Review

Sudden cardiac death: role of heart rate variability to identify patients at risk

Federico Lombardi\textsuperscript{a}, Timo H. Mäkikallio\textsuperscript{b}, Robert J. Myerburg\textsuperscript{c}, Heikki V. Huikuri\textsuperscript{b,*}

\textsuperscript{a}Cardiologia, Dipartimento di Medicina, Chirurgia e Odontoiatria, Ospedale S. Paolo, University of Milan, Milan, Italy
\textsuperscript{b}Division of Cardiology, Department of Medicine, University of Oulu, Kajaanintie 50, 90220 Oulu, Finland
\textsuperscript{c}Division of Cardiology, Department of Medicine, University of Miami School of Medicine, Miami, FL, USA

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1. Introduction

Sudden, unexpected cardiac death stands as one of the most important and unresolved problems in clinical cardiology also in the new millennium. Despite unanticipated advancement in the understanding of the mechanisms that concur to determine such a dramatic event \cite{1}, our capability of identifying patients at risk has not reached satisfactory levels. In most instances, our attention is focused on selected small subgroups of patients at highest risk while ignoring the majority of subjects in whom sudden cardiac death is the first and last manifestation of a cardiac disease \cite{2}.

In the last 20 years, the appraisal \cite{3} of the pro-arrhythmic role exerted by transient or persistent alterations in sympathetic and vagal control mechanisms has stimulated the development of techniques capable of providing information on autonomic modulation and of its alteration in different clinical conditions such as ischemic heart disease, hypertension and congestive heart failure \cite{4,5}. Among these methodologies, analysis of heart rate (HR) variability and of baroreflex sensitivity are the two that have provided the most interesting results in terms of feasibility, clinical results and predictive value \cite{6,7}.

The aim of the present article is to specifically address the value of HR variability analyses, not only for identifying patients at risk but also for describing changes in autonomic control mechanisms immediately prior to onset of malignant ventricular arrhythmias. A brief description of available methodologies, limitations of the study designs and of future directions in HR variability utilisation is also included.

2. Methodological aspects of measurement of HR variability

There are numerous methods to describe regulation of HR and constant fluctuation of R–R intervals. An optimal method for clinical work would be an index that could be easily computed with a simple and widely available analysis method. Despite the efforts of the Task Force of the North American Society of Pacing and Electrophysiology and the European Society of Cardiology to unify and standardise the measuring methodology \cite{6}, there is currently no consensus about the best available index of HR variability for clinical use in different situations.

2.1. Time domain indices of HR variability

Conventionally, HR variability has been assessed by calculating indices based on statistical operations on R–R intervals (means and variance). The most widely used time domain parameters are average HR and standard deviation of all normal-to-normal RR intervals over a specific time period \cite{6}. The absolute value of average variability depends on the length of the analysed period. Cardiologists commonly use a recording length of 24 h, which makes the 24-h standard deviation of R–R intervals probably the
best-known HR variability index. This estimate reflects primarily the very low-frequency fluctuations in HR behaviour, not instantaneous short-term fluctuations, because fast fluctuations of R–R intervals ‘drown’ under the slower ‘waves’. Therefore, also other indexes measuring instantaneous differences between R–R intervals are commonly used in analyses of HR variability with time domain measures [6].

2.2. Spectral analysis

Since the introduction of spectral analysis as a method for studying HR variability [8], an increasing number of investigators have utilised this method. Spectral analysis of HR variability has also been applied to populations with cardiovascular disease [9]. The main advantage of spectral analysis of signals as compared to time domain indices is the possibility to study frequency-specific oscillations. Investigators usually divide the power spectrum into different spectral bands and calculate the powers in these bands. European Society of Cardiology and the North American Society of Pacing and Electrophysiology [6] have recommended the bands that should be used in physiological studies. Methods based on Fast Fourier transformation and autoregressive analysis are most commonly used to transform signals into the frequency domain. In practise, both yield similar results.

2.3. Non-linear dynamics

Analysis methods derived from non-linear system theory have opened up a new approach for studying and understanding the characteristics of HR behaviour [10–14]. These analysis methods differ from the conventional HR variability measures, because they are not designed to assess the magnitude of variability, but rather quality, scaling and correlation properties of the signal. Several algorithms have been developed to describe non-linear fluctuation of HR data [15–19].

