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Heart rate variability: a noninvasive electrocardiographic method to measure the autonomic nervous system

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Summary

The autonomic nervous system (ANS) plays an important role not only in physiological situations, but also in various pathological settings such as diabetic neuropathy, myocardial infarction (MI) and congestive heart failure (CHF). Autonomic imbalance associating increased sympathetic activity and reduced vagal tone has been been strongly implicated in the pathophysiology of arrhythmogenesis and sudden cardiac death.

Among the different available noninvasive techniques for assessing the autonomic status heart rate variability (HRV) has emerged as a simple, noninvasive method to evaluate the sympatho-vagal balance at the sinoatrial level. It has been used in a variety of clinical situations including diabetic neuropathy, MI, sudden death and CHF.

The standard measurements intervening in the analysis of HRV comprise time domain indices, geometric methods and components of the frequency domain. Measurements of HRV are generally performed on the basis of 24 hour Holter recordings (long-term recordings) or on shorter periods ranging from 0.5 to 5 minutes (short-term recordings). The use of long or short-term recordings depends on the type of study that has to be realised.

Established clinical data based on numerous studies published during the last decade consider decreased global HRV as a strong predictor of increased all-cause cardiac and/or arrhythmic mortality, particularly in patients at risk after MI or with CHF.

This article reviews the mechanism, the parameters and the use of HRV as a marker reflecting the activity of the sympathetic and vagal components of the ANS on the sinus node, and as a clinical tool for screening and identifying patients particularly at risk for cardiac mortality.

Key words: autonomic nervous system; arrhythmogenesis; sudden cardiac death; heart rate variability; risk stratification; myocardial infarction; congestive heart failure

Introduction

In the course of the last two decades numerous studies in both animals and human beings have shown a significant relationship between the ANS and cardiovascular mortality, particularly in patients with MI and CHF. Perturbations of the ANS and its imbalance consisting of either increased sympathetic or reduced vagal activity may result in ventricular tachyarrhythmias and sudden cardiac death, which is nowadays one of the leading causes of cardiovascular mortality [1]. There are presently various methods available for assessing the status of the ANS, which include cardiovascular reflex tests [2–4], and biochemical [5] and scintigraphic tests [6]. Techniques giving direct access to receptors at the cellular level or to neural traffic, are not routinely available. In recent years noninvasive techniques based on the electrocardiogram (ECG) have been used as markers of autonomic modulation of the heart, these include HRV [7, 8], baroreflex sensitivity (BRS) [9], QT interval [10], and heart rate turbulence (HRT), a new method based on fluctuations of sinus rhythm cycle length after a single premature ventricular contraction [11]. Among these techniques analysis of HRV has emerged as a simple, noninvasive method to evaluate the sympatho-vagal balance at the sinoatrial level.

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The autonomic nervous system and the heart

Although automaticity is intrinsic to different cardiac tissues with pacemaker properties, the electrical and contractile activity of the myocardium is largely modulated by the ANS. This neural regulation is effected through the interplay of the sympathetic and vagal outflows. In most physiological conditions the efferent sympathetic and parasympathetic branches have opposing actions: the sympathetic system enhances automaticity, whereas the parasympathetic system inhibits it. While the effect of vagal stimulation on the cardiac pacemaker cells is to cause hyperpolarisation and to reduce the rate of depolarisation, sympathetic stimulation causes chronotropic effects by increasing the rate of pacemaler depolarisation. As seen in figure 1 both branches of the ANS influence ion channel activity implicated in the regulation of depolarisation of the cardiac pacemaker cells [12].

Abnormalities of the ANS have been demonstrated in diverse conditions such as diabetic neuropathy [13] and coronary heart disease, particularly in the context of MI [14]. A dysregulation in the autonomic nervous control of the cardiovascular system associating increased sympathetic and reduced parasympathetic tone plays an important role in coronary artery disease and in the genesis of life-threatening ventricular arrhythmias [15, 16]. The occurrence of ischemia and/or myocardial necrosis may induce a mechanical distortion of the afferent and efferent fibers of the ANS due to changes in the geometry related to necrotic and noncontracting segments of the heart. Newly recognised is the phenomenon of electrical remodeling due to local nerve growth and degeneration at the level of the myocardial cell in the setting of ischemia and/or myocardial necrosis [17]. Taken as a whole, in patients with coronary artery disease and a history of MI, cardiac autonomic function associating increased sympathetic and decreased vagal tone are conditions favourable to the complex phenomenon of life threatening arrhythmias because they modulate cardiac automaticity, conduction and importantly haemodynamic variables.

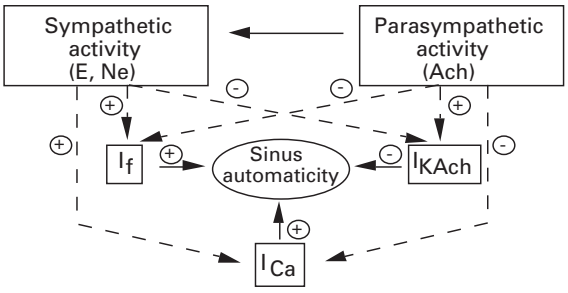

Figure 1

Effects of the autonomic nervous regulation on the ionic currents and the resulting changes of sinus automaticity. E = epinephrine; NE = norepinephrine; Ach = acetylcholine; Ica = calcium current; If = hyperpolarisation-activated "pacemaker" current; IKAch = potassium current. (Adapted from reference [12].)

