variability. As the above oscillations remained after sinoaortic and vagal resection, it was assumed that the central nervous system is able to generate such oscillations. In humans, an increased LF component in heart rate variability has been documented in various conditions that decrease baroreflex gain and increase sympathetic outflow (tilt, mental stress, exercise). Apnoea, in which there is an absence of peripheral inputs, is also associated with a low frequency component in heart rate and blood pressure variability.[16,17]

However, the dominant theory remains the baroreflex feedback loop model. It seems that a change in blood pressure is sensed by arterial baroreceptors, which adjust heart rate through the central nervous system via both the fast vagal action and the slower sympathetic action. At the same time, baroreceptors induce a slow sympathetic withdrawal in the vessels. The delay in the sympathetic branch of the baroreflex in turn determines a new oscillation, which is sensed by the baroreflex and induces a new oscillation in heart rate. It has also been proposed that the LF oscillation arises from the interaction of slow sympathetic and fast vagal responses, where baroreflex buffering of the slow, respiratory-induced blood pressure oscillations results in resonant low frequency oscillations due to the delay in the slow conducting sympathetic loop of the baroreflex.[15,16,18]

In conclusion, it must be stressed that the low frequency oscillations of heart rate reflect the ability of the individual components of the baroreflex feedback loop to respond to different inputs that can alter the power of such oscillations and are not just a measure of sympathetic nerve activity.

Clinical implications of altered heart rate variability

A healthy state exhibits some degree of stochastic variability in physiological variables such as heart rate. Loss of such variability means a loss of complex-

ity that accompanies cardiovascular disease, critical illness and trauma, while it is associated with an increased mortality rate after acute myocardial infarction. It seems that physiological systems consist of various components that interact with each other in such a way that small changes in one component could elicit profound effects on the behaviour of the system as a whole. Heart rate variability is accepted as a measure of autonomic regulation of cardiac activity, and can reflect the coupling between the autonomic nervous system and the sinoatrial node.[19] Figure 1 illustrates the different heart rate dynamics of a healthy subject and of someone suffering from congestive heart failure. Both patients have nearly identical means and variances of heart rate. However, in the first case the heart rate signal shows complex and rather unpredictable behaviour, whereas in the second there are periodic oscillations that are associated with a Cheyne-Stokes pattern of breathing, indicating loss of complexity and low variability within the heart rate time series.

The observation that in acute myocardial infarction the absence of respiratory sinus arrhythmia is associated with an increased mortality was published in 1978 and was the first report that demonstrated the prognostic value of heart rate variability analysis for identification of high risk patients.[14] The first large prospective population study that proved the significant prognostic value of low heart rate variability after an acute myocardial infarction was the Autonomic Tone and Reflexes After Myocardial Infarction Study

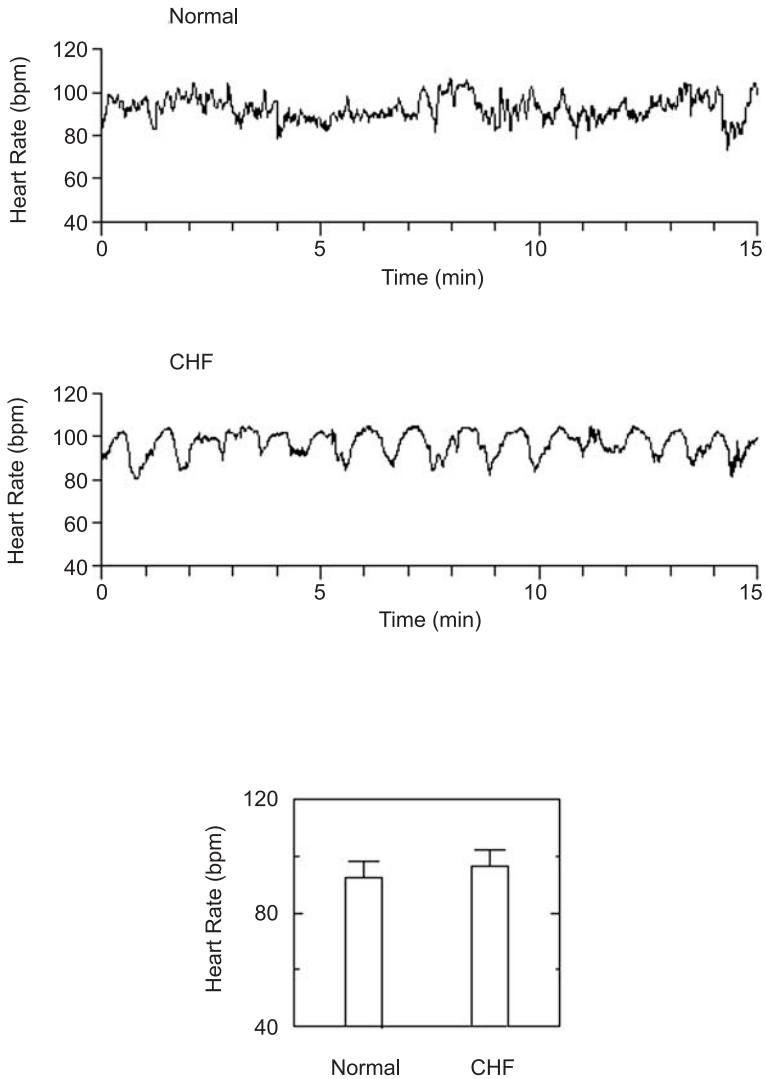

Figure 1. Time series of heart rate signals in two different situations. The plot of heart rate (beats/min, bpm) versus time (min) is called a tachogram. The top signal is from a healthy subject and the middle tracing is from a patient with severe congestive heart failure (CHF). Both patients have nearly identical means and variances of heart rate (bottom), however their dynamics differ significantly. (Downloaded from the open-source website: www.physionet.org).