The detrended fluctuation analysis technique is a method that has given most promising results in risk stratification of patients in terms of sudden death. It quantifies the presence or absence of fractal correlation properties of RR intervals and has been validated for time series [10]. Details of detrended fluctuation analysis have been described previously elsewhere [10], but are also briefly discussed here. Scaling exponents obtained by detrended fluctuation analysis quantify the relations of HR fluctuations at different time scales. Low exponent values (<1.0) correspond to dynamics where the magnitude of beat-to-beat HR variability is close to the magnitude of longer-term variability. On the contrary, high exponent values (>1.3) correspond to dynamics where the magnitude of long-term variability is significantly higher than the short-term variability. Different scaling exponent values can also be understood via spectral properties of data. Exponent values correlate with normalised spectral measures in controlled situations, and e.g. low to high frequency spectral ratio is closely related to short-term fractal scaling exponent in controlled external situation with fixed respiratory rate [20]. However, this is not the case during ‘free-running’ ambulatory conditions [20], because fractal analysis by the detrended fluctuation technique provides precise information on the relative differences of HR fluctuations over highly segmented time windows, while conventionally computed spectral measures vaguely describe HR fluctuations in pre-determined time windows. Fractal analysis can be considered to be a modification of spectral analysis, but unlike the spectral analysis, it is not ‘polluted’ by changes in external environment, such as rate of respiration and physical activity. Therefore, fractal scaling exponents are not surrogates of spectral components when analysed from the ambulatory Holter recordings. Fig. 1 describes examples of power spectra in cases with various scaling exponent values. Normal healthy subjects have shown scaling exponent values between 1.0 and 1.2, indicating fractal-like HR behaviour, and altered fractal-like behaviour has been reported in patients with cardiovascular diseases. In most studies, reduced short-term fractal scaling exponent (values <1.0) has been shown to...
predict both arrhythmic mortality and precede the spontaneous onset of life-threatening arrhythmias (see Fig. 1).

Scaling analysis techniques based solely on the power spectral density of the signal have also been used in risk stratification studies [12,21,22]. A plot of spectral power and frequency on a logarithmic scale (see Fig. 1, middle portion) and the slope of this relation has been found to be altered among patients with cardiovascular disorders [15,22]. Taken together, increasing evidence support the interpretation of important role of new dynamical HR variability analysis methods in stratification of subjects with high risk for sudden and non sudden cardiac death, as will be discussed below.

### 3. Study designs assessing the HR variability as a predictor of sudden death

Table 1 summarises the designs and the main outcome of most important studies assessing the role of HR variability in prediction of sudden death. Three different study designs have been used: (1) observational follow-up studies, (2) case-control studies, and (3) retrospective observational studies before the arrhythmia onset. Each of the study design has some benefits and also some potential limitations, which are shortly discussed below.

Observational studies have focused on baseline assessment of HR variability in pre-defined patient groups,

