ANALYSIS OF HEART RATE DYNAMICS BY METHODS DERIVED FROM NONLINEAR MATHEMATICS

Clinical applicability and prognostic significance

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ABSTRACT

The traditional methods of analysing heart rate variability based on means and variance are unable to detect subtle but potentially important changes in interbeat heart rate behaviour. This research was designed to evaluate the clinical applicability and prognostic significance of new dynamical methods of analysing heart rate behaviour derived from nonlinear mathematics.

The study covered four different patient populations, their controls and one general population of elderly people. The first patient group consisted of 38 patients with coronary artery disease without previous myocardial infarction, the second of 40 coronary artery disease patients with a prior Q-wave myocardial infarction, and the third of 45 patients with a history of ventricular tachyarrhythmia. The fourth group comprised 10 patients with a previous myocardial infarction who had experienced ventricular fibrillation during electrocardiographic recordings. The fifth group comprised a random sample of 347 community-living elderly people invited for a follow-up of 10 years after electrocardiographic recordings.

Heart rate variability was analysed by traditional time and frequency domain methods. The new dynamical measures derived from nonlinear dynamics were: 1) approximate entropy, which reflects the complexity of the data, 2) detrended fluctuation analysis, which describes the presence or absence of fractal correlation properties of time series data, and 3) power-law relationship analysis, which demonstrates the distribution of spectral characteristics of RR intervals, but does not reflect the magnitude of spectral power in different spectral bands.

Approximate entropy was higher in postinfarction patients (1.170.22), but lower in coronary artery disease patients without myocardial infarction (0.930.17) than in healthy controls (1.03014, $p<0.01$, $p<0.05$ respectively). It did not differ between patients with and without ventricular arrhythmia. The short term fractal-like scaling exponent of the detrended fluctuation analysis was higher in coronary artery disease patients without myocardial infarction (1.340.15, $p<0.001$), but not in postinfarction patients without arrhythmia (1.060.13) compared with healthy controls (1.090.13). The short term exponent was markedly reduced in patients with life-threatening arrhythmia (0.850.25 ventricular tachycardia patients, 0.680.18 ventricular fibrillation patients, $p<0.001$ for both). The long term power-law slope of the power-law scaling analysis was lower in the ventricular fibrillation group than in postinfarction controls without arrhythmia risk (-1.630.24 vs. -1.330.23, $p<0.01$) and predicted mortality in a general elderly population with an adjusted relative risk of 1.74 (95% CI 1.42-2.13).

The present observations demonstrate that dynamic analysis of heart rate behaviour gives new insight into analysis of heart rate dynamics in various cardiovascular disorders. The breakdown of the normal fractal-like organising principle of heart rate variability is associated with an increased risk of mortality and vulnerability to life-threatening arrhythmias. .

Keywords: dynamic analysis, non-linear methods, heart rate variability.

Prediction is difficult, especially of the future

NEILS BOHR

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Abbrevations

α_1	short term fractal-like correlations of RR interval data
α_2	long term fractal-like correlations of RR interval data
β	slope of the power-law relationship of RR interval data
CAD	coronary artery disease
ECG	electrocardiography
EF	ejection fraction
HF	high frequency
HR	heart rate
LF	low frequency
MI	yocardial infarction
NSVT	nonsustained ventricular tachycardia
NYHA	New York Heart Association
SD	standard deviation
SD1	standard deviation of instantaneous beat-to-beat variability
SD2	standard deviation of continuous long term RR interval variability
SDANN	standard deviation of RR intervals of measured segment
SDNN	standard deviation of RR intervals of 24-hour recording
VF	ventricular fibrillation
VLF	very low frequency
VPB	ventricular premature beat
VT	ventricular tachycardia
ULF	ultra low frequency

List of original communications

This thesis is based on the following five publications, which are cited in the text using the Roman numerals I-V.

I Mäkikallio TH, Ristimäe T, Airaksinen KEJ, Peng CK, Golgberger AL, Huikuri H V: Heart rate dynamics in patients with stable angina pectoris and utility of fractal and complexity measures. Am J Cardiol 1998;81:27-31

II Mäkikallio TH, Seppänen T, Niemelä M, Airaksinen KEJ, Tulppo M, Huikuri HV: Abnormalities in beat to beat complexity of heart rate dynamics in patients with a previous myocardial infarction. J Am Coll Cardiol 1996;28:1005-11

III Mäkikallio TH, Seppänen T, Airaksinen KEJ, Koistinen JM, Tulppo MP, Peng CK, Goldberger AL, Huikuri HV: Dynamic analysis of heart rate may predict subsequent ventricular tachycardia after myocardial infarction. Am J Cardiol 1997;80:779-783

IV Mäkikallio TH, Koistinen J, Jordaens L, Tulppo MP, Wood N, Golosarsky B, Peng CK, Goldberger AL, Huikuri HV: Heart Rate dynamics before the spontaneous onset of ventricular fibrillation. Submitted to J Am Coll Cardiol 1998

V Huikuri HV, Mäkikallio TH, Airaksinen KEJ, Seppänen T, Puukka P, Räihä IJ, Sourander LB: Power-law relationship of heart rate variability as a predictor of mortality in the elderly. Circulation 1998, in press

1. Introduction

The cardiovascular concept of homeostasis refers to the tendency of the organism to maintain a relatively regular heart rate and blood pressure in the face of changing environmental conditions. No physiological variable, however, will give a time sequence that is absolutely stationary or periodic. Spontaneous fluctuations can be observed in cardiovascular functions, such as heart rate and blood pressure, even when the environmental parameters are maintained at as constant a level as possible and no perturbing influences can be identified. Since the possible significance of this fluctuation was realised, heart rate variability has been widely studied. Several studies have shown that decreased fluctuation of RR intervals implicates an increased risk for arrhythmic events and an increased mortality rate in patients with a previous myocardial infarction (Kleiger *et al*. 1987, Farrell *et al*. 1991, Bigger *et al*. 1992).