(ATRAMI), which included 1284 patients with a recent (<28 days) myocardial infarction.[20] Twenty-four-hour Holter monitoring was performed in order to quantify heart rate variability (using SDNN values) and ventricular arrhythmias. Low values of heart rate variability (SDNN <70 ms) carried a significant multivariate risk of cardiac mortality. Furthermore, the association of low SDNN with left ventricular ejection fraction (LVEF) <35% carried a relative risk of 6.7, compared with patients with LVEF above 35%. Investigators from the Framingham Heart Study studied heart rate variability time and frequency domain measures in 736 patients and correlated them with all-cause mortality during 4 years of follow-up.[5] They concluded that heart rate variability offers prognostic information independent of that provided by traditional risk factors. During the Zutphen study, 885 middle-aged (40-60 years old) and elderly (aged 65-85) Dutch men were followed from 1960 until 1990 with SDNN being determined from the resting 12-lead ECG. It was shown that low heart rate variability was predictive of mortality from all causes, indicating that it can be used as an index of compromised health in the general population.[21] It seems that the predictive value of low heart rate variability is independent of other factors such as depressed left ventricular ejection fraction and presence of late potentials. It is supposed that the change in the geometry of a beating heart due to necrosis may abnormally increase the firing of sympathetic afferent fibres by mechanical distortion of their sensory endings.[6,7] This excitation attenuates the vagal activity in the sinus node, while there is a parallel reduced responsiveness of sinus nodal cells to neural modulations. Apart from a global reduction in all heart rate variability values after myocardial infarction, normalised values of low frequency (LF/total power) components are increased and high frequency components are decreased, indicating a shift of sympathovagal balance toward a sympathetic predominance.[6,7,22] After acute myocardial infarction, heart rate variability has been found to be reduced for a period of few weeks, while it is maximally but not fully recovered after 6 to 12 months.[23]

Apart from the value of altered heart rate variabil-

Table 2. Some selected studies investigating different heart rate variability values in cardiac diseases.

Disease	Authors	Study population	Methods	Clinical Findings
Hypertension	Guzzetti 1991[25]	49 with hypertension vs. 30 controls	Autoregressive modelling	↑ LH in hypertension,
	Langewitz 1994[26]	34 with hypertension vs. 54 controls	Fast Fourier transformation (FFT)	↓ HF component and loss of circadian variation (both studies)
Heart failure	Saul 1998[27]	25 with heart failure vs. 21 controls	Statistical methods	Low HRV
NYHA III & IV	Binkley 1991[28]	10 with heart failure vs. 10 controls	4 minutes FFT	↓ HF (>0.1 Hz), ↑ LF/HF
	Townend 1992[29]	12 with heart failure	FFT and statistical methods	↑ HRV with treatment with inhibitors of converting activation enzyme (ACEs)
Cardiomyopathies	Counihan 1993[30]	104 patients with cardiomyopathy	FFT and statistical methods	↓ HF (>0.1 Hz)
Sudden death,	Algra 1993[31]	193 survivors vs. 230 controls	Statistical methods in 24 recordings	↓ HRV induces ↑ in mortality by a factor of 2.6
Heart attack	Huikuri 1992[32]	22 survivors vs. 22 controls	Autoregressive modelling in 24 hour Holter	↓ HF in survivors
Ventricular arrhythmias	Huikuri 1993[33]	18 patients with ventricular fibrillation	Autoregressive modelling in 24 hour Holter recordings	↓ of all HRV components before the arrhythmic episode

NYHA – New York Heart Association.