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Study design</th>
<th>No. of patients</th>
<th>Underlying heart disease</th>
<th>HRV methodology</th>
<th>Main result of the study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bigger et al. [9]</td>
<td>Observational follow-up</td>
<td>715</td>
<td>Recent MI</td>
<td>Time and frequency domain analysis</td>
<td>2–3-fold relative risk for sudden cardiac death in patients with reduced frequency domain measures of HRV</td>
</tr>
<tr>
<td>Hartikainen et al. [29]</td>
<td>Observational follow-up</td>
<td>575</td>
<td>Recent MI</td>
<td>Time domain analysis</td>
<td>Reduced HRV was an independent predictor of arrhythmic death</td>
</tr>
<tr>
<td>Huikuri et al. [19]</td>
<td>Observational follow-up</td>
<td>446</td>
<td>Recent MI and impaired LV function</td>
<td>Time and frequency domain and fractal analysis</td>
<td>Reduced short-term fractal scaling exponent but not the other measures of HRV predicted sudden cardiac death</td>
</tr>
<tr>
<td>Martin et al. [36]</td>
<td>Case-control</td>
<td>5</td>
<td>CAD, CA</td>
<td>Time domain analysis</td>
<td>Cardiac arrest patients had a lower SDNN of normal RR intervals than healthy controls</td>
</tr>
<tr>
<td>Myers et al. [37]</td>
<td>Case-control</td>
<td>6</td>
<td>CAD, CA</td>
<td>Frequency domain analysis</td>
<td>Power of LF and HF was reduced in patients resuscitated from cardiac arrest in comparison to control patients</td>
</tr>
<tr>
<td>Huikuri et al. [39]</td>
<td>Case-control</td>
<td>22</td>
<td>CAD, CA</td>
<td>Time and frequency domain analysis</td>
<td>24-h time and frequency domain parameters of HRV were reduced in survivors of cardiac arrest in comparison to control patients</td>
</tr>
<tr>
<td>Perkiösmäki et al. [34]</td>
<td>Case-control</td>
<td>60</td>
<td>CAD, CA, sustained VT</td>
<td>Time domain and Poincare plot analysis</td>
<td>HRV was reduced in survivors of cardiac arrest but not in patients with stable, monomorphic VT</td>
</tr>
<tr>
<td>Mäkikallio et al. [16]</td>
<td>Case-control</td>
<td>45</td>
<td>CAD, VT</td>
<td>Frequency domain and fractal analysis</td>
<td>Fractal analysis identify better than other HRV analysis method the patients with VT</td>
</tr>
<tr>
<td>Magid et al. [40]</td>
<td>Observational before VF</td>
<td>11</td>
<td>CAD, CA</td>
<td>Time domain analysis</td>
<td>HRV decreased immediately before VF onset</td>
</tr>
<tr>
<td>Huikuri et al. [38]</td>
<td>Observational before NSVT and VT</td>
<td>18</td>
<td>CAD</td>
<td>Time and frequency domain analysis</td>
<td>HRV was reduced in the hours before VT. LF/HF ratio increased immediately before VT onset</td>
</tr>
<tr>
<td>Valkama et al. [33]</td>
<td>Observational before VT</td>
<td>54</td>
<td>CAD, VT or CA</td>
<td>Time and frequency domain analysis</td>
<td>SDNN, VLF and LF were reduced in patients with a VT episode in comparison to those without VT. No changes in HRV immediately before the onset of VT</td>
</tr>
<tr>
<td>Pozzati et al. [42]</td>
<td>Observational before CA</td>
<td>8</td>
<td>CAD</td>
<td>Time domain analysis</td>
<td>SDNN was reduced before CA. Ischaemic ST changes were also evident</td>
</tr>
<tr>
<td>Shusterman et al. [41]</td>
<td>Observational before VT</td>
<td>53</td>
<td>CAD, VFVF</td>
<td>Time and frequency domain analysis</td>
<td>Time and frequency domain parameters and, in particular, LF and LF/HF ratio decreased before VT</td>
</tr>
<tr>
<td>Pruvot et al. [44]</td>
<td>Observational before VT/VF</td>
<td>58</td>
<td>CAD, ICD</td>
<td>Time and frequency domain analysis</td>
<td>HRV declined before VT/VF. HF was reduced before VT/VF in patients treated with sotalol</td>
</tr>
<tr>
<td>Mäkikallio et al. [52]</td>
<td>Observational before VT/VF</td>
<td>48</td>
<td>CAD, ICD</td>
<td>Time and frequency domain and fractal analysis</td>
<td>Short-term fractal scaling exponent is reduced before the VT/VF events</td>
</tr>
<tr>
<td>Lombardi et al. [45]</td>
<td>Observational before VT</td>
<td>48</td>
<td>CAD, DCM, ICD</td>
<td>Time, frequency and non-linear analysis</td>
<td>HRV declined before VT. LF/HF ratio increased immediately before VT. Value of scaling exponent was also reduced before VT</td>
</tr>
</tbody>
</table>