Definition and mechanisms of heart rate variability

Heart rate variability is a noninvasive electrocardiographic marker reflecting the activity of the sympathetic and vagal components of the ANS on the sinus node of the heart. It expresses the total amount of variations of both instantaneous HR and RR intervals (intervals between QRS complexes of normal sinus depolarisations) [7, 8]. Thus, HRV analyses the tonic baseline autonomic function. In a normal heart with an integer ANS, there will be continuous physiological variations of the sinus cycles reflecting a balanced sympthovagal state and normal HRV [8]. In a damaged heart which suffered from myocardial necrosis, the changes in activity in the afferent and efferent fibers of the ANS and in the local neural regulation will contribute to the resulting sympathovagal imbalance reflected by a dimished HRV.

Measurements of heart rate variability

Analysis of HRV consists of a series of measurements of successive RR interval variations of sinus origin which provide information about autonomic tone [18]. Different physiological factors may influence HRV such as gender, age, circadian rhythm, respiration and body position [19]. Measurements of HRV are noninvasive and highly reproducible. They may generally be performed on the basis of 24 hour Holter recordings or on shorter periods ranging from 0.5 to 5 minutes particularly in the field of dynamic electrocardiography [8]. Most Holter apparatus manufacturers nowadays propose HRV analysis programs which are incorporated into their instrument systems [20]. Although computer analysis of tape recordings has improved, human intervention is required in most measurements of HRV parameters in order to detect erroneous beats, artifacts, and alterations in tape speed that may alter timing intervals.

In 1996 a Task Force of the European Society of Cardiology (ESC) and the North American Society of Pacing and Electrophysiology (NASPE) defined and established standards of measurement, physiological interpretation and clinical use of HRV [21]. Time domain indices [22, 23], geometric measures [24, 25] and frequency domain indices [26–28] constitute nowadays the standard clinically used parameters.

Time domain analysis

Time domain analysis measures the changes in heart rate over time or the intervals between successive normal cardiac cycles [21–23]. From a continuous ECG recording (Holter), usually of 24 hours, each QRS complex is detected and the normal RR intervals (NN intervals), due to sinus depolarisations, or the instantaneous heart rate are then determined (fig. 2A). The calculated time domain variables may be simple, such as the mean RR interval, the mean heart rate, the difference between the longest and shortest RR interval and the difference between night and day heart rate, or more complex based on statistical measurements. These statistical time domain indices are divided into two categories, including beat-to-beat intervals or variables derived directly from the intervals themselves or the instantaneous HR and intervals derived from the differences between adjacent NN intervals. Table 1 summarizes the most frequently used parameters of the time domain. Parameters of the first category are SDNN, SDANN and SD and those of the second category are RMSSD and pNN50.

SDNN is a global index of HRV and reflects all the long-term components and circadian rhythms responsible for variability in the recording period (fig. 2B). SDANN is an index of the variability of the average of 5-minute intervals over 24 hours. Thus, it provides long-term information. It is a sensitive index of low frequencies like physical activity, changes in position, circadian rhythm. SD is generally considered to reflect the day/night changes of HRV. RMSSD and pNN50 are the most common parameters based on interval differences. These measurements correspond to short-term HRV changes and are not dependent on day/night variations [8, 18, 21, 22]. They reflect alterations in autonomic tone that are predominantly vagally mediated. Compared to pNN50, RMSSD seems to be more stable and should be preferred for clinical use.

Geometric methods

Geometric methods are derived and constructed from the conversion of sequences of NN intervals. Different geometrical forms allowing to assess HRV are available: the 24-hour histogram,