Since the observation that heart rate fluctuation is related to various cardiovascular disorders, the analysis of heart rate variability has become a widely used tool in the assessment of the regulation of heart rate behaviour (Akselrod *et al*. 1981, Pagani *et al*. 1986, Huikuri *et al.* 1995). Because cardiovascular function is not a stationary system, the traditional indexes of heart rate variability (Kleiger *et al*. 1992, Öri *et al.* 1992) may lack the ability to detect subtle but important changes in heart rate behaviour. Because nonlinear mechanisms are also involved in the genesis of heart rate dynamics (Goldberger & West 1987, Babyloyantz & Destexhe 1988), analysis of the dynamic behaviour of cardiac signals has opened up a new approach towards the assessment of normal and pathological cardiovascular behaviour. It has been hypothesised that spontaneous fluctuation in the dynamics of cardiovascular function may protect the system in case of acute perturbations, and that abnormalities in dynamic behaviour may predispose to abrupt changes in cardiovascular function (Goldberger 1996). A number of new methods have been recently developed to quantify complex heart rate dynamics (Peng *et al.* 1995, Pincus *et al*. 1992, Yamamoto *et al*. 1991). They may reveal abnormalities in time-series data that are not apparent when conventional statistics are used (Goldberger 1996, Pincus *et al*. 1994, Iyengar *et al.* 1996, Fleisher *et al.* 1993).

This study was designed to test the hypothesis that some dynamical analysis methods can reveal subtle abnormalities in heart rate behaviour and complement the traditional methods of analysing heart rate variability in various pathological conditions.

2. Review of the literature

2.1. History of heart rate variability

Various cardiovascular variables, such as heart rate and blood pressure, fluctuate from one beat to another. Stephen Hales (Hales 1733) reported beat-to-beat heart rate variability to be synchronous with respiration (respiratory sinus arrhythmia). Although the temporal fluctuations in cardiovascular signals were noted in ancient times, physicians have overlooked for a long time the possible significance of beat-to-beat fluctuation of cardiovascular signals. This variability has generally been treated as noise to be either ignored or averaged out. The field in which the potential clinical significance of beat-to-beat variability in cardiovascular signals was first recognised was obstetrics. In 1965, the importance of sinus arrhythmia was described in relation to fetal monitoring. This variability correlated with fetal viability; diminution of beat-to-beat variability indicated fetal compromise (Hon & Lee 1965). Initially, heart rate variability measurements were based on simple measurements of RR intervals in studies on diabetics (Murray *et al*. 1975).

Subtle beat-to-beat fluctuations in cardiovascular signals have received only little attention until recently, most probably due to a lack of high resolution electrocardiographic recordings and digital computers with adequate calculation capacity. Since the introduction of such computers, computation of heart rate variability using various algorithms to assess the frequency and amplitude of the oscillatory components of heart rate behaviour has been possible (Kay & Marple 1981, Akselrod et al. 1981). Recent studies have shown that decreased fluctuation of RR intervals is not noise, but implicates an increased risk for arrhythmic events and an increased mortality rate in patients with a previous myocardial infarction (Kleiger et al. 1987, Farrell et al. 1991, Bigger et al. 1992). Time and frequency domain measures of heart rate variability have provided prognostic information and also made it possible to perform noninvasive studies on the significance of changes in the regulation of heart rate behaviour. Most recently, new methods based on nonlinear dynamics have also been introduced for heart rate behaviour analysis.

2.2. Physiological background of heart rate variability

Beat-to-beat fluctuation in heart rate partly reflects the interplay between various perturbations of cardiovascular function and the response of the cardiovascular regulatory systems to these perturbations and also initially raised behaviour. The changes in heart rate behaviour may be either exogenous or endogenous. Continuous changes in sympathetic and parasympathetic neural impulses exhibits changes in heart rate and cause oscillation around the mean heart rate.

A relatively well known event that causes oscillations in heart rate is respiration. Heart rate fluctuation is related to respiration due to the inspiratory inhibition of vagal tone. The inspiratory inhibition is evoked primarily by central impulses from the medullary and cardiovascular center (Davidson et al. 1976). This parasympathetically mediated fluctuation can be abolished by atropine or vagotomy (Akselrod et al. 1985, McCabe et al. 1985, Raczkowska et al. 1983, Pomeranz et al. 1985). RR interval fluctuation in relation to respiration is used as a noninvasive index of vagal nerve excitation in humans (Hyano et al. 1991, Eckberg 1983, Kollai & Mizsei 1990). However, respiration related high-frequency heart rate fluctuation has been shown to be a somewhat imperfect index of vagal activity (Kollai & Mizsei 1990). There are situations in which high frequency changes of RR intervals may not reflect changes in vagal modulation at all (Brown et al. 1993), but can be explained by the kinetics of sino-atrial node responses to acetylcholine (Saul et al. 1991). This respiration caused fluctuation occurs at both high and low frequencies (Koh et al. 1994).

Sympathetic excitations have been suggested to correspond to RR interval fluctuation at around 0.1 Hz frequency (Malliani et al. 1991, Pagani et al. 1997). However, most evidence does not support the notion that low frequency spectral power detect changes of sympathetic nerve activity (Koh et al. 1994, Hopf et al. 1995, Saul et al. 1990, Kingwell et al. 1994). The phenomenon of sympatho-vagal balance in heart rate variability analysis can also be questioned (Eckberg 1997). One fluctuation loop affecting heart rate variability is the vasomotor part of the baroreflex loop, which is responsible for arterial pressure oscillations (Madwed et al. 1989), causing low frequency fluctuation. Several other factors, such as peripheral vascular resistance and thermoregulation, are suggested to cause very low frequency oscillation (Rosenbaum & Race 1968, Kitney 1975), but the relevance of these suggestions can be questioned. In addition, rapid control systems of pressoreceptors and chemoreceptors maintain the cardiovascular homeostasis by altering the heart rate through small frequent adjustments (Ravenswaaij-Arts et al. 1993). Heart rate fluctuation is also a result of various factors, which are often difficult to discern from total behaviour, which combine different wave forms. Thus, by studying heart rate variability, we have an opportunity to study the cardiac dynamic behaviour influenced by a variety of endogenous and exogenous factors. It is possible to obtain information about the nature of the perturbations to which the cardiovascular system is exposed as well as the regulatory responses to these perturbations. Since the process is dynamic and nonlinear, the usefulness of studying the behaviour of fluctuations rather than static averages is acknowledged.