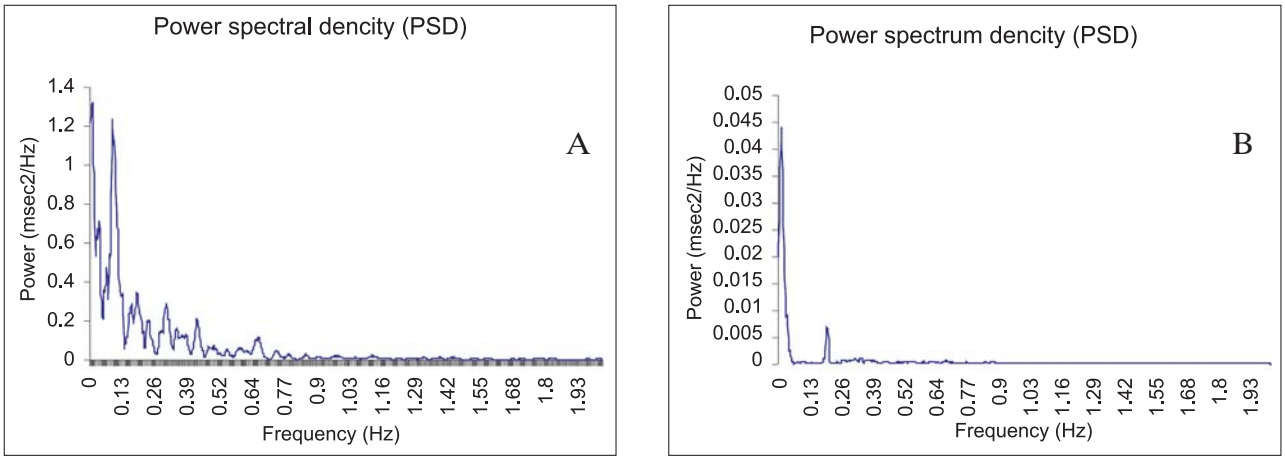

Figure 2. Power spectrum density, analysed in two patients treated in the intensive care unit. Patient A was hospitalised for a scheduled carotid endarterectomy and patient B suffered from cardiogenic shock post myocardial infarction. The latter patient displays low heart rate power (area under the curve), while all frequency components are barely visible in comparison with the first subject. The scale of power in the second case has been changed and the x-axis has been omitted for better visualisation of the plot; otherwise it would be impossible to detect any peaks in the graph.

ity for risk stratification after acute myocardial infarction, it has been demonstrated recently that patients suffering from congestive heart failure (retrospective electrocardiographic data analysis from 127 patients in the Veterans Affairs' Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure) with SDNN <65.3 ms had a significantly increased risk of sudden death ($p=0.016$), while each increase of 10 ms in SDNN conferred a 20% decrease in risk of mortality ($p=0.0001$).[24] Table 2 summarises some of the studies investigating the possible association between different heart rate variability measures and various cardiovascular disorders, while Figure 2 shows power spectral density plots of two characteristic patients (survivor and non-survivor), treated in the intensive care unit.

Baroreflex function and cardiovascular disease

The baroreflex feedback loop is responsible for neurocardiovascular control. Baroreceptors in the walls of the carotid arteries and the aorta sense systemic blood pressure via stretching and, through afferent discharge transmitted to the central nervous system, buffer or oppose the changes in blood pressure. A rise in pressure results in reflex parasympathetic activation with sympathetic inhibition and a subsequent decrease in heart rate, whereas a decrease in pressure reduces baroreceptor discharge and elicits an increase in sympathetic outflow. In addition, the increase in shear stress by blood pressure stimulates augmented endogenous nitric oxide production. Due to its potent vasodilatory action the initial rise in blood pressure is counterbalanced.[16,18]

Methods of measurement

The function of baroreflex can be estimated by the degree of change in heart rate for a given unit change in blood pressure. This can be quantified through the application of an external stimulus, mechanical or pharmacological.[25] An alternative method evaluates heart rate modulation by identifying consecutive RR intervals in which progressive increases in systolic blood pressure are followed by progressive lengthening in pulse interval and *vice versa*. The slope of the regression line between these two values is considered as the magnitude of the reflex gain.[34] This method is called the 'sequence technique'. Another method for the assessment of baroreflex sensitivity estimates the transfer function magnitude between systolic blood pressure and heart rate. The transfer magnitude represents the relative amplitude or gain of the output signal for a given input signal at a given frequency. Its estimation can be obtained by computing the alpha (α) index.[35,36]

Origin and regulation of baroreflex function

Myelinated and unmyelinated fibers in cranial nerves X and XI connect different brain regions to neurons in the dorsal medial region of the *nucleus tractus solitarius* (NTS). Projections from the NTS are connected to the

caudal ventral lateral medulla (CVLM) and subsequently synapse to excitatory neurons in the rostral ventral lateral medulla (RVLM). This region increases the firing of the sympathetic preganglionic motor neurons in the spinal cord. Any increase in blood pressure can activate baroreceptors that project to the NTS, with subsequent activation of RVLM and CVLM neurons. The final activation of CVLM neurons by the RVLM inhibits the descending excitatory input to the spinal cord. The resulting decrease in sympathetic activity opposes the initial increase in blood pressure.[37]

Respiration can significantly alter the baroreflex influence on heart rate. Inspiration decreases and expiration enhances the cardiac vagal response to baroreflex activation. Hyperventilation can also result in modulation of sympathetic regulation of heart rate.[38] In critically ill patients suffering from adult respiratory distress syndrome, the resistive load breathing can by itself affect the respiratory arrhythmia.[39] There is also the possibility that respiration-induced changes in blood volume and central venous pressure may produce changes in heart rate independent of systolic blood pressure, via activation of low-pressure receptors.[18]

The interrelation between heart rate variability frequency components and baroreflex feedback loop has already been discussed. The contribution of the baroreflex to the strength of low frequency oscillations has also been confirmed in different animal models of sinoaortic denervation.[40] Such a condition results in selective changes in the heart rate variability spectrum, where there is a significant reduction in LF power with or without a reduction in HF, but different species manifest different patterns of change. Conversely, the overall blood pressure variability increases.[40] A possible role of nitric oxide has been described, where the latter buffers blood pressure and subsequently heart rate variability, especially in the very low frequency domain.[41]