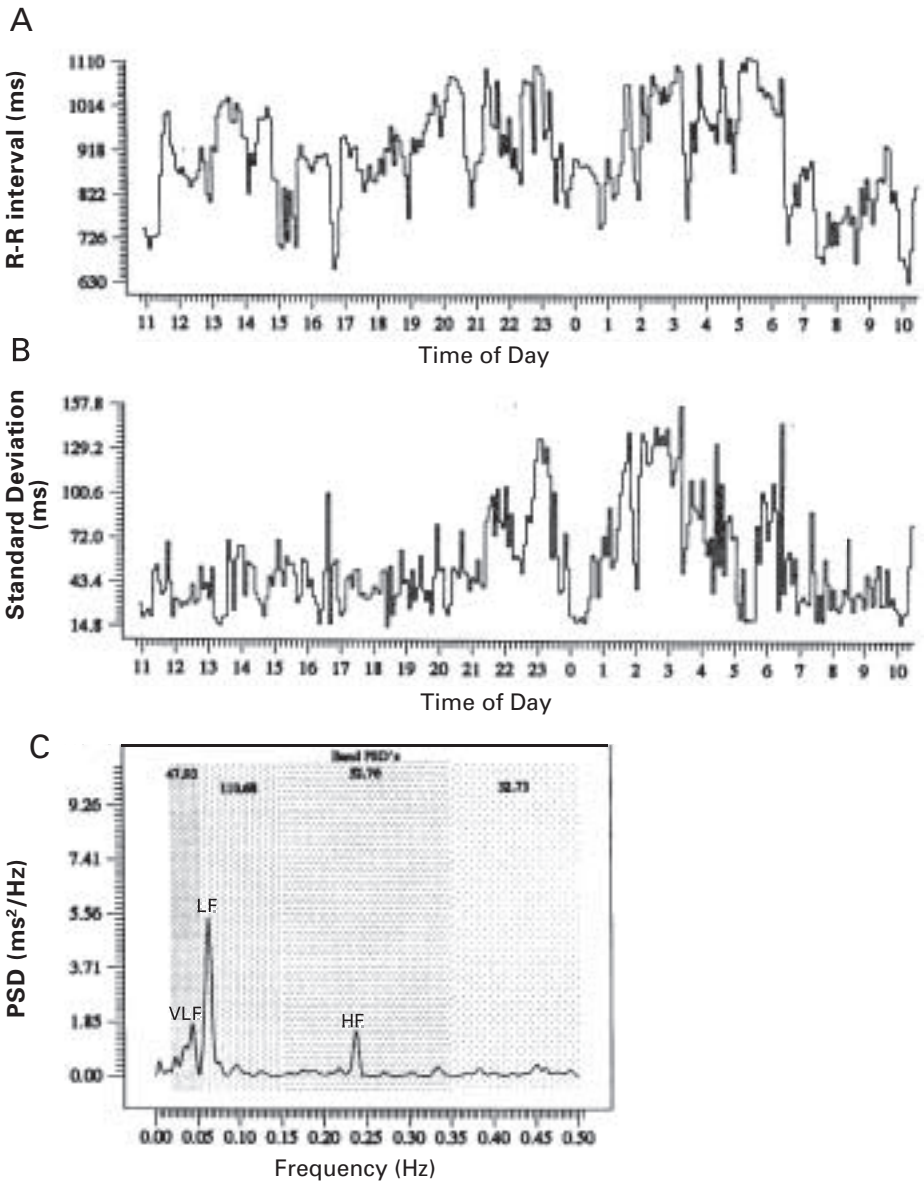

Figure 2

Time domain and power spectral recordings taken from a 72-year-old man after myocardial infarction.
A. 24-hour RR interval variation.
B. 24-hour standard deviation of all normal RR intervals.
C. Power spectral components corresponding to three different pics of frequency bands: the VLF, the LF and the HF bands.
HF = high frequency power; LF = low frequency power; PSD = power spectral density; VLF = very low frequency power.

the HRV triangular index and its modification, the triangular interpolation of NN interval histogram, and the method based on Lorentz or Poincaré plots [21, 22, 24, 25]. The 24-hour histogram assesses the relationship between the total number of RR intervals detected and the 24 hour RR interval variation. The triangular HRV index considers the major peak of the histogram as a triangle with its baseline width corresponding to the amount of RR interval variability, its height corresponds to the most frequently observed duration of RR intervals, and its area corresponds to the total number of all RR intervals used to construct it. The triangular HRV index is an estimate of the overall HRV.

Geometrical methods are less affected by the quality of the recorded data and may provide an alternative to less easily obtainable statistical parameters. However, the time duration of recording should be at least 20 minutes, which means that short-term recordings cannot be assessed by geometric methods.

Among the various time domain and geometric methods available the Task Force of the ESC and the NASPE has recommended the use of four measures for HRV assessment: SDNN, SDANN, RMSSD and the HRV triangular index [21].

Frequency domain analysis

Frequency domain (power spectral densitiy) analysis describes the periodic oscillations of the heart rate signal decomposed at different frequencies and amplitudes, and provides information on the amount of their relative intensity (termed variance or power) in the heart's sinus rhythm [21, 22, 26–29]. Schematically, spectral analysis may be compared to the results obtained when white light passes through a prism, resulting in different lights of different colour and wave length. Power spectral analysis can be performed in two ways: 1) by a nonparametric method, the fast Fourier transformation (FFT), which is characterized by discrete peaks for the several frequency components, and 2) by a parametric method, the autoregressive model estimation [22, 26–28], resulting in a continuous smooth spectrum of activity. While the FFT is a simple and rapid method, the parametric method is more complex and needs verfication of the suitability of the chosen model.

When using the FFT the individual RR intervals stored in the computer are transformed into bands with different spectral frequencies. This process is similar to decomposing the sound of a symphony orchestra into the underlying notes. The results obtained can be transformed in Hertz (Hz) by dividing by the mean RR interval length.

The power spectrum consists of frequency bands ranging from 0 to 0.5 Hz and can be classified into four bands: the ultra low frequency band (ULF), the very low frequency band (VLF), the low frequency band (LF) and the high frequency band (HF).

Short-term spectral recordings (5 to 10 minutes) are characterized by the VLF, HF and LF components (fig. 2C), while long-term recordings include a ULF component in addition to the three others. Table 2 shows the most frequently used frequency domain parameters. The spectral components are evaluated in terms of frequency (Hertz) and amplitude which is assessed by the area (or power spectral density) of each component. Thus, squared units are used for the absolute values expressed in ms squared (ms^2). Natural logarithms (ln) of the power values can be used because of the skewness of the distributions. LF and HF powers may be expressed in absolute values (ms^2) or in normalised values (nu). The normalisation of LF and HF is performed by substracting the VLF component from the total power. It tends to reduce, on one hand, the effects of noise due to artifacts and,

Table 1
Time domain parameters.

Variable	Units	Description
SDNN	ms	standard deviation of all NN intervals
SDANN	ms	standard deviation of the averages of NN intervals in all 5-minute segments of the entire recording
SD (or SDSD)	ms	standard deviation of differences between adjacent NN intervals
RMSSD	ms	square root of the mean of the sum of the squares of differences between adjacent NN interval
pnn50	%	percent of difference between adjacent NN intervals that are greater than 50 ms

Table 2
Frequency domain parameters.

