Heart rate variability (HRV) has been conventionally analysed with time- and frequency-domain methods, which measure the overall magnitude of RR interval fluctuations around its mean value or the magnitude of fluctuations in some predetermined frequencies. Analysis of heart rate dynamics by novel methods, such as heart rate turbulence after ventricular premature beats, deceleration capacity of heart rate and methods based on chaos theory and nonlinear system theory, have gained recent interest. Recent observational studies have suggested that some indices describing nonlinear heart rate dynamics, such as fractal scaling exponents, heart rate turbulence and deceleration capacity, may provide useful prognostic information in various clinical settings and their reproducibility may be better than that of traditional indices. For example, the short-term fractal scaling exponent measured by the detrended fluctuation analysis method has been shown to predict fatal cardiovascular events in various populations. Similarly, heart rate turbulence and deceleration capacity have performed better than traditional HRV measures in predicting mortality in post-infarction patients. Approximate entropy, a nonlinear index of heart rate dynamics, which describes the complexity of RR interval behaviour, has provided information on the vulnerability to atrial fibrillation. There are many other nonlinear indices which also give information on the characteristics of heart rate dynamics, but their clinical usefulness is not as well established. Although the concepts of nonlinear dynamics, fractal mathematics and complexity measures of heart rate behaviour, heart rate turbulence, deceleration capacity in relation to cardiovascular physiology or various cardiovascular events are still far away from clinical medicine, they are a fruitful area for research to expand our knowledge concerning the behaviour of cardiovascular oscillations in normal healthy conditions as well as in disease states.

**Keywords:** heart rate; heart rate dynamics; nonlinear methods; mortality
1. Introduction

Several methods of heart rate variability (HRV) have been used to describe the complex regulatory system between heart rate and the autonomic nervous system (Task Force 1996). The conventional methods based on statistical methods of variance and power spectral analysis of HRV are most often used. The physiological background of these measurements is rather well understood. The high-frequency (from 0.18 to 0.4 Hz) fluctuations of heart rate (and blood pressure) are determined by respiration. These oscillations represent autonomic neural fluctuations and central blood volume alterations (Cohen & Taylor 2002). These high-frequency fluctuations are modified by the phenomenon called respiratory gating, whose magnitude depends on the level of stimulation of autonomic motor neurons. When the level of the stimulation is low (low vagal activity at low arterial pressure), respiratory oscillations of vagal activity are also low (Eckberg 2003). The low-frequency (from 0.03 to 0.15 Hz) fluctuations of heart rate have been proposed to be derived from the arterial pressure Mayer waves, whose major determinant is considered to be sympathetic vasomotor activity (Cohen & Taylor 2002). The very-low-frequency fluctuations (below 0.03 Hz) have been attributed to the renin–angiotensin system, other humoral factors and thermoregulation. The conventional measures of HRV have been shown to provide prognostic information in several patient populations (Kleiger et al. 1987; Bigger et al. 1992, 1993; Fei et al. 1996; Zuanetti et al. 1996; Nolan et al. 1998). Methods of HRV analysis based on nonlinear system theory and beat-to-beat dynamics have gained recent interest as they may reveal delicate changes of heart rate time series. Therefore, novel methods of HRV analysis are constantly being developed (Saul et al. 1987; Goldberger 1990b; Yamamoto & Hughson 1991; Skinner et al. 1993; Pincus & Goldberger 1994; Peng et al. 1995; Goldberger 1996; Voss et al. 1998; Schmidt et al. 1999; Bauer et al. 2006; Tuzcu et al. 2006; Norris et al. 2008a). Several types of different fractal scaling measures, power-law analyses, complexity measures, measures of symbolic dynamics, turbulence and deceleration capacity of heart rate have been studied in various patient populations. These methods of analysing HRV aim to assess qualitative properties rather than the magnitude of the signal. The fractal-like scaling property, the complexity, the turbulence and the deceleration capacity analyses are examples of the novel methods of investigating heart rate dynamics whose clinical impact in the evaluation of cardiovascular control has been assessed in large patient populations. In a few recent studies, many of these measures have been suggested to have better clinical relevance than the conventional measurements of HRV in prediction of future adverse events in various patient groups. The physiological background of these novel methods of analysing heart rate dynamics is much more poorly understood.