Baroreflex gain, heart rate variability and complexity in cardiovascular disease

Apart from a reduced variability of heart rate signals, impaired baroreflex sensitivity has been observed in cardiovascular patients with conditions such as postmyocardial infarction, hypertension and heart failure.[42-44] Depressed heart rate variability and baroreflex gain seem to result from altered responsiveness of sinus node pacemaker cells, cardiac remodelling, and reduced parasympathetic cardiovascular control.[22,44] Pincus has proposed that the uncoupling of oscillations of different origin, such as heart rate, central nervous system firing neurons, and vasomotor waves, due to baroreflex gain impairment may induce an increased periodicity within time series (heart rate and blood pressure signals) and has proposed the use of a new statistic named approximate entropy (ApEn).[45,46] ApEn is a family of statistics that addresses the question: "given a sequence of two (or three or four) inter-beat intervals, what is the probability that the next consecutive interval falls within a predetermined range?" Thus, approximate entropy is a measure of short-range correlation. Approximate entropy in general quantifies the creation of information in a time series. A low value indicates that the signal is deterministic: a high value indicates randomness.[47] Decreased ApEn values have been associated with increased mortality after coronary artery bypass surgery.[48]

In heart failure patients, despite increased sympathetic activity, there is depressed baroreflex sensitivity and heart rate variability, especially in the LF band. This finding suggests that the LF component of the heart rate variability power spectrum is not solely linked with increased sympathetic drive in such pathological conditions. It has been speculated that the attenuation of low frequency oscillations can contribute to the increased activity of the renin-angiotensin system that is observed in heart failure patients.[18,49]

Heart rate turbulence

Another recently discovered 'physiomarker' extrapolated from heart rate recordings is currently under investigation for its applicability to cardiovascular patients. It is called heart rate turbulence, it is a physiological phenomenon, and it describes the short-term fluctuation in sinus cycle length associated with a ventricular premature complex (VPC). More precisely, it describes the increase in heart rate for 1 or 2 beats and its subsequent decrease after a VPC. The mechanism responsible for these alterations relies mainly on the baroreflex arc. During a ventricular premature beat blood pressure falls, as diastolic filling becomes incomplete with a subsequent low ejection volume. In addition, different membrane ion channels have not fully recovered, leading to a short action potential. This drop in blood pressure stimulates aortic baroreceptors, which increase heart rate through the baroreflex loop. The compensatory pause that follows a premature ventricular beat is associated with a rise in blood pressure which is higher than the pressure originating from a sinus beat, a phenomenon called postextrasystolic potentiation. This upward shift in blood

pressure again reduces heart rate via the baroreflex loop.[50,51] When the autonomic control system is intact, this change is registered immediately with an instantaneous response in the form of heart rate turbulence. If the autonomic control system is impaired, this reaction is either weakened or entirely missing. However, many fine details of the mechanism of heart rate turbulence remain elusive. For example, what is the role of the sympathetic/parasympathetic system during the sinus acceleration/deceleration period? It has been hypothesised that heart rate turbulence is a vagal phenomenon, since atropine eliminates it completely, whereas intravenous esmolol does not alter it at all.[52,53] Despite the above lines of evidence that favour the vagal theory of origin, others believe that the importance of a sympathetic role cannot be ruled out, since both divisions of the autonomic nervous system interact with each other in such a way that vagal predominance is stronger in the presence than in the absence of sympathetic tone.[50]

Heart rate turbulence measurements

Sinus acceleration and deceleration after a ventricular premature complex can be quantified by two numerical parameters: turbulence onset, which is the amount of acceleration, and turbulence slope, which estimates the rate of deceleration. Turbulence onset is the percentage difference between the average value of the first two normal RR intervals following the ventricular premature complex and the last two normal intervals preceding the VPC (Figure 3B). Turbulence slope is the steepest slope of a linear regression line through five consecutive measurement points in the averaged tachogram (plot of heart rate versus time) and is expressed in milliseconds per RR interval (Figure 3C). The methodology of measurement has been described by George Schmidt's research group in Munich and is available with free downloadable software on the website www.h-r-t.org; however, the measurement of turbulence has not yet been standardised.[54] Heart rate turbulence analysis can be based on Holter records, but it can also be studied after induction of intra-cardiac pacing in the lab or in patients with implanted cardiac defibrillators (induced heart rate turbulence). In relation to heart rate variability analysis, turbulence measurements pose opposite problems, because in the first method ectopic beats have to be excluded, whereas in the second measurements cannot be undertaken in subjects who do not have premature ventricular beats, making the study of heart rate turbulence in healthy states unreliable. Another issue concerning turbulence analysis is its relation with heart rate. Many studies have demonstrated that turbulence is reduced during increased heart rate, leading to warnings about false positive results.[55,56]