Variable	Units	Description	Frequency range
Total power	ms^2	variance of all NN intervals	<0.4 Hz
ULF	ms^2	ultra low frequency	<0.003 Hz
VLF	ms^2	very low frequency	<0.003–0.04 Hz
LF	ms^2	low frequency power	0.04–0.15 Hz
HF	ms^2	high frequency power	0.15–0.4 Hz
LF/HF ratio		ratio of low-high frequency power	

on the other hand, to minimize the effects of the changes in total power on the LF and HF components. It is useful when evaluating the effects of different interventions in the same subject (graded tilting) or when comparing subjects with major differences in total power [30]. Normalised units are obtained as follows:

$$\text{LF or HF norm (nu)} = \frac{\text{LF or HF (ms}^2\text{)}}{\text{total power (ms}^2\text{)} - \text{VLF (ms}^2\text{)}} \times 100$$

The total power of RR interval variability is the total variance and corresponds to the sum of the four spectral bands, LF, HF, ULF and VLF [28, 29]. The HF component is generally defined as a marker of vagal modulation. This component is respiration-mediated and thus determined by the frequency of breathing. The LF component is modulated by both the sympathetic and parasympathetic nervous systems. In this sense, its interpretation is more controversial. Some authors consider LF power, particularly when expressed in normalised units, as a measure of sympathetic modulations, others interpret it as a combination of sympathetic and parasympathetic activity [21, 26–28]. The consensus is that it reflects a mixture of both autonomic inputs. In practical terms, an increase of the LF component (tilt, mental and/or physical stress, sympathomimetic pharmacologic agents) has been generally considered to be a consequence of sympathetic activity. Conversely, β-adrenergic blockade resulted in reduction of the LF power. However, in some conditions associated with sympathetic overexcitation, for example in patients with advanced CHF, the LF component was found to be drastically diminished, reflecting thereby the decreased responsiveness of the sinus node to neural inputs.

The LF/HF ratio reflects the global sympatho-vagal balance and can be used as a measure of this balance. In a normal adult in resting conditions, the ratio is generally between 1 and 2.

ULF and VLF are spectral components with very low oscillations. The ULF component might reflect circadian and neuroendocrine rhythms and the VLF component long period rhythms. The VLF component has been found to be a major determinant of physical activity and was proposed as a marker of sympathetic activity.

Correlations between time and frequency domain indices and normal reference values

There are established correlations between time domain and frequency domain parameters: pNN50 and RMSSD correlate between themselves and with HF power (r = 0.96), SDNN and SDANN indices correlate significantly with total power and the ULF component [7, 22, 31]. Normal reference values and values in patients with a MI for standard measures of heart rate variability are shown in table 3.

Limitations of standard HRV measurements

Because HRV deals with RR interval variations its measurement is limited to patients in sinus rhythm and to those with a low number of ectopic beats. In this sense, approximately 20 to 30% of high risk post-MI patients are excluded from any HRV analysis due to frequent ectopy or episodes of atrial arrhythmias, particularly atrial fibrillation. The latter one may be observed in up to 15 to 30% of patients with CHF, excluding these patients from any HRV analysis.

Nonlinear methods (fractal analysis) of HRV measurement

Nonlinear methods are based on the chaos theory and fractals. Chaos has been defined as the study of multivariable, nonlinear and nonperiodic systems [32, 33]. Chaos describes natural systems in a different way because it can account for nature's randomness and nonperiodicity. Perhaps the theory of chaos may help in better understanding HR dynamics, taking into account that the healthy heartbeat is slightly irregular and to some extent chaotic. In the near future nonlinear fractal methods may give new insights into HR dynamics in the context of physiological changes and in high risk situations, particularly in patients after MI or in the context of sudden death [21, 22, 32, 33].

Recent data suggest that fractal analysis [33] in comparison to standard HRV measurements seems to detect abnormal patterns of RR fluctuations more efficiently.

Table 3

Reference values for measurement of time domain and spectral parameters in healthy middle-aged subjects and in patients after myocardial infarction.

Variable	Healthy subjects (n = 274)	Recent MI (n = 684)	One year after MI (n = 278)
SDNN (ms)	141 ± 39	81 ± 30	112 ± 40
SDANN (ms)	127 ± 35	70 ± 27	99 ± 38
RMSSD (ms)	27 ± 12	23 ± 12	28 ± 15
pNN50 (%)	9 ± 7	7 ± 9	10 ± 11
Total power (ms^2)	21222 ± 11663	7323 ± 5720	14303 ± 19353
LF (ms^2)	791 ± 563	277 ± 335	511 ± 538
HF (ms^2)	229 ± 282	129 ± 203	201 ± 324
LF/HF ratio	4.61 ± 2.33	2.75 ± 2.13	3.60 ± 2.43

MI = myocardial infarction

Clinical use of HRV

Heart rate variability has been used in different clinical settings, including diabetes [34], arterial hypertension [35], coronary artery disease [36–38], sudden cardiac death [39], CHF [40], and more recently for the screening of patients with obstructive sleep apnoea [41]. Furthermore, the effects of a variety of pharmacological and nonpharmacological interventions on HRV have been studied, such as antiarrhythmic drugs [42], physical effort [43] and after radiofrequency ablation procedures [44]. Despite these numerous clinical investigations a general consensus of the practical clinical use of HRV has been reached only in patients with diabetic neuropathy and in those after MI [21].

We will consider the use of HRV for risk stratification after MI and in CHF patients.

Heart rate variability and risk stratification after MI

Total mortality during the first year after a non-lethal MI is about 5–15% and may be due to sudden arrhythmic cardiac death in 3 to 4%, to progressive heart failure in 4 to 6% and to lethal reinfarction in 3 to 4%. Post-MI risk stratification helps to identify patient subgroups at very high and at very low risk for subsequent major cardiac events such as sudden cardiac death, progressive heart failure or reinfarction. Prophylactic treatment of this population would be of benefit from a public health viewpoint, particularly because there is now evidence that aggressive prophylactic treatment of the highest risk subsets of this population with an implantable cardioverter defibrillator (ICD) can effectively improve survival [45].

Since the first report by Wolf et al. [46] in 1977 on the association between decreased HRV and increased mortality numerous studies were performed using HRV alone [24, 47, 48] or in combination with other variables [49–51], such as as left ventricular ejection fraction (LVEF), late potentials (LP), or ventricular arrhythmias on Holter, as a predictor of outcome in post-myocardial patients.

