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 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.
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 pacemaker 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.

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 sympathetic-vagal 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 sympathetic-vagal imbalance reflected by a diminished 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.
Heart rate variability

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,
the HRV triangular index and its modification, the triangular interpolation of NN interval histogram, and the method based on Lorenz 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 density) 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 verification 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 (ms²). 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 (ms²) or in normalised values (nu). The normalisation of LF and HF is performed by subtracting the VLF component from the total power. It tends to reduce, on one hand, the effects of noise due to artifacts and,

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Units</th>
<th>Description</th>
<th>Frequency range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total power</td>
<td>ms²</td>
<td>variance of all NN intervals</td>
<td>&lt;0.4 Hz</td>
</tr>
<tr>
<td>ULF</td>
<td>ms²</td>
<td>ultra low frequency</td>
<td>&lt;0.003 Hz</td>
</tr>
<tr>
<td>VLF</td>
<td>ms²</td>
<td>very low frequency</td>
<td>&lt;0.003–0.04 Hz</td>
</tr>
<tr>
<td>LF</td>
<td>ms²</td>
<td>low frequency power</td>
<td>0.04–0.15 Hz</td>
</tr>
<tr>
<td>HF</td>
<td>ms²</td>
<td>high frequency power</td>
<td>0.15–0.4 Hz</td>
</tr>
<tr>
<td>LF/HF ratio</td>
<td></td>
<td>ratio of low-high frequency power</td>
<td></td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Healthy subjects (n = 274)</th>
<th>Recent MI (n = 684)</th>
<th>One year after MI (n = 278)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDNN (ms)</td>
<td>141 ± 39</td>
<td>81 ± 30</td>
<td>112 ± 40</td>
</tr>
<tr>
<td>SDANN (ms)</td>
<td>127 ± 35</td>
<td>70 ± 27</td>
<td>99 ± 38</td>
</tr>
<tr>
<td>RMSSD (ms)</td>
<td>27 ± 12</td>
<td>25 ± 12</td>
<td>28 ± 15</td>
</tr>
<tr>
<td>pNN50 (%)</td>
<td>9 ± 7</td>
<td>7 ± 9</td>
<td>10 ± 11</td>
</tr>
<tr>
<td>Total power (ms²)</td>
<td>21222 ± 11663</td>
<td>7323 ± 5720</td>
<td>14303 ± 19353</td>
</tr>
<tr>
<td>LF (ms²)</td>
<td>791 ± 563</td>
<td>277 ± 335</td>
<td>511 ± 538</td>
</tr>
<tr>
<td>HF (ms²)</td>
<td>229 ± 282</td>
<td>129 ± 203</td>
<td>201 ± 324</td>
</tr>
<tr>
<td>LF/HF ratio</td>
<td>4.61 ± 2.33</td>
<td>2.75 ± 2.13</td>
<td>3.60 ± 2.43</td>
</tr>
</tbody>
</table>

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 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 stratifiers, 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 accuracy 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 cardiac 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 (PVCs) >10/hour, runs of NSVT, LP, and BRS, its positive predictive accuracy can be improved. In the large international prospective ATRAMI trial [49] the concomitant use of HRV and BRS for post-MI risk stratification showed that values of SDNN <70 ms

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sens (%)</th>
<th>Spec (%)</th>
<th>PPA (%)</th>
<th>NPA (%)</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDNN &lt;50 ms</td>
<td>60–67</td>
<td>63</td>
<td>14–25</td>
<td>95</td>
<td>3.1–5.3</td>
</tr>
<tr>
<td>HRV index &lt;20</td>
<td>52–92</td>
<td>56–77</td>
<td>15–47</td>
<td>77–98</td>
<td>7.0</td>
</tr>
<tr>
<td>ULF &lt;1600 ms²</td>
<td>28</td>
<td>93</td>
<td>41</td>
<td>93</td>
<td>7.0</td>
</tr>
<tr>
<td>VLF &lt;180 ms²</td>
<td>30</td>
<td>92</td>
<td>39</td>
<td>77</td>
<td>2.3</td>
</tr>
<tr>
<td>ULF + VLF + PVC &gt;10/hour</td>
<td>8</td>
<td>98</td>
<td>53</td>
<td>95</td>
<td>2.5</td>
</tr>
<tr>
<td>ULF + VLF + LVEF &lt;40%</td>
<td>14</td>
<td>98</td>
<td>56</td>
<td>93</td>
<td>18.5</td>
</tr>
<tr>
<td>HRV index &lt;20 + NSVT + LP</td>
<td>29</td>
<td>99</td>
<td>58</td>
<td>95</td>
<td>23.5</td>
</tr>
<tr>
<td>HRV index &lt;20 + LVEF &lt;40%</td>
<td>42</td>
<td>90</td>
<td>22</td>
<td>91</td>
<td>6.3</td>
</tr>
<tr>
<td>SDNN &lt;70 ms + LVEF &lt;35%</td>
<td>6.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDNN &lt;70 ms² + BRS &lt;3.0 ms/mm Hg + NSVT</td>
<td>22.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BRS = baroreflex sensitivity; LP = late potentials; LVEF = left ventricular ejection fraction; PPA = positive predictive accuracy; NSVT = non sustained ventricular tachycardia; NPA = negative predictive accuracy; PVC = premature ventricular couplets; RR = relative risk; sens = sensitivity; spec = specificity.
Heart rate variability 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 MIs 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 $\beta$-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 $\beta$-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, resembling 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 approach 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 electrophysiologic 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 multi-marker risk index.
Heart rate variability


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