Clinical applications of heart rate turbulence

In the first clinical study of turbulence as a predictor of mortality after myocardial infarction, by Schmidt et al, different threshold values were determined from Holter recordings of 100 patients, three months after an acute myocardial infarction.[54] Turbulence onset ≥ 0 and slope ≤ 2.5 were considered abnormal, meaning that a healthy state is associated with a strong acceleration followed by a rapid deceleration, whereas the inverse findings characterise pathological responses. These metrics were blindly applied to Holter records from a total of 1191 patients from two large clinical trial groups, the placebo arm of the European Myocardial Infarction Amiodarone Trial (EMIAT, number of patients: 614)[57] and the Multicentre Post Infarction Program (MPIP, number of patients: 577).[58] Univariate and multivariate analysis showed that turbulence slope, turbulence onset, previous infarction history, ejection fraction and heart rate >75 were independent predictors of mortality. In particular, the slope was the strongest risk stratifier in EMIAT (relative risk 2.7) and the second strongest in the MPIP trial (relative risk 3.5). A relative risk of approximately 3 means that patients with abnormal turbulence slope values are 3 times more likely to die than those with normal measurements. Data from the ATRAMI trial were also used to study heart rate turbulence and its relation with cardiac arrest.[20] It was demonstrated that turbulence slope and onset could discriminate survivors versus non-survivors. From these two studies, the sensitivity and positive predictive value of the combination of turbulence slope and turbulence onset were estimated as 30%, meaning that one in three post-myocardial infarction patients whose slope and onset are both abnormal 2 weeks after their infarction (Holter recordings in the Schmidt study were made in the 2nd week after the event) are likely to die within 2 years (mean follow-up in the ATRAMI study).[50,51] In another study of 199 patients with congestive heart failure, abnormality of both onset and slope turbulence was associated with a risk ratio of 4.1 for cardiac deaths, implying that patients with abnormal turbulence

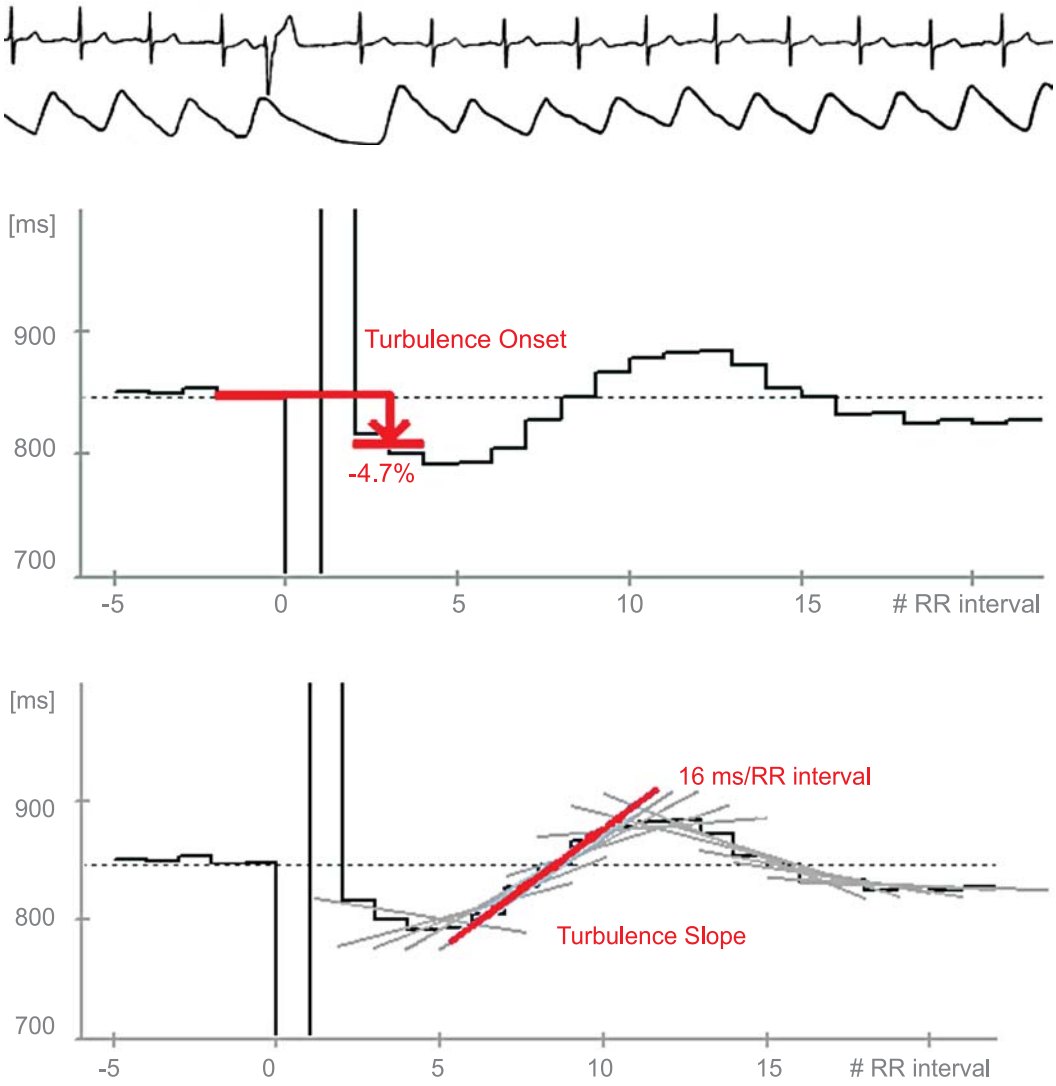

Figure 3. Schematic diagrams showing measurements of turbulence onset (B) and turbulence slope (C) after a ventricular premature complex (A). RR intervals (y-axis) are plotted against beat number (x-axis), for 2 beats preceding and 20 beats following the premature beat, with the compensatory pause being beat 0. In this example, turbulence onset is -4.7%. For measurement of turbulence slope, the slopes of 5-beat RR sequences after the compensatory pause are fitted with a straight line. The turbulence slope in this example is 16 ms/RR interval. (Downloaded from the open-source website: www.h-r-t.org).