2.3. Conventional methods of assessing heart rate variability

2.3.1. General

The changes in the sinus rate over time have been termed heart rate variability. Heart rate variability analysis has become an important tool in cardiology, because its measurements are noninvasive and easy to perform, have relatively good reproducibility and provide prognostic information on patients with heart disease (Kleiger et al. 1992, Öri et al. 1992, Huikuri et al. 1995, David et al. 1994, Baselli et al. 1987, Ewing et al. 1984b).

2.3.2. Time domain analysis of heart rate variability

Conventionally, heart rate fluctuation has been assessed by calculating indices based on statistical operations on RR intervals (means and variance). The most widely used time domain index is the average heart rate. It is easy to calculate over a suitable length of time. The calculations of other different time domain indices naturally require precise timing of R waves. Time domain analysis can be performed on short electrocardiogram segments (lasting from 0.5 to 5 minutes) or on 24-hour electrocardiographic recordings. Beat-to-beat or short term variability represents fast changes in heart rate. Long-term variability indices mainly reflect slower fluctuation of RR intervals. These indices are calculated from the RR intervals occurring in a chosen time window. An example of a short term variability index is the standard deviation of beat-to-beat RR interval differences within the time window. The standard deviation of all the RR intervals or the difference between maximum and minimum RR interval length, within the window are examples of long term indices. The value of the estimate depends on the record length. Therefore, the measures should be compared within segments of similar length.

The most commonly used index is the standard deviation of all normal-to-normal RR intervals (SDNN) over a 24 h period. This recording length is commonly used by cardiologists to calculate heart rate variability. This index is probably also the best known heart rate variability index. Kleiger et al. (1987) estimated RR interval standard deviation over a 24 h period as a predictor of mortality in postmyocardial infarction patients. This estimate reflects primarily the very low frequency fluctuation in heart rate behaviour, not the heart rate fluctuations in segments with a duration of < 1 minute, because these fast fluctuations of RR intervals “drown” under the slower waves. Other example of time domain variables are NN50, which is a measure of the instantaneous difference over 50 ms between two consecutive normal-to-normal RR intervals (Ewing et al. 1984), and RMSSD, which is the square root of the mean squared differences of successive RR intervals. All the time domain measure indices could be affected by artefacts and outliers, and these measures therefore require data from which artefacts and ectopic beats have been carefully eliminated.

2.3.2.1. Geometrical methods of heart rate variability analysis

Geometrical methods present RR intervals in geometric patterns and various approaches have been used to derive measures of heart rate variability from them. The triangular index is a measure where the length of RR intervals serves as the x-axis of the plot and the number of each RR interval length serves as the y-axis. The length of the base of the triangle is used and approximated by the main peak of the RR interval frequency distribution diagram. Triangular interpolation approximates the RR interval distribution by a linear function and the baseline width of this approximation triangle is used as a measure of the heart rate variability index (Malik et al 1989, Farrell et al. 1991). This triangular index had a high correlation with the standard deviation of all RR intervals, but it is highly insensitive to artefacts and ectopic beats, because they are left outside the triangle. This reduces the need for preprocessing of the recorded data (Malik et al. 1989)

The Poincaré plot as another geometrical measure, is a diagram (scattergram) in which each RR interval is plotted as a function of the previous RR interval. Poincaré plots can be interpreted visually and also quantitatively (Huikuri et al. 1996, Tulppo et al. 1996). Instantaneous beat-to-beat variability of data and continuous long-term variability of RR intervals can be calculated. In addition to the present quantitation, which can be classified as geometrical, the Poincaré plot also gives a useful visual scheme of the RR data by representing qualitatively with graphic means the kind of RR variations included in the recording. The shape of the plot can be used to classify the signal into one of several classes (Woo et al. 1994, Schechtman et al. 1993), and the irregular shapes quanfied from Poincaré plots may then be classified as nonlinear.

2.3.3. Frequency domain measures of heart rate variability

Since the introduction of spectral analysis as a method for studying heart rate variability (Akselrod et al. 1981, Bloomfield 1976), an increasing number of investigators have utilized this method. The main advantage of spectral analysis of signals is the possibility to study their frequency-specific oscillations. Spectral analysis involves decomposition of the series of sequential RR intervals into a sum of sinusoidal functions of different amplitudes and frequencies. The result can be displayed with the magnitude of variability as a function of frequency (power spectrum). The power spectrum reflects the amplitude of the heart rate fluctuations present at different oscillation frequencies. Methods based on Fast Fourier transformation and autoregressive analysis are most commonly used to transform signals into the frequency domain. Practically speaking, both yield similar results. Investigators usually divide the power spectrum into different spectral bands and calculate the powers in these bands. The boundaries of these bands are defined differently by different authors. The spectrum is usually divided into three or four different bands, depending on the major frequency bands. The boundaries of the most commonly used frequency bands are as follows: ultra low frequency < 0.0033 Hz, very low frequency from 0.0033 – 0.04 Hz, low frequency from 0.04 – 0.15 Hz and high frequency from 0.15 to 0.4 Hz. The boundaries that should be used in physiological studies have been

recommended by European Society of Cardiology and the North American Society of Pacing and Electrophysiology (Task Force, 1996). These recommendations are based on a suggested, but only partly proved, physiological background of heart rate variability.