There are several other indices and mathematical methods that have been used in characterizing the human heartbeat dynamics. Owing to the abundance of these indices, we focus here only on those methods that have been used in well-designed clinical studies, including relevant numbers of patients and well-defined clinical endpoints, and that have been reproduced by independent investigators in multiple population samples.

In this review, the clinical impact of evaluation of cardiovascular control by novel methods of analysing heart rate dynamics is mainly dealt with in cardiac patients.
2. Fractal measures of HRV

A basic feature of a fractal system is scale invariance, i.e. the same features repeat themselves on different measurement scales (Goldberger 1996). Fractal dynamics can be considered as a specific form of deterministic chaos and can be explained by a nonlinear rule. Healthy subjects’ erratic fluctuations of sinus rhythm have fractal-like characteristics (Denton et al. 1990; Goldberger 1990a). Fractal (1/f) organization is flexible, and breakdown of this scale invariance (self-similarity) may lead to a more rigid and less adaptable system with either random or highly correlated behaviour of heart rate dynamics. Complex interaction of vagal and sympathetic input to the sinus node is thought to be an origin of the fractal-like heart rate behaviour (Goldberger & West 1987; West & Goldberger 1987).

(a) Power-law HRV analysis

A plot of spectral power and frequency on a bi-logarithmic scale shows linear portion between 10^{-4} and 10^{-2} Hz. The slope of this relationship reflects long-term scaling characteristics of heart rate fluctuations in the region of the ultralow- and very-low-frequency bands (Saul et al. 1987). The value of this exponent is around $-1$ in healthy subjects (Saul et al. 1987; Bigger et al. 1996). The slope of the power-law relationship analysis has been observed to decrease with advancing age (Pikkuja¨msä et al. 1999).

(b) Detrended fluctuation analysis

Detrended fluctuation analysis (DFA) quantifies intrinsic fractal-like correlation properties of dynamic systems (Peng et al. 1994). After preprocessing, the integrated RR interval data time series is divided into the windows of the same size. The RR interval variability is then analysed in relation to a local trend in each window. This process is repeated for all different window sizes. The variability is shown on a log–log scale as a function of the size of the observation window. In the presence of scaling, this slope is linear and describes fractal-like correlation properties of the signal. The slope has a crossover phenomenon at window size less than 11 beats. (Also, different cut-off points, such as 16 beats for window sizes, have been used.) The first part of the slope (for window sizes less than 11 beats) corresponds to the short-term scaling exponent ($\alpha_1$) and the second part (for window sizes more than 11 beats) to the intermediate-term scaling exponent ($\alpha_2$). The short-term scaling exponent describes the short-term fractal-like scaling properties and the intermediate-term scaling exponent the longer term fractal-like scaling properties of the RR interval fluctuations. The details of this method have been described by Peng et al. (1995). A scaling exponent value of approximately 1 corresponds to 1/f fluctuations. Healthy middle-aged subjects have been found to have short-term scaling exponent values somewhat over or around 1 (Pikkujäämsä et al. 2001). Healthy elderly subjects may have changes in the fractal correlation properties of heart rate dynamics (Iyengar et al. 1996; Pikkujäämsä et al. 1999).
Physiological background of fractal measures of HRV

Power-law HRV analysis can be considered as a qualitative measure of the power spectrum in the region of the ultralow- and very-low-frequency bands obtained from long-term recordings. The importance of the autonomic nervous system in determining the power-law slope is supported by the observation that denervated hearts have a substantially steeper slope (Bigger et al. 1996). However, the physiological background of this measure is not well established.