 CA, cardiac arrest; CAD, coronary artery disease; DCM, dilated cardiomyopathy; HF, high frequency component; HRV, heart rate variability; ICD, implantable cardioverter-defibrillator; ML, myocardial infarction; LF, low frequency component; LV, left ventricular; VF, ventricular fibrillation; VLF, very low frequency component; VT, ventricular tachycardia; SDNN, standard deviation of normal RR intervals.
mostly shortly after acute myocardial infarction, and subsequent follow-up of the patients. These studies have been commonly used in the assessment of value of HR variability in predicting arrhythmic deaths [9,17,19,22–29]. Information obtained by this type of studies may have practical importance, but the study designs are also confounded by some biases, which prevent generalisation of the results. A major limitation is the problem of defining the occurrence sudden arrhythmic death (‘end-point bias’), as all definitions suffer from biases in classifying the precise mode of death. Sudden death occurring within an hour of the onset of symptoms has been commonly attributed to arrhythmia, but many other pathophysiological conditions that evolve rapidly can also lead to sudden death [30,31]. On the other hand, many of the deaths defined as non-arrhythmic may be due to arrhythmias. Another problem in all studies estimating the prognostic value of HR variability in terms of arrhythmic events has been the relatively small size of the patient sample enrolled (‘sample size bias’). The incidence of both non-sudden and sudden death among patients surviving a myocardial infarction, and those with mild to moderate heart failure, has declined significantly during the past two decades, likely due to the impact of improvements in therapy. In view of the low number of deaths and the uncertainties about the mode of death in follow-up studies, even the largest multicenter observational studies, such as ATRAMI trial [32], are not able to give a definite answer regarding the value of HR variability or other markers as predictors of arrhythmic death.

In case-control studies, risk markers are compared between survivors of documented arrhythmic events and matched controls without a history of life-threatening arrhythmia [33–35]. These lack some of the problems of observational studies, such as the end-point and sample size bias, and their results show an even better accuracy of HR variability in differentiating between patients with and without vulnerability to fatal arrhythmias [34,35]. However, the results of these studies can neither be generalised, because the study designs partly ignore the potential for temporal changes in risk factors. HR variability may be temporarily abnormal immediately after a life-threatening arrhythmic event but return to normal with time after the event.

Retrospective analysis of changes in HR variability immediately before the onset of life-threatening arrhythmia events is perhaps the best study design in attempts to study the role of abnormal HR variability as a trigger of sudden arrhythmic event. Both Holter recordings and memory functions of the implantable cardioverter-defibrillators (ICD) have been used in these studies. Although, these studies provide unique mechanistic information on the role of changes in HR variability as a trigger of life-threatening arrhythmia events, the generalisation of the results to broader populations is neither possible, because the studies have focused only on selected high-risk subsets of patients.

Despite some limitations of the study designs, HR variability is perhaps most extensively studied among all arrhythmia risk markers. The main observations and results of these studies are discussed below.

4. Conventional HR variability indices as predictors of sudden death

In all observational studies of patients after myocardial infarction, a depressed HR variability measured from a 24-h period as well as from short-term recordings has been consistently associated with an increased risk of cardiac and overall mortality [24–27]. Similar evidence has been more recently reported also among patients with heart failure [28]. More controversy is in the reports dealing with the association between reduced HR variability and arrhythmic mortality, particularly when other factors such as depressed ejection fraction or runs of ventricular tachycardia are taken into consideration [28]. In one study, it was shown that [29] arrhythmic death was associated with depressed HR variability and ventricular tachycardia runs whereas non-arrhythmic death was related to low ejection fraction, ventricular ectopic beats and reduced HR variability. Moreover, with a combination of risk factors it was possible to identify patient groups in which a majority of deaths were either arrhythmic or non-arrhythmic [29]. In another study, reduced spectral components, mainly reduction in the power of very-low and low frequency spectral components were found to be the best predictor of arrhythmic mortality [27].

5. Conventional HR variability indices in survivors of cardiac arrest or ventricular tachycardia

A reduction in time domain parameters of HRV in patients with cardiac arrest during Holter recordings was first reported by Martin et al. [36]. These authors also observed that frequency domain parameters were reduced in patients resuscitated from cardiac arrest in comparison to controls [37]. More recently, Valkama et al. [33] analysed the relationship between spontaneous occurrence and inducibility of ventricular arrhythmias in patients with a history of sustained ventricular tachycardia or cardiac arrest in a carefully matched case-control study. The authors observed that standard deviation of R–R intervals and low and very low frequency spectral component of HR variability were significantly reduced in patients with sustained ventricular tachycardia in comparison to patients without repetitive ventricular arrhythmias. However, HR variability did not differ significantly between patients with and without inducible sustained ventricular tachycardia. In the same study, no alteration in HR variability was detectable in the last minutes before the onset of spontaneous episodes of ventricular tachycardia occurring during
Holter recording, although HR variability was clearly reduced when analysed from a period of several hours before the arrhythmia onset. These findings suggest that a depressed HR variability and in particular, a reduction in the power of low and very low frequency oscillations of HR, might reflect susceptibility to spontaneous occurrence of ventricular arrhythmias rather than represent an instantaneous trigger for life threatening arrhythmias or a specific marker of inducibility [33,38]. Of particular interest was the observation that, in survivors of cardiac arrest, a blunted circadian rhythmicity was still detectable despite the low 24 h HR variability [39]. Nevertheless, a further reduction of its value was evident in the early morning hours, i.e. in the time period where the incidence of sudden cardiac death is highest [39]. Another case-control study by the same investigators in the larger group of patients showed that HR variability is particularly reduced in the patients with a recent history of cardiac arrest, but not in those with stable monomorphic ventricular tachycardia [34].