In the late 80's and in the course of the 90's, most studies have reported that reduced HRV was a powerful predictor of cardiac mortality, arrhythmic events and sudden death in high risk post-MI patients, and it was furthermore independent of other risk stratifers, such as LVEF, ventricular ectopic activity or LP [24, 47–51]. In this sense, Kleiger et al. [36] were first to show in a large post-MI population that depressed HRV predicted mortality independently of other risk factors, which were LVEF, frequency of ventricular extrasystoles, and non sustained ventricular tachycardia (NSVT).

Among all studied HRV parameters, SDNN, HRV index, ULF and VLF power are probably the most accurate indices to be used in clinical settings [21]. SDNN is, however, by far the most common estimate of HRV. Table 4 shows cutpoint values for HRV parameters, as to their sensitivity, specificity, predictive accurary and relative risk of HRV alone or combined to other noninvasive markers for post-myocardial risk stratification. Although the exact time for the highest predictive value of depressed HRV is not clearly established, a general consensus is that HRV should be measured 1 week after MI because a rather high proportion of cardial events (25 to 30%) may occur at that time [21].

Taken alone the positive predictive accuracy of HRV hardly reaches 40%. It has, however, a higher negative predictive value, which means that post-MI patients with normal HRV can be considered at low risk for cardiac or arrhythmic events. Combined to other variables, such as diminished LVEF, premature ventricular couplets (PVC's) >10/hour, runs of NSVT, LP, and BRS, its positive predictive accuracy can be improved. In the large international prospective ATRAMI trial [49] the concomittant use of HRV and BRS for post-MI risk stratification showed that values of SDNN <70 ms

Table 4

Sensitivity, specificity, predictive accuracy and relative risk of heart rate variability alone or combined to other noninvasive markers for post-myocardial risk stratification.

Variable	Sens (%)	Spec (%)	PPA (%)	NPA (%)	RR
SDNN <50 ms	60–67	63	14-25	95	3.1–5.3
HRV index <20	52–92	56–77	15–17	77–98	7.0
ULF <1600 ms^2	28	93	41	93	7.0
VLF <180 ms^2	30	92	39	77	2.3
ULF + VLF + PVC >10/hour	8	98	53	95	2.5
ULF + VLF + LVEF <40%	14	98	56	93	18.5
HRV index <20 + NSVT + LP	29	99	58	95	23.5
HRV index <20 + LVEF <40%	42	90	22	91	6.3
SDNN <70 ms + LVEF <35%					6.7
SDNN <70 ms^2 + BRS <3.0 ms/mm Hg + NSVT					22.2

BRS = baroreflex sensitivity; LP = late potentials; LVEF = left ventricular ejection fraction; NPA = negative predictive accuracy; NSVT = non sustained ventricular tachycardia; PPA = postive predictive accuracy; PVC = premature ventricular couplets; RR = relative risk; sens = sensitivity; spec = specificity.

or BRS <3.0 ms/mm Hg were both independent predictors of cardiac mortality. Furthermore, the association of low SDNN and BRS in patients with a LVEF <35% carried a relative risk of cardiac mortality of 6.7 and 8.7, respectively.

More recent data [52], however, have shown that autonomic markers including HRV (SDNN) and BRS had limited predictive power in identifying high risk post-MI patients.

A major potential difference between the earlier and the more recent studies on HRV as post-MI risk stratifier may lie in the fact that patients are treated by early thrombolysis or by acute coronary revascularisation procedures resulting in smaller-sized MI's and that medications such angiotensin-converting enzyme inhibitors and beta-blockers are much more widely used.

Prognostic value of HRV in CHF

There is now clear evidence that the sympathetic nervous system plays an important role in the progression of heart failure [53]. It may affect the cardiovascular system in heart failure in several ways, including down-regulating β_1-receptors, exerting direct toxic effects on the myocardium and contributing to myocardial remodeling and life-threatening arrhythmias. In this sense, CHF patients are a high-risk group for death. Ventricular arrhythmias often occur in patients with compromised LVEF and up to 80% of patients may die suddenly with an average 60% survival at 4 years.

Because HRV depends on the activity of the ANS and on its integrity, it can be affected in CHF patients. In the initial phases of the disease a significant increase in LF and a decrease in HF is detectable, corresponding to sympathetic activation and reduced vagal tone. The sufficiently intact sympathetic innervation at less advanced stages may induce sympathetic activation reflected by the increased LF component and contribute to arrhythmogenesis and sudden death [54]. In the advanced stages of heart failure there is a loss of rhythmicity in the LF and HF bands. A particular finding is the highly reduced or even undetectable LF power in spite of the high levels of sympathetic activation. This behaviour of the LF component suggests that the integrity of the sympathetic innervation becomes defective as CHF progresses [54]. The highly reduced LF power in the advanced stage of heart failure may be secondary to abnormalities in central autonomic regulation and impairment of ß-adrenergic receptor sensitivity [55, 56]. Patients in very advanced stages of the disease behave as if they had cardiac denervation and loss of neural modulation of cardiac rate, ressembling patients with recently transplanted hearts [57].

Heart rate variability may be used in patients with CHF as a marker for prediction of mortality due to progressive LV dysfunction and to sudden cardiac death [40, 58–61]. In several studies, an SDNN <70 ms was an independent predictor of mortality of all-cause and of cardiac death (RR = 2.8–3.7) [58–60]. The 3-year mortality rate was of 56% [59]. Furthermore, values for LF <3.3 ln ms^2 (RR = 2.5) and <13 ms^2 (RR = 3.7) were found to have predictive power for sudden cardiac death [59, 61].