The short-term scaling exponent has a relatively good correlation with the ratio of the low- to high-frequency spectral components (LF/HF ratio) in controlled recording conditions, but the association is weaker when recordings are done in ‘free-running’ conditions such as 24-hour Holter recordings. This may partly be explained by the fact that the spectra of the low-frequency and high-frequency components of HRV are based on frequencies (time), whereas the windows used in the DFA are based on the number of the beats (Francis et al. 2002). During normal daily life when the level of physical activity varies, heart and respiratory rate change accordingly. As a consequence, the short-term scaling exponent reflects different spectra of the power spectrum at different time points depending on the physiological state, which, in turn, is influenced not only by the level of physical activity but also by autonomic nervous and humoral responses caused by emotions and other triggers. In other words, the short-term scaling exponent reflects higher spectral frequencies at higher heart rates than at lower heart rates, which can be considered as an adjustment of spectral scale for heart rate. Respiratory activity and gating modulate the high-frequency component of HRV in a complex way (Eckberg 2003). Presumably, these phenomena can also be attributed to the higher frequency content of the short-term scaling exponent. The Mayer waves of arterial pressure are considered to be the origin of the low-frequency fluctuations of HRV (Cohen & Taylor 2002). These fluctuations obviously contribute to the lower frequency content of the short-term scaling exponent. Recent experimental observations in healthy men have suggested that increased levels of circulating noradrenaline decrease the short-term scaling exponent values (Tulppo et al. 2001). In alignment with this notion, recent data have suggested that beta-blocker therapy increases the values of the short-term scaling exponent in patients with heart failure, indicating the reversal of the deteriorated heart rate scaling behaviour (Lin et al. 2001; Ridha et al. 2002). It has been shown that parasympathetic blocking by atropine increases the values of the short-term scaling exponent in healthy subjects (Tulppo et al. 2001; Perkiömäki et al. 2002). Finally, a recent study showed that concomitant activation of both vagal and sympathetic outflows typically decreases the short-term fractal scaling exponent resulting in a random heart rate behaviour (Tulppo et al. 2005).

Clinical studies using fractal measures of heart rate dynamics

The fractal measures of HRV analysis have been shown to provide incremental prognostic information compared with the conventional measures of heart rate fluctuations. Bigger and co-workers first reported that the slope of the power-law relationship predicts death in post-infarction patients (Bigger et al. 1996). According to their observations, a steep power-law slope was a powerful predictor of all-cause mortality or arrhythmic death and predicted these
outcomes better than the traditional power spectral bands. The power-law slope has also been shown to be a better predictor of mortality than the traditional measurements of HRV in the elderly (Huikuri et al. 1998).

Recently, there has been a growing body of evidence that the short-term fractal-like scaling properties of heart rate dynamics analysed by the DFA technique can yield prognostic information beyond that obtained by the conventional measures of HRV. Post-infarction studies have suggested that a reduced short-term scaling exponent is a more powerful predictor of mortality than the traditional measurements of HRV (Mäkikallio et al. 1999a; Huikuri et al. 2000), and that reduced short-term scaling exponent values are associated with vulnerability to ventricular tachycardia (Mäkikallio et al. 1997), ventricular fibrillation (Mäkikallio et al. 1999b), arrhythmic death and non-arrhythmic cardiac death (Huikuri et al. 2000). The prognostic power of the short-term scaling exponent has been confirmed in a general post-infarction population without a marked left ventricular dysfunction and a high proportion of patients on beta-blocking medication (Tapanainen et al. 2002). More recently, fractal HRV has been shown to retain its prognostic power even when the vast majority of patients were taking beta-blockers after an acute myocardial infarction (Jokinen et al. 2003).

Patients with heart failure show loss of fractal organization in heart rate dynamics (Peng et al. 1995). Additionally, altered fractal correlation properties have been observed to be associated with mortality in heart failure patients (Ho et al. 1997). The observations in a relatively large population with congestive heart failure suggest that a reduced short-term scaling exponent is more closely related to the risk of mortality in patients with less severe than in those with more advanced heart failure (Mäkikallio et al. 2001a). In patients with chronic heart failure, the fractal scaling exponent analysed by the DFA method has shown a modest correlation with left ventricular ejection fraction (r=0.28, p<0.0001) and age (r=−0.25, p=0.002), a strong association with functional class (p=0.003), and a lack of correlation with the number of premature beats (p=0.79), non-sustained ventricular tachycardia (p=0.71) and aetiology (p=0.91) (Maestri et al. 2006). The prognostic value of 20 nonlinear indices of HRV in 200 stable heart failure patients in sinus rhythm was recently assessed (Maestri et al. 2007a). The endpoint of the study was cardiac death or urgent transplantation. Although the fractal scaling exponent was a strong univariate predictor of the endpoint, it failed to show independent prognostic information. Taken together, the evidence supporting an independent prognostic value of fractal HRV in heart failure patients is not very strong. The short-term scaling exponent has also been suggested to be a specific risk marker of cardiac death in the elderly (Mäkikallio et al. 2001b). Interestingly, altered short-term fractal-like scaling properties of heart rate dynamics have been observed to precede the spontaneous onset of atrial fibrillation among patients without structural heart disease (Vikman et al. 1999). Moreover, the short-term scaling exponent has been shown to change towards a more random direction in ectopic tachycardia reflecting disturbances in autonomic regulation or in ectopic atrial pacemakers per se (Huikuri et al. 1999). Figure 1 shows two typical cases of RR interval behaviour in high-risk patients with a low short-term fractal scaling exponent and in one case with a normal fractal scaling exponent.
Some of the nonlinear measures of HRV, such as the short-term scaling exponent, have some advantageous features compared with the traditional measures of HRV considering risk stratification purposes and test–retest experiments. These features include less dependency on heart rate, less inter-individual and intra-individual variations (Perkio¨ma¨ki et al. 2001c; Pikkuja¨msa¨ et al. 2001; Maestri et al. 2007b), smaller relative changes of individual values over time after an acute myocardial infarction (Perkio¨ma¨ki et al. 2001c) and relatively good comparability of individual values between long-term and short-term electrocardiographic recordings (Perkio¨ma¨ki et al. 2001b).