In conclusion, most of the published case-control reports are concordant in demonstrating a significant reduction of HR variability in survivors of cardiac arrest in comparison to both post-myocardial infarction patients and controls, thus confirming the link between susceptibility to fatal arrhythmias and low HR variability.

6. Conventional HR variability indices before the onset of ventricular tachycardia or fibrillation

The experimental evidence that an increased sympathetic and a reduced vagal activity directed to the heart might exert a pro-arrhythmic effect has stimulated the use of HR variability analysis to detect changes in autonomic modulation of sinus node before arrhythmic events. Magid et al. [40] initially reported a reduction in time domain parameters of HR variability measured during the 5 min immediately before the onset of ventricular fibrillation in comparison to the preceding 5-min period. The presence of a sympathetic activation and a reduced vagal activity before ventricular tachycardia was hypothesised by Shusterman et al. [41] who analysed HR variability from Holter electrocardiograms of post-infarction patients with ventricular tachycardia. These authors observed an increase in the average HR and a reduction in almost all HR variable parameters 30 min before ventricular tachycardia compared to 24-h values.

Characteristics in the spectral HR variability measures in the hour preceding the onset of sustained and non sustained ventricular tachycardia has been previously reported by Huikuri et al. [38] who described the changes in HR variability spectral parameters of patients with coronary artery disease. The authors observed that all frequency domain parameters of HR variability were significantly lower before sustained ventricular tachycardia in comparison to non-sustained tachycardia. In a follow-up study [33], however, when survivors of cardiac arrest were also considered, these authors were unable to detect any significant changes in spectral parameters in the minutes before the onset of ventricular tachycardia and concluded that impaired autonomic control may be not directly related to the process initiating ventricular tachycardia.

An additional factor capable of determining changes in HR variability pattern and favouring arrhythmia occurrence is transient myocardial ischemia. Recently, Pozzati et al. [42] described an association among the reduction in time domain parameters of HR variability before sustained ventricular arrhythmias and ST segment displacement suggestive of acute ischemia, thus confirming, in the clinical setting, the possibility that acute ischemia together with altered autonomic regulation could have played a critical role in triggering arrhythmic events. Airaksinen et al. [43] also showed that an increase in vagal activity, manifested as an increase in the high-frequency spectral component of HR variability, prevents the occurrence of repetitive ventricular ectopy during myocardial ischemia caused by balloon occlusion of a coronary artery during angioplasty, suggesting to a protective role of vagal activity on ischemia induced ventricular arrhythmias.

The storage function of ICD has been recently utilised [44,45] to evaluate time and frequency domain parameters of HR variability in the minutes before the detected arrhythmic event in large sample sizes of patients. Pruvot et al. [44] observed changes in time and frequency domain parameters of HRV consistent with a state of sympatho-excitation before ventricular arrhythmia onset. This pattern was independent of presence or absence of anti-arrhythmic therapy. Lombardi et al. [45] reported higher values of low and high frequency ratio before the arrhythmic event in comparison to both control conditions and to a period corresponding to about 20 min before tachycardia onset. This finding along with the significant reduction in total power and in cycle length duration was interpreted as an evidence that a shift of sympatho-vagal balance toward a sympathetic predominance might play a pro-arrhythmic role. In the same study, an altered dynamic pattern of HR variability was also observed before ventricular tachycardia onset [45].