2.4. Dynamical analysis methods of heart rate behaviour

There is increasing evidence to suggest that the heart is not a periodic oscillator under normal physiologic conditions (Babyloyantz & Destexhe 1988, Kaplan & Goldberger 1987, Goldberger & West 1987), and the commonly employed moment statistics of heart rate variability may not be able to detect subtle, but important changes in heart rate time series. Therefore several new analysis method of heart rate behaviour, motivated by nonlinear dynamics and chaos theory, have been developed to quantify the dynamics of heart rate fluctuations (Goldberger & West 1987, Pincus 1991, Yamamoto & Hughson 1991). The development of these new methods has been based on the Chaos Theory (Crutchfield et al. 1987).

2.4.1. History of chaotic and nonlinear dynamics

At the beginning of the 17th century, Johannes Kepler tried to prove the harmony of the structure of the solar system. The success of Newton's principles of mechanics led to the ultimate predominance of determinism. The past and future of the material world was particularised. Everything seemed to be perfectly predictable and causal. It was assumed that a small inaccuracy in the baseline data leads to only a small error in prediction. This is true of linear systems, where effect is proportional to cause.

After the development of the rules of statistical thermodynamics, however, it became clear that there was a limit to the mechanics of nature. Henry Poincare (1854–1912) showed that there are stable and unstable types of orbits and that sometimes even a tiny disturbance in the system can bring about a change in the nature of the orbit. He examined predictability and noticed that systems are deterministic on the one hand, but the strong principle of causality is violated on the other. He noticed that similar causes do not lead to similar effects. He concluded that there is no formula that relates the state of a system at a given time to the state at some future time. Edward Lorenz was interested in computerized weather forecasting and recognised that starting the computer program with slightly different initial conditions eventually resulted in totally different weather conditions. This was clear evidence of a failure of the principle of causality (Lorenz 1963).

2.4.1.1. Chaos

Chaos, in the technical sense, is used to denote a type of time evolution in which the difference between two states that are initially closely similar grows exponentially over time. All systems have been shown to be linear, close to any static equilibrium, unless or until there is a continuous injection of energy to excite the system enough to make non-linearity appreciable and chaos possible. Chaos also requires a dissipative mechanism to prevent the system from blowing apart (Crutchfield et al. 1987, Gleick 1987).

Chaos is more easily understood through a comparison with randomness and periodicity. Random behaviour never repeats itself and is inherently unpredictable and disorganised. Unlike random behaviour, periodic behaviour is highly predictable, because it always repeats itself over some finite time interval. A sine wave is a typical example. If we know the amplitude, frequency and phase of a sine wave at any instant, we can predict the wave perfectly at any other point in time. Chaos is distinct from periodicity and randomness, but has characteristics of both. It looks disorganised, but is actually organised. The most important criteria for chaotic behaviour are summarised as follows: 1. Chaos is deterministic and aperiodic and it never repeats itself exactly. There are no identifiable cycles that recur at regular intervals. 2. Most chaotic systems have sensitive dependence on the initial conditions. In other words, very small differences in the initial conditions will later result in large differences in behaviour. 3. Chaotic behaviour is constrained. Although a system appears random, the behaviour is bounded, and does not wander off to infinity. 4. Chaotic behaviour has a definite form. The behaviour is constrained, and there is a particular pattern to the behaviour (Crutchfield et al. 1987, Gleick 1987, Ruelle 1979, Grassberger & Procaccia 1984, Procaccia 1988).

2.4.1.2. Nonlinearity and its relation to chaos

Nonlinear equations are of two types, monotonic and folded (i.e. exponential or parabola-like). This ambiguity gives rise to chaos under suitable conditions. Nonlinearity is necessary and fundamental to chaos and can also endow stability. Nonlinear systems can seek out and maintain essentially the same optimum state in response to a wide variety of external conditions (Procaccia 1988, Jensen 1987, Devaney 1987).

2.4.1.3. Strange attractors

A simple attractor in which the orbit is a closed loop corresponds to sustained oscillation. This attractor is not chaotic. A chaotic attractor is a continuous curve confined to a finite region of phase space, which never crosses itself , and yet never closes on itself. These attractors are called “strange attractors”. Chaotic behaviour is also constrained, and there is a particular pattern to it (Freeman 1988, Mandelbrot 1982) .

2.4.1.4. Fractal form

A Fractal system is a specific form of chaos. The geometry of chaotic attractors often suggests the existence of fractals. A fractal is a system which has the same structure on many measurement scales. Mathematician Benoit Mandelbrot introduced the word “fractal” to refer to one of the fundamental properties of a specific structure: self-scaling similarity over a wide range of scales. This self-similarity occurs over an infinite range of scales in pure mathematical fractal structures and over a limited range in natural objects or systems. The normal heart rate time series is fractal-like and seems to display the fractal property of self-similarity over different time scales without a characteristic time scale. The power spectra of heart rate time series have been shown to concur with 1/f behaviour, which is essential for fractal-like behaviour and also characteristic of chaotic behaviour. Normal heart rate time series have been shown to demonstrate a “strangelike” attractor, which is characteristic of chaotic as opposed to random or periodic signals. Based on this Ary Goldberger has concluded that “the most compelling clinical example of cardiac chaos is paradoxically found in the dynamics of the normal sinus rhythm”. These chaotic, fractal and nonlinear qualities of heartbeat behaviour have inspired investigators to develop new analysing methods of heart rate behaviour (Mandelbrot 1982, Goldberger 1996, Goldberger & West 1987, Yamamoto et al. 1995).

2.4.2. Approximate entropy analysis

Approximate entropy is a measure and parameter that quantifies the regularity or predictability of time series data. It has been developed for time series to classify complex systems that include both deterministic chaotic and stochastic processes. (Pincus 1991, Pincus & Goldberger 1994, Pincus & Huang 1992, Pincus & Viscarello 1992). Reduced complexity of heart rate dynamics has been found in sick neonates and in patients with postoperative complications after cardiac surgery (Pincus & Viscarello 1992, Fleisher et al. 1993). The obvious advantage of this method is its capability to discern changing complexity from a relatively small amount of data. This makes the approximate entropy measure applicable to a variety of contexts. This measure cannot certify chaos.