3. Complexity measures of HRV

Several indices, such as the Lyapunov exponent (Eckmann & Ruelle 1985), the Hausdorff dimension D (Eckmann & Ruelle 1985; Babyloyantz & Destexhe 1988), the correlation dimension D_2 (Grassberger & Procaccia 1983a; Eckmann & Ruelle 1985), Kolmogorov entropy K (Grassberger & Procaccia 1983b), nonlinear predictability (Porta et al. 2000), the wavelet transform modulus maxima (Ohashi et al. 2003), time asymmetry/irreversibility parameters (Costa et al. 2005; Porta et al. 2008) and the permutation entropy (Frank et al. 2006), have been used to estimate the complexity of time series, but the clinical applicability of these methods has not been well established. The below-mentioned measurements of entropy are the nonlinear complexity measures of HRV that are most widely studied in clinical settings.

(a) Measures of entropy

Several different measures of entropy have been used to quantify the complexity of heart rate dynamics. Approximate entropy quantifies
the unpredictability of fluctuations in a time series, measuring the logarithmic probability that patterns of observations will repeat themselves within predetermined tolerance limits on next incremental comparisons (Pincus & Viscarello 1992; Pincus & Goldberger 1994). A time series containing many repetitive patterns is more predictable than one in which such patterns are absent, resulting in a relatively smaller approximate entropy. Although approximate entropy can be calculated from relatively short datasets, the number of data points has an influence on the value of approximate entropy (Pincus & Huang 1992). Healthy middle-aged subjects have been found to have approximate entropy of RR intervals somewhat over or around 1 (Pikkujärvi et al. 2001). Increasing age has been associated with a decrease in the complexity of heart rate dynamics (Kaplan et al. 1991; Pikkujärvi et al. 1999). The sample entropy is a measure similar to the approximate entropy. However, it excludes self-matches and as a consequence reduces the superimposed bias (Richman & Moorman 2000; Tuzcu et al. 2006; Heffernan et al. 2007). It is also less dependent on the length of the time series. The conventional entropy calculations are based on a single scale and may therefore paradoxically indicate higher complexity in some pathological conditions which have random heart rate dynamics. Complex heart rate dynamics is structured from multiple spatial and temporal scales. Therefore, a multiscale entropy technique was introduced. It was found to robustly separate healthy and pathological groups (Costa et al. 2002).

(b) Physiological background of entropy measures of RR intervals

Experiments with healthy subjects have not shown significant changes in approximate entropy of heart rate fluctuations after atropine administration, suggesting that vagal tone is not a major determinant of approximate entropy (Tulppo et al. 1996; Perkiömäki et al. 2002). Approximate entropy has been shown to increase during exercise after the ventilatory threshold level has been reached and during exercise after administration of atropine (Tulppo et al. 1996). However, observations in patients with advanced congestive heart failure have suggested that beta-blocker treatment does not alter approximate entropy values (Lin et al. 2001). Approximate entropy did not change during graded head-up tilt in 17 healthy subjects, a finding which was explained to be due to the bias of considering self-matches. Instead, corrected approximate entropy, sample entropy and corrected conditional entropy showed a progressive decrease as a function of the tilt table inclination (Porta et al. 2007a). This may indicate that a shift of the sympathovagal balance towards sympathetic activation and vagal withdrawal decreases the complexity of heart rate dynamics. In general, data on the physiological counterparts of the entropy measures of HRV are limited.