slope and turbulence onset are 4 times more likely to die than those with normal values.[59] These studies show that heart rate turbulence is diminished not only in post-myocardial infarction patients but also in the case of heart failure, providing clinically useful risk stratification information. At the same time, it has been demonstrated that turbulence parameters are strongly correlated with almost all heart rate variability time domain measurements and with baroreflex sensitivity alpha index.[60,61]

Another important issue concerning the applicability of heart rate turbulence in cardiovascular disease is its advantage for prediction of post-myocardial infarction outcome in patients receiving beta-blockers. Whereas in the EMIAT trial mean heart rate, previous history of myocardial infarction and low ejection fraction proved to be independent predictors for patients not taking beta-blockers, they failed when applied to the patients on beta-blockers. In these subjects, combined turbulence

onset and turbulence slope was found to be the only independent predictor of mortality, with a relative risk of 3.8.[50]

Conclusions

Heart rate variability, heart rate turbulence and baroreflex sensitivity, like many other physiological phenomena, reflect complex interactions between cells, tissues and organs. The Task Force on Sudden Cardiac Death of the European Society of Cardiology recently recommended a risk stratification strategy which combines a marker of structural damage (such as LVEF) with markers of autonomic imbalance.[62] Different studies and methods of analysis have suggested that heart rate variability is related to the baroreflex gain and is mainly influenced by the autonomic nervous system. Its prognostic value as a risk stratifier has been verified in different groups of patients suffering from myocardial infarction, hypertension, heart failure, and also from septic shock and neurotrauma.[2,8,37] In addition, heart rate turbulence is a new field of intensive research with a limited number of full length publications. In addition to the parameters discussed in this review, novel heart rate turbulence measures are under investigation, but further and well designed studies are needed to see if any of these parameters provide superior risk stratification compared to other already standardised 'physiomarkers'. However, many important questions remain unanswered, such as the value of single or longitudinal heart rate variability measurements for clinically useful information, its prognostic capability for risk stratification between patients or within the same patient (trend analysis), and the fact that most results were obtained from animal data.

In conclusion, the most important aspect of research on heart rate dynamics remains the free access of different investigators to international databases of various biosignals, (ECG, ST, QT) that contain different software tools for signal processing, such as the Web site Physionet (www.physionet.org), which is a public service of the Research Resource for Complex Physiologic Signals,[63] and the website www.h-r-t.org for heart rate turbulence analysis.[54] Through international collaboration, basic researchers and clinicians will be able to cooperate and address difficult questions concerning the pathophysiology of diseases, bedside monitoring implementation and possible impact of new diagnostic tools on final outcome.

References

1. Akselrod S, Gordon D, Ubel FA, Shannon DC, Barger AC, Cohen RJ: Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat to beat cardiovascular control. Science 1981; 213: 220-222.
2. Goldstein B, Fiser DH, Kelly MM, et al: Decomplexification in critical illness and injury: Relationship between heart rate variability, severity of illness, and outcome. Crit Care Med 1998; 26: 352-357.
3. Kennedy H: Heart rate variability - a potential, non-invasive prognostic index in the critically ill patient. Crit Care Med 1998; 26: 213-214.
4. Seely AJ, Christou NV: Multiple organ dysfunction syndrome: Exploring the paradigm of complex nonlinear systems. Crit Care Med 2000; 28: 2193-2200.
5. Tsuzi H, Venditti FJ, Manders ES, et al: Reduced heart rate variability, mortality risk in an elderly cohort: the Framingham Heart Study. Circulation 1994; 90: 878-883.
6. Kleiger RE, Miller JP, Bigger JT: Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. Am J Cardiol 1987; 59: 256-262.
7. Lombardi F, Sandrone G, Pernptuner S, et al: Heart rate variability as an index of sympathovagal interaction after myocardial infarction. Am J Cardiol 1987; 60: 1239-1245.
8. Haji-Michael P: G, Vincent J L, Degaute J P, et al: Power spectral analysis of cardio-vascular variability in critically ill neurosurgical patients. Crit Care Med 2000; 28: 2578-2583.
9. Kita Y, Ishise J, Yoshita Y, et al: Power spectral analysis of heart rate and arterial blood pressure oscillation in brain-dead patients. J Auton Nerv Syst 1993; 40: 101-107.
10. Pomeranz B, Macaulay RJB, Caudill MA, et al: Assessment of autonomic function in human by heart rate spectral analysis. Am J Physiol 1985; 248: 151-153.
11. Malik M, Camm A: J: Components of heart rate variability: What they really mean, what we really measure. Am J Cardiol 1993; 72: 821-822.
12. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology: Standards of measurement, physiological interpretation, clinical use. Circulation 1996; 93: 1043-1065.
13. Hon EH, Lee ST: Electronic evaluations of the fetal heart rate patterns preceding fetal death: further observations. Am J Obstet Gynecol 1965; 87: 814-826.
14. Wolf MM, Varigos GA, Hunt D, Sloman JG: Sinus arrhythmia in acute myocardial infarction. Med J Aust 1978; 2: 52-53.
15. DeBoer RW, Karemaker JM, Strackee J: Hemodynamic fluctuations and baroreflex sensitivity in humans: a beat-to-beat model. Am J Physiol 1987; 253: 680-689.
16. Malpas SC: Neural influences on cardiovascular variability: possibilities, pitfalls. Am J Physiol Heart Circ Physiol 2002; 282: H6-H20.
17. Montano N, Gnecchi-Ruscone T, Porta A, Lombardi F, Malliani A, Barman SM: Presence of vasomotor and respiratory rhythms in the discharge of single medullary neurons involved in the regulation of cardiovascular system. J Auton Nerv Syst 1996; 57: 116-122.
18. Lanfranchi PA, Somers VK: Arterial baroreflex function and cardiovascular variability: interactions and implications. Am J Physiol Regul Integr Comp Physiol 2002; 283: 815-826.
19. Clermont G, Andus DC: Towards understanding pathophysiology in critical care: the human body as a complex system, in Vincent J-L (ed.): Yearbook of Intensive Care and Emergency Medicine. Springer-Verlag, Berlin, 2001; pp 13-22:
20. La Rovera MT, Bigger JT, Marcus FI, Mortara A, Maestri R,