2.4.3. Detrended fluctuation analysis

The detrended fluctuation analysis technique is a measurement which quantifies the presence or absence of fractal correlation properties and has been validated for time series data (Peng et al. 1995). It was developed to characterise fluctuations on scales of all lengths. The self-similarity occurring over an large range of time scales can be defined for a selected time scale with this method. The details of this method have been described by Peng et al. (1995). Normal healthy subject have shown scaling exponent values (α) near

1, indicating fractal-like heart rate behaviour, and altered fractal-like behaviour has been reported in patients with cardiovascular diseases and with advancing age (Peng et al. 1995, Ho et al. 1997, Hausdorff et al. 1995, Iyengar et al. 1996).

2.4.4. Power-law relationship analysis of heart rate dynamics

The power-law relationship of RR interval variability is a spectral measure different from the traditional measures of heart rate variability, because it does not reflect the magnitude of heart rate variability, but the distribution of the spectral characteristics of RR interval oscillations. In this method, the power-law relationship of RR interval variability is calculated from the frequency range of 10^{-4} to 10^{-2} Hz, characterising mainly slow heart rate fluctuations. The physiological background of the spectral distribution is not exactly known, but the observation of a significantly steeper slope in denervated hearts suggests that it is influenced by the autonomic input to the heart (Bigger et al. 1996). The details of this method have been described previously (Saul et al. 1987, Bigger et al. 1996, Press et al. 1995).

2.4.5. Two dimensional vector analysis

As described above, the Poincaré plot is a diagram in which each RR interval is plotted as a function of the previous one. The Poincaré plot gives a useful visual representation of the RR data by illustrating qualitatively with graphic means the kind of RR variations included in the recording. The shape of the plot can be used to identify “attractors” (Tulppo et al. 1996). In chaotic behaviour a particular pattern of behaviour needs to be found. The nonlinear relationship and structure in the plots indicate that the process might be chaotic rather than random. It does not prove the existence of chaos, but indicates that chaotic behaviour is likely.

2.4.6. Other nonlinear analysis methods

The Lyapunov numerical method (Wolf et al. 1985, Eckmann & Ruelle 1985) is used as an adjunct to graphic analysis. The Lyapunov exponent is a quantitative measure of separation the trajectories that diverge widely from their initial close positions. The magnitude of this exponent is related to how chaotic the system is. The larger the exponent, the more chaotic the system. For periodic signals, the Lyapunov exponent is zero. A random signal will also have an exponent of zero. A positive Lyapunov exponent indicates sensitive dependence on the initial conditions and is diagnostic of chaos, although these exponents are not easily measured (Grassberger & Procaccia 1984). The

major limitation in their calculation is that the currently available algorithms require large amounts of data and long computing times. Also, the system must remain stable over the recording time, but biologic systems seldom remain stable.

By evaluating the Haussdorff correlation dimension D, evidence of the chaotic nature of cardiac activity can be obtained (Bergé et al. 1984, Eckmann & Ruelle 1985). Haussdorff dimension D is a measure of the complexity of the system. The lower the value of D, the more coherent the dynamics. D = 1 presents periodic oscillations. If D has non-integer values greater than two, it defines a chaotic behaviour (Grassberger & Procaccia 1983, Bergé et al. 1984, Eckmann & Ruelle 1985, Mayer-Kress et al 1988). Although D is a convenient measure, because it does not require the system to be stationary, it unfortunately always involves a potentially large error of estimation. Therefore, instead of using D, it is more convenient to evaluate the correlation dimension D2 from a time series with the help of the existing algorithms (Grassberger & Procaccia 1983 and b, Eckmann & Ruelle 1985).

Another important quantity of the characterisation of deterministic chaotic activity is Kolmogorov entropy K, which may be estimated by a procedure (Grassberger & Procaccia 1983b, Eckmann & Ruelle 1985) close to the one used for dimension D. This quantity measures how chaotic an experimental signal is. In the case of deterministic chaos, K is positive and measures the average rate at which the information about the state of the system is lost over time. In other words, K is inversely proportional to the time interval over which the state of the system can be predicted. Moreover, K is related to the sum of the positive Lyapunov exponents (Eckmann & Ruelle 1985). The above methods can be evaluated quantitatively and are diagnostic of chaos, whereas spectral analysis, time autocorrelation function and Poincaré plot construction are qualitative methods.

The fractal dimension can be employed as an estimate of the minimal number of degrees of freedom that a process obeys. A fractal has the same overall structure on multiple scales. A fractal dimension can be quantified in a meaningful way (Lipsitz & Goldberger 1992, Eckmann & Ruelle 1985, Grassberger & Procaccia 1984, Grassberger & Procaccia 1983b, Mandelbrot 1982, Goldberger 1996). To do this, the object has to be observed under many different magnifications; by varying magnification and measuring the amount of space the object occupies, its fractal dimension can be determined. The algorithms used for the analysis of unknown signals are still evolving. The most common algorithm is that developed by Grassberger and Procaccia (1983b). Chaotic systems often exhibit low dimension, but periodic and random signals can also exhibit the same magnitude of dimension. For this reason, a diagnosis of chaos should not be made, based exclusively on a fractal dimension.

Spectral analysis alone cannot distinguish a chaotic process either, but some investigators have suggested that a particular spectral pattern (one in which the power density is inversely related to frequency) is highly suggestive of a nonlinear or chaotic process (Goldberger & West 1987, Goldberger 1996, Goldberger et al. 1987). However, the diagnostic value of this 1/f pattern has also been questioned (Pool 1989). Wrinkle fluctuations occur in the human heart rate dynamics, which have many of the characteristics of nonlinear dynamics and deterministic chaos. These features cannot be detected by traditional measures of heart rate variability, suggesting that methods motivated by nonlinear dynamics may have important clinical applications to analysis of heart rate behaviour. Whether the various nonlinear methods detect chaotic behaviour is

an important academic issue, but from the practical point of view, it is important to know whether they are applicable for clinical purposes. The prognostic accuracy and clinical applicability of these measures are not well known.