All the above findings seem to indicate that additional changes in HR variability can be detected preceding the initiation of the arrhythmic event. These changes, however, may be represented by a further reduction in time domain parameters in some patients, by a change in low and high frequency spectral ratio or by altered dynamic pattern of RR interval time series in others. The prevalence of one change in respect to the others appears to be dependent not only on methodological aspects such as type of analysis and duration of recording but also on the type of underlying heart disease, severity of left ventricular dysfunction and drug therapy.
7. Non-linear analysis of HR variability as a predictor of sudden death

The prognostic power of the methods based on nonlinear dynamics does not have a long history of large-scale studies. The ability of spectral scaling properties of long-term fluctuation to predict death after myocardial infarction was first reported by Bigger et al. [22]. The scaling power law slope of slow fluctuations was found to be a powerful predictor of all-cause mortality or arrhythmic death and it predicted these outcomes better than the traditional power spectral bands.

Recently, analysis of short-term fractal properties of HR fluctuation has yielded superior prognostic power compared to conventional measures among patients with acute myocardial infarction and depressed left ventricular function [17,19]. First, short-term fractal-like correlation properties of RR intervals were studied in 159 patients with acute myocardial infarction and left ventricular ejection fraction <35% with 4-year follow-up. Among all analysed variables, reduced short-term scaling exponent was the best predictor of mortality [17]. More recently, in a large population of 446 survivors of acute myocardial infarction with a left ventricular ejection fraction <35%, reduced short-term fractal exponent was the most powerful HR variability measure as a predictor of all-cause mortality. It predicted both arrhythmic death and non-arrhythmic cardiac death and yielded more powerful prognostic information than the traditional measures of HR variability [19] (Fig. 2).

In addition to patients with myocardial infarction, altered short and long term scaling properties have been observed to predict mortality among patients with chronic congestive heart failure [46,47] and also among elderly people [48]. Altered short-term fractal scaling exponent of HR dynamics has shown to be a powerful predictor of cardiac death, and particularly powerful predictor of sudden cardiac death, in an unselected general elderly population [48]. All other HR variability measures were surpassed by this variable in prediction of cardiac mortality, and in particular the occurrence of sudden death [48]. This is the first study documenting the prognostic power of altered HR variability as a predictor of sudden death in general population.

8. Non-linear HR behaviour before ventricular tachycardia or fibrillation

In addition to changes in some time and frequency domain HR variability indices before the life-threatening arrhythmia events, some nonlinear measures have shown to be able to detect alterations before the onset of arrhythmic events [13,49,50]. Skinner et al. [51] observed significant decline in point correlation dimension of RR intervals preceding ventricular fibrillation after coronary occlusions of conscious pigs. The same authors also demonstrated a decrease of correlation dimension before arrhythmias among patients with pre-existing heart disease [13].

Recently [44], a further reduction of the power law slope of slow fluctuations in the minutes preceding the onset of ventricular tachycardia in comparison to control was shown by the analysis of the storage memory function of ICD patients. Altered short-term fractal scaling exponent has also been observed to precede ventricular fibrillation among patients who experienced ventricular fibrillation during the Holter recordings [50]. A preliminary analysis of ICD memory in a large patient sample also showed that fractal analysis of HR variability is able to predict the onset of both ventricular tachycardia and ventricular fibrillation [52]. These results suggest that the fractal analysis methods of RR intervals identify more accurately

Fig. 2. Survival curves of patients with a prior myocardial infarction and depressed left ventricular function. Left curves represent survival of patients with a low and normal fractal scaling of patients with low and normal standard deviation of N–N intervals (SDNN <65 and >65 ms, respectively). (Reprinted with permission from Ref. [19]).
than the traditional HR variability indices the altered HR behaviour before ventricular tachycardia and fibrillation.

9. Conclusions and future perspectives

It is evident that altered cardiovascular autonomic regulation has an important role in the genesis and perpetuation of life-threatening cardiac arrhythmias. Measurement of HR variability by conventional and new nonlinear methods is a useful research tool for documenting changes in neural regulation in relation to arrhythmia events in various clinical settings. However, the specificity and predictive accuracy of altered HR variability in predicting imminent or future fatal arrhythmia events have still been relatively low. Therefore, the widespread clinical application of this method has not been established for monitoring the HR behaviour in individual patients. More research will be needed to identify the best methodology in HR variability analysis for clinical use. Carefully designed clinical studies will also be needed to assess the clinical applicability of HR variability measurement in risk stratification of patients at high risk of sudden cardiac death. Finally, well-designed intervention trials in patients with abnormal autonomic function will be of importance to reveal the potential clinical role of assessment of HR variability by current methods.

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References