Schwartz PJ: Baroreflex sensitivity and heart rate variability in prediction of total cardiac mortality after myocardial infarction: ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators. Lancet 1998; 351: 478-484.
21. Dekker JM, Schouten EG, Klootwijk P, Pool J, Swenne CA, Kromhout D, from the ZUTPHEN STUDY: Heart rate variability from short electrocardiographic recordings predicts mortality from all causes in middle-aged, elderly men. Am J Epidemiol 1997; 145: 899-908.
22. Brown AM, Malliani A: Spinal sympathetic reflexes by coronary receptors. J Physiol 1971; 212: 685-705.
23. Bigger JT, Kleiger RE, Fleiss JL, Rolnitzki LM, and the Multicenter Post-Infarction Research Group: Components of heart rate variability measured during healing of acute myocardial infarction. Am J Cardiol 1998; 61: 729-736.
24. Bilchick KC, Fetics B, Djoukeng R, et al: Prognostic value of heart rate variability in chronic congestive heart failure (Veterans Affairs' Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure). Am J Cardiol 2002; 90: 24-28.
25. Guzzetti S, Dassi S, Pecis M, et al: Altered pattern of circadian neural control of heart period in mild hypertension. J Hypertens 1991; 9: 831-838.
26. Langewitz W, Ruddel H, Schachinger H: Reduced parasympathetic cardiac control in patients with hypertension at rest and under mental stress. Am Heart J 1994; 127: 122-128.
27. Saul JP, Arai Y, Berger RD, et al: Assessment of autonomic regulation in chronic congestive heart failure by the heart rate spectral analysis. Am J Cardiol 1988; 61: 1292-1299.
28. Binkley PF, Nunziata E, Haas GJ, Nelson SD, Cody RJ: Parasympathetic withdrawal is an integral component of autonomic imbalance in congestive heart failure: demonstration in human subjects and verification in a paced canine model of ventricular failure. J Am Coll Cardiol 1991; 18: 464-472.
29. Townend JN, West JN, Davies MK, Littler WA: Effect of quinapril on blood pressure and heart rate in congestive heart failure. Am J Cardiol 1992; 69: 1587-1590.
30. Counihan PJ, Fei L, Bashir Y, Farrel TG, Haywood GA, McKenna WJ: Assessment of heart rate variability in hypertrophic cardiomyopathy: association with clinical and prognostic features. Circulation 1993; 88: 1682-1690.
31. Algra A, Tijssen JGP, Roelandt JRTC, Pool J, Lubsen J: Heart rate variability from 24-hours electrocardiography and the 2-year risk for sudden death. Circulation 1993; 88: 180-185.
32. Huikuri HV, Linnaluoto MK, Seppanen T, et al: Circadian rhythm of heart rate variability in survivors of cardiac arrest. Am J Cardiol 1992; 70: 610-615.
33. Huikuri HV, Valkama JO, Airaksinen KEJ, et al: Frequency domain measures of heart rate variability before the onset of non sustained and sustained ventricular tachycardia in patients with coronary artery disease. Circulation 1993; 87: 1220-1228.
34. Bertinieri G, Di Rienzo M, Cavallazzi A, Ferrari AU, Pedotti A, Mancia G: A new approach to analysis of the arterial baroreflex. J Hypertens Suppl 1985; 3: S79-S81.
35. Saul JP, Berger RD, Albrecht P, et al: Transfer function analysis of the circulation: Unique insights into cardio-vascular regulation. Am J Physiol 1991; 261: 1231-1245.
36. Parati G, DiRienzo M, Bertinieri G, et al: Evaluation of the baroreceptor-heart rate reflex by 24-hour intra-arterial blood pressure monitoring in humans. Hypertension 1988; 12: 214-222.
37. Goldstein B, Toweill D, Lai S, et al: Uncoupling of the autonomic and cardiovascular systems in acute brain injury. Am J Physiol Regul Integr Comp Physiol 1998; 275: 1287-1292.
38. Eckberg DL, Orshan CR: Respiratory and baroreceptor reflex interactions in man. J Clin Invest 1977; 59: 780-785.
39. Calabrese P, Perrault H, Dinh TP, Eberhard A, Benchetrit G: Cardiorespiratory interactions during resistive load breathing. Am J Physiol Regul Integr Comp Physiol 2000; 279: 2208-2213.
40. Di Rienzo M, Parati G, Castiglioni P, Tordi R, Mancia G, Pedotti A: Baroreflex effectiveness index: an additional measure of baroreflex control of heart rate in daily life. Am J Physiol Regul Integr Comp Physiol 2001; 280: 744-751.
41. Cerutti C, Ducher M, Landelme P, Gustin MP, Paultre CZ: Assessment of spontaneous baroreflex sensitivity in rats: a new method using the concept of statistical dependence. Am J Physiol Regul Integr Comp Physiol 1995; 268: 382-388.
42. Di Rienzo M, Parati G, Castiglioni P, et al: Role of sinoaortic afferents in modulating BP and pulse-interval spectral characteristics in unanesthetized cats. Am J Physiol Heart Circ Physiol 1991; 261: 1811-1818.
43. Just A, Wittman U, Nafz B, et al: The blood pressure buffering capacity of nitric oxide by comparison to the baroreceptor reflex. Am J Physiol Heart Circ Physiol 1994; 267: 521-527.
44. Thames MD, Kinugawa T, Smith ML, Dibner-Dunlap ME: Abnormalities of baroreflex control in heart failure. J Am Coll Cardiol 1993; 22:
45. Saul JP: Heart rate variability during congestive heart failure: observations and implications, in DiRienzo M, Mancia G, Parati G, Pedotti A, Zanchetti A, (eds.): Blood Pressure and Heart Rate Variability: Computer Analysis, Methodology and Clinical Applications. IOS Press, Amsterdam, the Netherlands, 1993; pp 266-275.
46. Pincus SM: Approximate entropy (ApEn) as a complexity measure. Chaos 1995; 5: 110-117.
47. Pincus SM, Goldberger AL: Physiological time-series analysis: What does regularity quantify? Am J Physiol 1994; 266: (Heart Circ Physiol) 1643-1656.
48. Fleisher LA, Pincus SM, Rosenbaum SH: Approximate entropy of the heart rate as a correlate of post-operative ventricular dysfunction. Anesthesiology 1993; 78: 683-692.
49. Van de Borne P, Montano N, Pagani M, Oren RM, Somers VK: Absence of low-frequency variability of sympathetic nerve activity in severe heart failure. Circulation 1997; 95: 1449-1454.
50. Watanabe MA: Heart rate turbulence: a review. Indian Pacing Electrophysiol J 2003; 3: 10-22.
51. Watanabe MA, Schmidt G: Heart rate turbulence: A 5-year review. Heart Rhythm 2004; 1: 732-738.
52. Marine JE, Watanabe MA, Smith TW, Monahan KM: Effect of atropine on heart rate turbulence. Am J Cardiol 2002; 89: 767-769.
53. Lin LY, Lai LP, Lin JL, et al: Tight mechanism correlation between heart rate turbulence, baroreflex sensitivity: sequential autonomic blockade analysis. J Cardiovasc Electrophysiol 2002; 13: 427-31.
54. Schmidt G, Malik M, Barthel P, et al: Heart rate turbulence after ventricular premature beats as a predictor of mortality after acute myocardial infarction. Lancet 1999; 353: 1390-1396.
55. Watanabe MA, Marine JE, Sheldon M, Josephon ME: Effects of ventricular premature stimulus coupling interval on blood pressure and heart rate turbulence. Circulation 2002; 106: 325-330.
56. Bauer A, Schneider R, Barthel P, Malik M, Schmidt G: Heart rate turbulence dynamicity. Eur Heart J 2001; 22: 436.
57. Julian DG, Camm AJ, Frangin G, et al: Randomized trial of effect of amiodarone on mortality in patients with left-ventricular dysfunction after recent myocardial infarction: EMIAT. Lancet 1997; 667-674.