2.5. Heart rate variability in pathological conditions

2.5.1. Heart rate variability in uncomplicated coronary artery disease

Heart rate variability is reduced in patients with stable coronary artery disease, and has been suggested to be reduced even before the development of symptomatic coronary artery disease. Eckberg et al. (1971) reported that reduced baroreflex sensitivity is related to coronary artery disease. Airaksinen et al. (1987) observed reduced vagal activity in patients with coronary artery disease manifested as lower heart rate variability. A disturbed circadian rhythm of heart rate variability was found in patients with coronary artery disease by Huikuri et al. (1994), but 24-hour heart rate variability was not reduced. There is also evidence to suggest that the reduction of heart rate variability correlates with the angiographic severity of coronary artery disease (Hyano et al. 1990), and especially high frequency fluctuation seemed to be reduced in relation to the severity of coronary artery disease, although no association of this kind was not found by Rich et al. (1988) or Airaksinen et al. (1987). Although heart rate variability has been shown to be decreased in patients with coronary artery disease, the exact mechanisms of reduced heart rate variability are not known. The effect of the severity of coronary artery disease is controversial. Ischaemia has been suggested to destroy the cardiac receptors resulting in altered autonomic regulation (Minisi & Thames 1989), but ageing also affects autonomic activity (Airaksinen et al. 1987). The contribution of transient myocardial ischaemia is unresolved, but recent clinical data have demonstrated that short term coronary occlusion during coronary angioplasty causes divergent changes in heart rate variability, which could not be predicted on the basis of the location of the coronary stenoses (Airaksinen et al. 1991).

2.5.2. Heart rate variability after acute myocardial infarction

In 1965, Schneider & Costiloe proposed that heart rate fluctuation is decreased in patients with an acute myocardial infarction. In the late 1980's a few landmarking studies confirmed the strong and independent predictive value for mortality following myocardial infarction (Kleiger et al. 1987, Malik et al. 1989). Later, several reports have shown a decrease in the spectral measures of heart rate variability after a myocardial infarction (Pipilis et al. 1991, Bigger et al. 1991, Valkama et al. 1994). The reduction in heart rate variability after a myocardial infarction seems to be a transient feature. Evidence of a recovery of heart rate variability after myocardial infarction has been observed (Bigger et

al. 1991, Flapan et al. 1993), but heart rate variability remains still on a lower level than in healthy controls (Bigger et al. 1991) after an infarction, and this may be related to adverse prognosis.

2.5.3. Prognostic significance of heart rate variability

Reduced short term (30 consecutive RR intervals) heart rate variability was found to be associated with a higher in-hospital mortality rate in patients with acute myocardial infarction (Wolf et al. 1978). Heart rate variability from 24-hour continuous electrocardiographic recordings was computed in a large multicenter postinfarction study (Kleiger et al. 1987), and the population was followed up for a mean of 31 months. Heart rate variability was found to be an indicator of long term prognosis after an acute myocardial infarction. The relative risk of death was 5.3 times higher in the patients with poor heart rate variability (SDNN < 50 ms) than in the patients with good (SDNN > 50 ms) 24-hour heart rate variability. Decreased heart rate variability remained a significant prognostic indicator after adjustment for clinical, demographic and other Holter variables and left ventricular ejection fraction. The association between postinfarction mortality and low heart rate variability was confirmed by Bigger et al. (1992). They studied the frequency domain measures of heart rate variability in 715 patients two weeks after a myocardial infarction. The population was followed up for four years. After adjustment for the known risk markers, slow fluctuation spectral bands (ultra low and very low frequencies) of heart rate variability remained a significant predictor of mortality. Very low frequency power was the only variable that was a more powerful predictor of arrhythmic death than cardiac or all-cause mortality. The association between low heart rate variability and mortality after acute myocardial infarction was also confirmed by Vaishnav et al. (1994). Rich et al. (1988) showed that decreased heart rate variability and low left ventricular ejection fraction were the best and independent predictors of mortality also in patients with angina pectoris but without recent myocardial infarction.

Impaired heart rate variability was proposed to be a better predictor of cardiac death and arrhythmic events than left ventricular ejection fraction in patients with prior myocardial infarction (Farrell et al. 1991) and confirmed by Odemuyiwa et al. (1991). Cripps et al. (1991) found that the relative risk of sudden death or ventricular tachycardia was seven times greater in postinfarction patients with low heart rate variability than in those with high heart rate variability. Pedretti et al. (1993) found that heart rate variability, in addition to various other risk indicators, was significantly related to late arrhythmic events. Heart rate variability was found to provide more prognostic information than left ventricular ejection fraction or the occurrence of ventricular premature depolarizations and to predict independently arrhythmic events. Huikuri et al. (1992) compared heart rate variability in 22 survivors of cardiac arrest not associated with acute myocardial infarction and 22 clinically matched controls. The survivors of cardiac arrest had lower heart rate variability than the controls without a history of life-threatening arrhythmias. Heart rate variability has been observed to be an independent predictor of sudden death (Odemuyiwa et al. 1994). Hartikainen et al. (1996) showed decreased heart rate variability to be related to both arrhythmic and nonarrhythmic death in postinfarction

patients. Both case-control and epidemiological studies have suggested that low heart rate variability increases the risk of arrhythmic events and death. The recent data suggest that impaired heart rate variability increases the risk of non-fatal cardiac events, e.g. myocardial infarction and unstable angina pectoris, suggesting that low heart rate variability analysed with conventional methods is strongly related to cardiovascular events and not specifically to arrhythmic events (Tsuji et al. 1996).