Current limitations and future directions for the use of HRV

Despite the large number of experimental and clinical studies published the measurement of HRV is still a research technique and not a routine clinical tool [62]. There are several potential reasons that can explain this situation. First, the physiopathological mechanism of HRV establishing the direct link between mortality and reduced HRV is still not fully elucidated. Second, the clinical application of HRV assessment is limited by a lack of standardized methodology due to variability of the parameters according to gender, age, drug interferences and concomitant diseases. Third, despite the relative evidence of the robust character of parameters such as SDNN and the HRV index, there is still no consensus about the most accurate HRV parameter for clinical use. Fourth, the sensitivity, specificity and positive predictive accuracy of HRV are limited. Particularly, its positive predictive accuracy is modest, ranging from 14 to 40%. It has, however, a higher negative predictive value ranging from 77 to 98%. Finally, conflicting results [52] have been found regarding HRV measured after MI, suggesting that this technique may be insufficient by itself to adequately risk stratify these high risk patients.

The combination of HRV with other risk stratifiers, including LVEF, NSVT, LP and BRS may increase the overall predictive accuracy [49–51]. Recently an apporach using various non-invasive and invasive tests in a stepwise fashion was proposed [63]. In stage1 LP and LVEF were obtained, followed in stage 2 by the use of an ambulatory 24-hour ECG recording for the documentation of complex ventricular arrhythmias and for the measurement of HRV, and in stage 3 by an electrophyisiologic study with potential induction of ventricular tachycardia.

Conclusions

Heart rate variability has gained importance in recent years as a technique employed to explore the ANS, which plays an important role in the pathophysiology of arrhythmogenesis. Decreased HRV has been shown to be a strong predictor of increased cardiac and/or arrhythmic mortality, particularly in the post-MI setting. However, the wider use of acute coronary interventions and of medications such angiotensin-converting enzyme inhibitors and beta-blockers has improved the clinical course of patients after discharge from the hospital, rendering the predictive value of HRV more limited.

Given the human and economic costs of sudden cardiac death and the potential benefits to be gained by early identification of patients at increased risk and by the use of ICD devices, today the most important problem is to identify patients best suited for this treatment and those who do not need an ICD.

An important challenge for the near future will be to obtain a universally accepted standardization of HRV methodology and improvement of its positive predictive accuracy mostly by combining it to other available risk stratifiers. The future lies in an easily, rapidly obtainable and reproducible multimarker risk index.

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References

1 Zipes DP, Wellens HJJ. Sudden cardiac death. Circulation 1998;98:2334–51.
2 Korner PI, Tonkin AM, Uther JB. Reflex and mechanical circulatory effects of graded Valsalva maneuver in normal man. J Appl Physiol 1976;40:434–40.
3 Ewing DJ, Hume L, Campbell IW, Murray A, Neilson JMM, Clarke BF. Autonomic mechanisms in the initial heart rate response to standing. J Appl Physiol 1980;49:809–14.
4 Robotis DA, Huang DT, Faubert JP. Head-up tilt-table testing: an overview. Ann Non Invas Electrocardiol 1999;4:212–8.
5 Richards AM, Nicholls MG, Yandle TG, Ikram H, Espiner EA, Turner JG, et al. (The Christchurch cardioendocrine research group). Neuroendocrine prediction of left ventricular function and heart failure after myocardial infarction. Heart 1999;81: 114–20.
6 Wellman HN, Zipes DP. Cardiac sympathetic imaging with radioiodinated metaiodobenzylguanidine (MIBG). Prog Cardiol 1990;3/1:161–74.
7 Stein PK, Bosner MS, Kleiger RE, Conger BM. Heart rate variability: A measure of cardiac autonomic tone. Am Heart J 1994; 127:1376–81.
8 Van Ravenswaaij-Arts CMA, Kollée LAA, Hopman JCW, Stoelinga GBA, van Geijn HP. Heart rate variability. Ann Intern Med 1993;118:436–47.
9 La Rovere MT, Pinna GD, Mortara A. Assessment of baroreflex sensitivity. In: Malik M, ed. Clinical guide to cardiac autonomic tests. Dordrecht, The Netherlands: Kluwer Academic Publishers, 1998: 257–281.
10 Schwartz PJ, Wolf S. QT interval prolongation as predictor of sudden death in patients with myocardial infarction. Circulation 1978;57:1074–7.
11 Schmidt G, Malik Barthel P, Schneider R, Ulm K, Rolnitzky L, Camm AJ, et al. Heart rate turbulence after ventricular premature beats as a predictor of mortality after acute myocardial infarction. Lancet 1999;353:1390–6.
12 Piot O, Copie X, Guize L, Lavergne T, Le Heuzey JY. Variabilité de la fréquence cardiaque: physiologie et méthodologie. Réalités cardiologiques 1997;120:8–14.
13 Hosking DJ, Bennett T, Hampton JR. Diabetic autonomic neuropathy. Diabetes 1978;27:1043–55.
14 Rothschild M, Rothschild A, Pfeifer M. Temporary decrease in cardiac parasympathetic tone after acute myocardial infarction. Am J Cardiol 1988;18:637–9.
15 Schwartz PJ, Priori SG. Sympathetic nervous system and cardiac arrhythmias. In: Zipes DP, Jalife J, eds. Cardiac Electrophysiology: From Cell to Bedside. Philadelphia, PA: WB Saunders Co, 1990: 330–343.
16 Kjellgren O, Gomes JA. Heart rate variability and baroreflex sensitivity in myocardial infarction. Am Heart J 1993;125:204–14.
17 Armour JA. Myocardial ischemia and the cardiac nervous system. Cardiovasc Res 1999;41:41–54.
18 Tsuji H, Venditti Jr FJ, Manders ES, Evans JC, Larson MG, Feldman CL, et al. Determinants of heart rate variability. J Am Coll Cardiol 1996;28:1539–46.
19 Bonnemeier H, Wiegand UKH, Brandes A, Kluge N, Katus HA, Richardt G, et al. Circadian profile of cardiac autonomic nervous system modulation in healthy subjects. J Cardiovasc Electrophys 2003;14:791–9.
20 Jung J, Heisel A, Tscholl D, Friess R, Schieffer H, Özbek C. Assessment of heart rate variability by using different commercially available systems. Am J Cardiol 1996;78:118–20.
21 Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Circulation 1996;93:1043–65.
22 Malik M. Measurement of heart rate variability. In: Malik M, Camm J, eds. Heart Rate Variability. Armonk, NY: Futura, 1995:33–132.
23 Kleiger RE, Stein PK, Bosner MS, Rottman JN. Time domain measurements of heart rate variability. Amb Electrocardiol 1992; 10:487–98.
24 Cripps TR, Malik M, Farrell FG, Camm AJ. Prognostic values of reduced heart rate variability after myocardial infarction: clinical evaluation of a new analysis method. Br Heart J 1991;65:14–9.
25 Hnatkova K, Copie X, Staunton A, Malik M. Numeric processing of Lorenz plots of R-R intervals from long-term ECGs: comparison with time-domain measures of heart rate variability for risk stratification after myocardial infarction. J Electrocardiol 1995;28(suppl):74–80.
26 Malliani A, Pagani M, Lombardi F, Cerutti S. Cardiovascular neural regulation explored in the frequency domain. Circulation 1991;84:428–492.
27 Öri Z, Monir G, Weiss J, Sayhouni X, Singer DH. Heart rate variability. Frequency domain analysis. Amb Electrocardiol 1992; 10:499–533.
28 Malliani A, Lombardi F, Pagani M. Power spectrum analysis of heart rate variability: a tool to explore neural regulatory mechanisms. Br Heart J 1994;71:1–2.
29 Eckberg DL. Sympathovagal balance. Circulation 1997;96: 3224–3232.
30 Montano N, Ruscone TG, Porta A, Lombardi F, Pagani M, Malliani A. Power sepctrum analysis of heart rate variability to assess the changes in sympathovagal balance during graded orthostatic tilt. Circulation 1994;80:1826–31.