(c) Clinical studies using entropy measures of heart rate dynamics

The entropy measures of heart rate dynamics have already provided some interesting information on abnormalities in heart rate behaviour in relation to cardiac disorders and physiological conditions. Reduced approximate and sample entropy values of heartbeat fluctuations have been found to precede spontaneous episodes of atrial fibrillation in patients without structural heart disease (Vikman et al. 1999; Tuzcu et al. 2006). Furthermore, the values of approximate entropy before the onset of atrial fibrillation were lower than the
values obtained from matched healthy control subjects. Increased predictability in heart rate behaviour, measured by approximate entropy, has also been reported to precede spontaneous episodes of atrial fibrillation after coronary artery bypass surgery (Hogue et al. 1998). Reduced complexity in heart rate dynamics has been shown to be associated with post-operative complications after vascular surgery (Fleisher et al. 1993). Reduced multiscale entropy of heart rate has been found to predict mortality in trauma patients (Norris et al. 2008a, b). Experiments in 14 young healthy men showed that heart rate complexity measured by the sample entropy and the Lempel–Ziv entropy increased after resistance training, but returned back to previous values after cessation of training. Resistance exercise training had no effect on spectral measures of HRV (Heffernan et al. 2007).

4. Heart rate turbulence

Heart rate turbulence, which describes the fluctuations of sinus-rhythm cycle length after ventricular premature depolarizations, was introduced in 1999 as a new risk stratifier (Schmidt et al. 1999). In healthy subjects and low-risk patients, there is an early acceleration and subsequent deceleration of sinus rhythm after a ventricular premature depolarization. However, in high-risk patients, this pattern is blunted. Heart rate turbulence is usually described by two variables, i.e. the turbulence onset and the turbulence slope. The turbulence onset corresponds to the difference between the mean of the first two sinus RR intervals after a ventricular premature depolarization and the last two sinus RR intervals before the ventricular premature depolarization. The turbulence slope is defined as the highest slope of the regression line over any of the five successive sinus beat RR intervals during the first 20 sinus beat RR intervals after a ventricular premature depolarization (Schmidt et al. 1999). The averaged RR intervals following the ventricular premature depolarizations are used in the analysis. The heart rate turbulence has a significant association with baroreflex sensitivity and its origin is considered to be an autonomic response to perturbations of blood pressure after a ventricular premature depolarization (Schmidt et al. 1999; Watanabe et al. 2002; Barthel et al. 2003). A limitation of the heart rate turbulence analysis is that it can only be analysed from electrocardiographic recordings with a sufficient number of ventricular premature depolarizations.

Blunted heart rate turbulence has been shown to powerfully predict mortality in post-infarction patients independently of general known risk factors (Schmidt et al. 1999; Barthel et al. 2003). A reduced post-ectopic turbulence slope has also been found to be a predictor of sudden cardiac death after an acute myocardial infarction, even after adjustment for age, diabetes and ejection fraction (Mäkikallio et al. 2005). In a subgroup analysis, the turbulence slope predicted sudden cardiac death, particularly in those post-infarction patients whose left ventricular ejection fraction was above 35 per cent, but not in those with an ejection fraction up to 35 per cent. Figure 2 shows RR interval behaviour in a patient with normal and abnormal heart rate turbulence.

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5. Deceleration capacity of heart rate

Previous scientific evidence shows that reduced vagal activity increases the risk for death (Lown & Verrier 1976; Billman et al. 1982). Deceleration capacity of the heart rate has been proposed as an analysis method of HRV that can provide an estimation of vagal function (Bauer et al. 2006). The deceleration capacity is determined using the phase-rectified signal averaging (PRSA) technique (Bauer et al. 2006). First, the RR intervals that are longer than the preceding intervals are defined as anchors. RR interval prolongations that are longer than 5 per cent are excluded to avoid errors caused by artefacts. Segments of the same size around the anchors are selected and aligned at the anchors. Then, the signals within the aligned segments are averaged, and the PRSA curve and deceleration capacity are determined by computer processing.