2.5.4. Other risk markers of arrhythmic death

Poor left ventricular function is an important determinant of both cardiac death and arrhythmic mortality after myocardial infarction (Ruberman et al. 1977, Moss et al. 1982). Residual ischemia may also associate with sudden cardiac death (Savage et al. 1987, Pepine et al. 1991).

In postinfarction patients, frequent premature depolarizations and the occurrence of nonsustained ventricular tachycardia have been shown to be risk markers of sudden cardiac death or arrhythmic events (Moss et al. 1979, Follansbee et al. 1980, Mukharji et al. 1984, Holmes et al. 1985). However, the predictive accuracy of spontaneous ventricular arrhythmias (excluding sustained ventricular tachycardia) for cardiac arrest is low (Bigger et al. 1984, Hartikainen et al. 1996).

Prolongation of the QT interval in postinfarction patients has been shown to predict the risk for ventricular tachyarrhythmias and sudden death (Schwartz & Wolf 1978, Ahnve et al. 1980). QT dispersion is defined as the variability of the length of the QT interval between the leads of a conventional 12-lead surface electrocardiogram, and it was introduced by Campbell et al. (1985). Broad QT dispersion reflects differences in the local myocardial repolarization/recovery times (Day et al. 1990, Zabel et al. 1995) and hence an electrophysiologic environment (substrate) that favours reentry (Mitchell et al. 1986, Perkiömäki et al. 1995). Increased QT dispersion has been shown to be associated with vulnerability to life-threatening ventricular arrhythmias in patients with a previous myocardial infarction (Perkiömäki et al. 1995 and 1997).

Signal-averaged ECG is a method of determining high-frequency low-amplitude potentials at the end of the QRS complex (Simson 1981). These late potentials have been observed to predict sudden death and arrhythmic events (Kuchar et al. 1987, Farrell et al. 1991).

Baroreflex sensitivity reflects the vagal activity exerted by baroreceptor reflexes (Smyth et al. 1969). In postinfarction patients, depressed baroreflex sensitivity is associated with ventricular arrhythmias and sudden death and does not correlate with ejection fraction, but is inversely related to age (La Rovere et al. 1988, Farrell et al. 1992).

The variation of every other T wave amplitude is defined as T wave alternans. This alternans can be measured with digital signal processing techniques, and has been suggested to be associated with the genesis of ventricular arrhythmias (Adam et al. 1984, Rosenbaum et al. 1994).

Using electrophysiologic indicators, postinfarction patients can be stratified into low- and high-risk groups in terms of the future risk for life-threatening arrhythmias (Bourke et al. 1991). Sustained monomorphic ventricular tachycardia during programmed electrical stimulation is suggested to be the only arrhythmia of prognostic relevance (Bourke et al. 1991, Zoni-Berisso et al. 1996). In a selected population of postinfarction patients, inducible sustained monomorphic ventricular tachycardia was the most important variable related to late arrhythmic events (Zoni-Berisso et al. 1996).

2.5.5. Heart rate variability in other disease states

Heart rate variability has been found to be decreased in congestive heart failure (Casolo et al. 1989, Kienzle et al. 1992). Brouwer et al. (1996) observed, however, that the conventional measures of heart rate variability were not related to survival in patients with heart failure, but abnormal Poincaré plots were independent mortality predictors. Decreased heart rate variability has also been observed in hypertensive patients with left ventricular hypertrophy (Petretta et al. 1995, Chakko et al. 1993). More recent data, however, suggest that decreased heart rate variability is not specifically related to ventricular hypertrophy, but rather to hypertension itself (Huikuri et al. 1996, Perkiömäki et al. 1996, Ylitalo et al. 1997). Heart rate variability has also been shown to be reduced in diabetic neuropathy (Smith 1982) and in several neurological conditions (Lowensohn et al. 1977, Kuroiwa et al. 1983, Korpelainen et al. 1996) as well as in chronic renal failure (Cloarec-Blanchard et al. 1992).

2.5.6. Influence of physical training and drugs on heart rate variability

The relation between physical fitness and heart rate variability is controversial. Physical fitness and regular endurance training have been suggested to be associated with increased heart rate variability (Seals & Chase 1989, De Meersman 1993, Boutcher & Stein 1995), but some studies have failed to show any association (Reiling & Seals 1988). Beta-blockers have been suggested to enhance heart rate variability (Niemelä et al. 1994, Rich et al. 1991). Scopolamine has been found to increase the high-frequency spectral component (Vybiral et al. 1990). Flecainide and propafenone have appeared to diminish heart rate variability (Zuanetti et al. 1991). Generally, studies on the effects of drugs on heart rate variability have shown that heart rate is often not normalised, and it is therefore difficult to conclude whether changes take place only due to an altered heart rate. Also, it is not known whether possible changes in heart rate variability have connections with the observed prognostic influences of these drugs.

3. Purpose of the present study

1. The main purpose of the present research was to assess the clinical applicability of new dynamical analysis methods derived from nonlinear dynamics of heart rate behaviour.
2. The specific aims of the individual substudies were:
   a) to compare dynamical measures of heart rate behaviour between coronary artery disease patients without a previous myocardial infarction and healthy controls.
   b) to compare dynamical measures of heart rate behaviour between postinfarction patients and healthy controls.
   c) to compare dynamical measures of heart rate behaviour between postinfarction patients with vulnerability to ventricular tachyarrhythmia and postinfarction patients without propensity to ventricular tachyacardia
   d) to compare dynamical measures of heart rate behaviour before ventricular fibrillation in postinfarction patients and postinfarction control patients without propensity to ventricular arrhythmias.
   e) to evaluate dynamical measures of heart rate behaviour as predictors of mortality in a general elderly population.

4. Populations

The study covered four different patient populations, their controls and a general population of elderly people. The demographic characteristics of the study populations (I-IV) are shown in Table 1.