31 Bigger JT, Fleiss JL, Steinmann RC, Rolnitzky LM, Kleiger RE, Rottman JN. Correlations among time and frequency domain measures of heart period variability two weeks after acute myocardial infarction. Am J Cardiol 1992;69:891–8.

32 Goldberger AL. Non-linear dymanics for clinicians: chaos theory, fractals, and complexity at the bedside. Lancet 1996;347: 1312–4.

33 Lombardi F. Chaos theory, heart rate variability, and arrhythmic mortality. Circulation 2000;101:8–10.

34 Malpas SC, Maling TJB. Heart rate variability and cardiac autonomic function in diabetes. Diabetes 1990;39:1177–81.

35 Chakko S, Mulingtapang RF, Huikuri HV, Kessler KM, Materson BJ, Myerburg RJ. Alterations in heart rate variability and its circadian rhythm in hypertensive patients with left ventricular hypertrophy free of coronary artery disease. Am Heart J 1993;126: 1364–72.

36 Kleiger RE, Miller P, Bigger JT, Moss AJ and the Multicenter Post-infarction Research Group. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. Am J Cardiol 1987;59:256–62.

37 Bigger JT, Fleiss JL, Steinmann RC, Rolnitzky LM, Kleiger RE, Rottmann JN. Frequency domain measures of heart period variability and mortality after myocardial infarction. Circulation 1992;85:164–71.

38 Dekker JM, Crow RS, Folsom AR, Hannan PJ, Liao D, Swenne CA, et al. Low heart rate variability in a 2-minute rhythm strip predicts risk of coronary heart disease and mortality from several causes. The ARIC Study. Circulation 2000;102:1239–44.

39 Dougherty CM, Burr RL. Comparison of heart rate variability in survivors and nonsurvivors of sudden cardiac arrest. Am J Cardiol 1992;70:610–5.

40 Ponikowski P, Anker SD, Chua TP, Szelemej R, Piepoli M, Adamopoulos S, et al. Depressed heart rate variability as an independent predictor of death in chronic congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. Am J Cardiol 1997;79:1645–50.

41 Roche F, Gaspoz JM, Court-Fortune I, Minini P, Pichot V, Duverney D, et al. Screening of obstructive sleep apnea syndrome by heart rate varibility analysis. Circulation 1999;100:1411–5.

42 Rohde LEP, Polanczyk CA, Moraes RS, Ferlin E, Ribeiro JP. Effect of partial arrhythmia suppression with amiodarone on heart rate variability of patients with congestive heart failure. Am Heart J 1998;136:31–6.

43 Stein PK, Ehsani AA, Domitrovich PP, Kleiger RE, Rottman JN. Effect of exercise training on heart rate variability in healthy older adults. Am Heart J 1999;138:567–76.

44 Sztajzel J, Vinolas X, Sobral J, Dumaresq L, Boveda S, Torner P, et al. Heart rate variability early after successful radiofrequency catheter ablation of left and right-sided accessory pathways and after selective ablation of the slow pathway. Ann Noninv Electrocardiol 1997;2:362–9.

45 Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, et al. Prophylactic implantation of a defibrillator in patients with a myocardial infarction and reduced ejection fraction. N Engl J Med 2002;346:877–83.