Impaired deceleration capacity of the heart rate has been found to be a powerful predictor of death in post-infarction patients. This novel risk stratifier performed better than the left ventricular ejection fraction or the traditional measurements of HRV. This risk marker worked particularly well in patients with preserved left ventricular function (Bauer et al. 2006).

6. Symbolic dynamics of heart rate

The analysis of the symbolic dynamics of the heart rate describes the nonlinear features of HRV. In this technique, the RR intervals are named by different symbols based on the length of the RR intervals. For shorter electrocardiographic recordings, for example, four different symbols can be used, and for longer 24-hour recordings, the number of the symbols can be increased, e.g. to six. After the definition of symbols (alphabets), words, which are from three or four successive alphabets in length and start from each successive beat, are formed. The complexity of the data time series is determined from the distribution of the words using appropriate mathematical methods (Voss et al. 1996, 1998; Wessel et al. 2000; Porta et al. 2007b).

Figure 2. RR interval tachograms before and after a ventricular premature beat in a patient with (a) normal heart rate turbulence (low risk) and (b) abnormal heart rate turbulence (high risk).
The clinical value of the analysis of symbolic dynamics of the heart rate has mainly been evaluated in small patient populations. In a study including 35 healthy subjects and 26 post-infarction patients, the nonlinear methods of HRV represented by the symbolic dynamics improved the discrimination between healthy subjects and high-risk patients \( \text{(Voss et al. 1996)} \). The measurements of the symbolic dynamics of heart rate were found to differ significantly between the time period preceding life-threatening ventricular tachyarrhythmia and the control period without arrhythmias in 17 patients with chronic heart failure and an implantable cardioverter–defibrillator (ICD) \( \text{(Wessel et al. 2000)} \). An experiment in 17 healthy subjects suggests that the analysis of the symbolic dynamics of the heart rate performs better than the spectral analysis in the assessment of alterations of cardiac vagal and sympathetic modulation induced by a graded head-up tilt test \( \text{(Porta et al. 2007b)} \). In a larger population including 572 survivors of acute myocardial infarction, a set of parameters, which included symbolic dynamics variables, was found to be a better predictor of high arrhythmia risk than the conventional assessment of global HRV \( \text{(Voss et al. 1998)} \).

7. Prediction of sudden cardiac death by measurement of HRV/dynamics

An ideal risk stratifier would be able to predict specifically sudden arrhythmic death, which would be valuable information as there is an effective therapy, namely ICD, for preventing such events. Several parameters that describe heart rate behaviour have been attributed to the risk for sudden cardiac death in post-infarction and chronic heart failure patients \( \text{(Galinier et al. 2000; La Rovere et al. 2003; Guzzetti et al. 2005; Mäkikallio et al. 2005)} \). However, the definitions of sudden death in follow-up studies lack the specificity for sudden arrhythmic death \( \text{(Huikuri et al. 2003)} \). Previous observations raised hopes that some of the nonlinear measures of heart rate behaviour, such as the short-term scaling exponent, could serve as a specific risk marker for arrhythmic death. However, increasing evidence supports the concept that the alteration of the fractal-like heart rate dynamics towards more random behaviour predicts cardiac death in general and not specifically sudden arrhythmic death. Recent observations in a relatively small group of high-risk patients with ICDs have supported this view by suggesting that a reduced short-term scaling exponent is more closely related to the risk for death than to the combined endpoint of appropriate ICD shock/death \( \text{(Perkiömäki et al. 2001a)} \). More recently, observations in the MADIT II population further support this notion by showing that the short-term scaling exponent is a predictor of non-arrhythmic mortality in post-infarction patients with low ejection fraction \( \text{(Zareba et al. 2003)} \).

8. Conclusions and future perspectives

Research of HRV has increased during the last decade. Novel methods assessing heart rate dynamics have shown new insights into the abnormalities in heart rate behaviour in various pathological conditions, providing additional prognostic information when compared with traditional HRV measures, and clearly
complementing the conventional analysis methods. Despite a large body of data documenting the predictive power of various HRV indices, none of these methods are in widespread clinical use at the moment, mainly because no prospective studies have yet been carried out to show that an intervention based on the assessment of these variables would improve the outcome. Therefore, more clinical studies by using new and traditional methods of HRV will be needed, before the clinical applicability of these methods can be definitively established.

References