58. Bigger JJ, Fleiss JL, Kleiger R, Miller JP, Rolnitzky LM: The relationships among ventricular arrhythmias, left ventricular dysfunction, and mortality in the 2 years after myocardial infarction. Circulation 1984; 69: 250-258.
59. Morley-Davies A, Dargie HJ, Cobbe SM, Schneider R, Schmidt G: Heart rate turbulence: a novel Holter derived measure and mortality in chronic heart failure. Eur Heart J 2000; 21: Suppl 408 (abstract).
60. Ghuran A, Reid F, La Rovere MT, et al: Heart rate turbulence-based predictors of fatal and nonfatal cardiac arrest (the Autonomic Tone, Reflexes After Myocardial Infarction substudy). Am J Cardiol 2002; 89: 184-190.
61. Davies LC, Francis DP, Polikowski P, Piepoli MF, Coats AJS: Relation of heart rate and blood pressure turbulence following premature ventricular complexes to baroreflex sensitivity in chronic congestive heart failure. Am J Cardiol 2001; 87: 737-742.
62. Priori SG, Aliot E, Blomstrom-Lundqvist C, et al: Task Force on Sudden Cardiac Death of the European Society of Cardiology. Eur Heart J 2001; 16: 1374-1450.
63. Moody GB, Mark RG: A database to support development and evaluation of intelligent intensive care monitoring. IEEE Comput Cardiol 1996; 23: 657-660.