46 Wolf MM, Varigos GA, Hunt D, Sloman JG. Sinus arrhythmia in acute myocardial infarction. Med J Aust 1978;2:52–3.

47 Bigger JT, Fleiss JL, Rolnitzky LM, Steinmann RC. Frequency domain measures of heart rate pediod variability to assess risk late after myocardial infarction. J Am Coll Cardiol 1993;21:729–36.

48 Quintana M, Storck N, Lindblad LE, Lindvall K, Ericson M. Heart rate variability as a means of assessing prognosis after myocardial infarction. A 3-year follow-up study. Eur Heart J 1997; 18:789–97.

49 La Rovere MT, Bigger JT, Marcus FI, Mortara A, Schwartz PJ, for the ATRAMI (Autonomic tone and reflexes after myocardial infarction) investigators. Lancet 1998;351:478–84.

50 Farrell TG, Bashir Y, Cripps T, Malik M, Poloniecki J, Bennett D, et al. Risk stratification for arrhythmic events in postinfarction patients based on heart rate variability, ambulatory electrocardiographic variables and signal-averaged electrocardiogram. J Am Coll Cardiol 1991;18:687–97.

51 Odemuyiwa O, Farrell TG, Malik M, Bashir Y, Millane T, Cripps T, et al. Influence of age on the relation between heart rate variability, left ventricular ejection fraction, frequency of ventricular extrasystoles, and sudden death after myocardial infarction. Br Heart J 1992;67:387–91.

52 Huikuri HV, Tapanainen JM, Lindgren K, Raatikainen P, Mäkikallio TH, Airaksinen KEJ, et al. Prediction of sudden cardiac death after myocardial infarction in the beta-blocking era. J Am Coll Cardiol 2003;42:652–8.

53 Packer M. The neurohumoral hypothesis: a theory to explain the mechanism of disease progression in heart failure. J Am Coll Cardiol 1992;20:248–54.

54 Brunner-La-Rocca HP, Esler MD, Jennings GL, Kaye DM. Effect of cardiac sympathetic nervous activity on mode of death in congestive heart failure. Eur Heart J 2001;22:1136–43.

55 Van de Borne P, Montno N, Pagani M, Oren R, Somers VK. Absence of low-frequency variability of sympathetic nerve activity in severe heart failure. Circulation 1997;95:1449–54.

56 Cooley RL, Montano N, Cogliati C, Van de Borne P, Richenbacher W, Oren R, et al. Evidence for a central origin of the low-frequency oscillation in RR-interval variability. Circulation 1998; 98:556–61.

57 Mortara A, La Rovere MT, Signorini M, Pantaleo P, Pinna G, Martinelli L, et al. Can power spectral analysis of heart rate variability identify a high risk subgroup of congestive heart failure patients with excessive sympathetic activation? A pilot study before and after heart transplantation. Br Heart J 1994;71:422–30.

58 Nolan J, Batin PD, Andrews R, Lindslay SJ, Brooksby P, Mullen M, et al. Prospective study of heart rate variability and mortality in chronic heart failure. Results of the United Kingdom Heart Failure Evaluation and Assessment of Risk trial (UK-Heart). Circulation 1998;98:1510–6.

59 Galinier M, Pathak A, Fourcade J, Androdias C, Curnier D, Varnous S, et al. Depressed low frequency power of heart rate variability as an independent predictor of sudden death in chronic heart failure. Eur Heart J 2000;21:475–82.

60 Bilchick KC, Fetics B, Djoukeng R, Fisher SG, Fletcher RD, Singh SN, et al. Prognostic values of heart rate variability in chronic congestive heart failure (Veterans Affairs' Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure). Am J Cardiol 2002;90:24–8.

61 La Rovere MT, Pinna GD, Maestri R, Mortara A, Capomolla S, Febo O, et al. Short-term heart rate variability strongly predicts sudden cardiac death in chronic heart failure patients. Circulation 2003;107:565–70.

62 Huikuri HV, Mäkikallio T, Airaksinen KEJ, Mitrani R, Castellanos A, Myerburg RJ. Measurement of heart rate variability: a clinical tool or a research toy? J Am Coll Cardiol 1999;34: 1878–83.

63 Bailey JJ, Berson AS, Handelsman H, Hodges M. Utility of current risk stratification tests for predicting major arrhythmic evants after myocardial infarction. J Am Coll Cardiol 2001;38: 1902–11.

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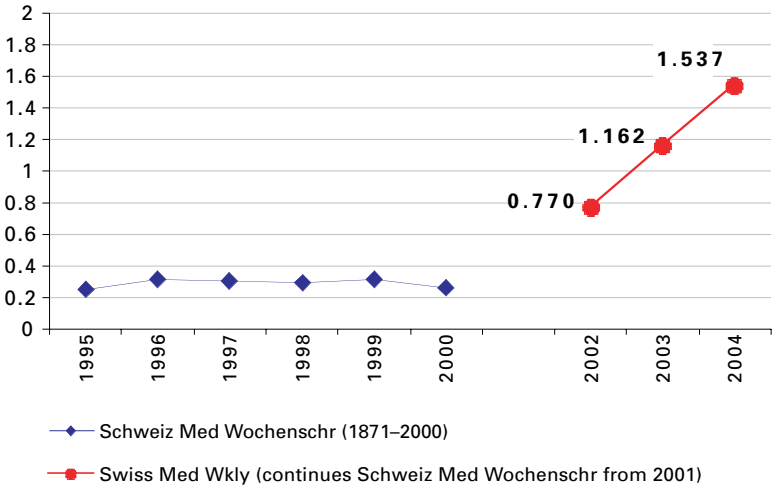

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