The first group consisted of 38 consecutive patients with stable angina pectoris and without previous myocardial infarction who had been referred for an angiographic examination because of a history of chest pain and evidence of ischemic ST-segment depression during an exercise test (I). Medication had been withdrawn before the examination. Age and sex matched healthy subjects served as controls. They had been selected from the general population of Oulu from among individuals participating in a larger trial. They had undergone a complete physical examination and their medical history revealed no cardiovascular disease or medication.

The second group comprised 40 consecutive patients with a prior Q-wave infarction referred for angiography on account of angina pectoris (II). Patients with diabetes or atrial fibrillation were excluded. Medication had been withdrawn before the examination. Age and sex matched healthy subjects served as controls.

The third group, the ventricular tachyarrhythmia group, consisted of 45 consecutive patients who had had a documented cardiac arrest or spontaneous sustained ventricular tachycardia and in whom sustained monomorphic ventricular tachycardia was inducible by programmed electrical stimulation. Antiarrhythmic treatment had been withdrawn at least 4 half-lives before the electrophysiological testing. The studies were performed 2 to 10 days after the occurrence of ventricular tachycardia. Two different control groups were used. The postinfarction controls consisted of 45 patients with a prior Q-wave myocardial infarction but without any history of ventricular tachycardia events. Patients with inducible nonsustained or sustained ventricular tachycardia were excluded. All of these control patients also showed arrhythmia-free survival during a follow-up of two years. The groups were matched with respect to age, sex and left ventricular ejection fraction. Forty-five age-matched healthy subjects without evidence of heart disease served as normal controls (III).

The fourth group consisted of 10 postinfarction patients, all of whom had spontaneous onset of ventricular fibrillation during 24-h electrocardiographic recordings without significant preceding ST segment changes and who also underwent electrophysiological

and angiographic examinations (IV). The control group consisted of postinfarction patients without any history of ventricular arrhythmia events. The controls were selected from among 83 consecutive postinfarction patients referred for angiography on account of angina pectoris or for prognostic reasons, on whom programmed electrical stimulation was performed. The ventricular fibrillation patients were matched with postinfarction controls with respect to age, sex, left ventricular ejection fraction, β-blocking and diuretic medication and functional class. Two postinfarction control subjects, who had had an arrhythmia-free follow-up period of two years, were matched to each ventricular fibrillation patient.

Table 1. Characteristics of patient populations

	healthy subjects (n = 45, I,II,III,IV)	uncomplicated CAD (n = 38, I)	post-MI group without arrhytmia (n= 45, II,III)	post-MI group with VT (n = 45, III)	VF group (n = 10, V)
Age	59 ± 9	55 ± 9	60 ± 6	62 ±14	67 ± 4
Men/women	39/6	39/6	39/6	39/6	7/3
NYHA I-II		23	17	19	–
NYHA III-IV		15	28	26	10
LV ejection fraction (%)		71 ± 7	45 ± 8	44 ± 11	38 ± 8
Number of major coronary arteries narrowed > 50% in diameter					
1		17	6	9	–
2		&	12	17	2
3		15	27	19	8

Abbreviations: the values are mean ± standard deviation; NYHA = New York Heart Association; LV = left ventricular; CAD = coronary artery disease; MI = myocardial infarction; VT = ventricular tachycardia; VF = ventricular fibrillation.

The fifth population consisted of a random sample of 480 persons aged 65 or older living in the community (V). They were obtained from the register of the Social Insurance Institution covering the population of the city of Turku. No exclusion criteria other than living in an institution were used. Ambulatory 24-hour electrocardiographic recordings of these subjects were analysed. A clinical history was obtained by personal interview, and a comprehensive clinical evaluation was carried out, including a physical examination, standard ECG, chest x-ray, blood pressure and biochemical analyses. Functional classes and levels of disability due to any cause were classified. Major diagnoses were established on the basis of the history and clinical evaluation. The population was followed up for ten years. Ten-year mortality and causes of death were recorded from the mortality statistics. The mode of death was defined after a review of the hospital records, autopsy findings and death certificates. The end-points of the follow-up were all-cause mortality, cardiac mortality, cerebrovascular mortality, cancer mortality, and mortality due to various other causes.

5. Methods

5.1. Electrocardiographic recordings

All the subjects in all studies (I,II,III,IV,V) were monitored for 24 hours (if possible) with an ambulatory electrocardiographic recorder. The Del Mar Avionics (I-IV) and Oxford Medilog, Oxford (V) recording systems were used. The data were sampled digitally and transferred to a microcomputer for the analysis of heart rate variability. For the detection and quantification of arrhythmias, a 2-channel oscilloscopic display and an arrhythmia analyser were used.

5.2. Analysis of heart rate behaviour

After transfer of the electrocardiographic data to a microcomputer, the RR interval series were edited manually and premature beats and noise were deleted (I-V). Questionable portions were printed out on a 2-channel electrocardiogram at a paper speed of 25 mm/sec to confirm the sinus origin of the RR interval data. Only segments with > 80% pure sinus beats were included.

An autoregressive model was used to estimate the power spectrum densities of RR interval variability (Burg 1975, Kay & Marple 1981) in which the computer program automatically calculates autoregressive coefficients (I-IV). The size of 20 was used as the model order in the analysis of the RR interval data. The Fourier transform method was used to estimate the power spectrum densities of heart rate variability in one substudy (V). The power spectra were quantified by measuring the area in four frequency bands: < 0.0033 Hz (ultra low frequency) 0.0033 – 0.04 Hz (very low frequency), 0.04 – 0.15 Hz (low frequency) and 0.15 – 0.40 Hz (high frequency). The standard deviation and mean length of the RR intervals both in the whole measured epoch and in shorter segments were used as time domain measures (I-V).

5.2.1. Poincaré plot analysis

The Poincaré plot is a diagram (scattergram) in which each RR interval of a tachogram is plotted as a function of the previous RR interval. The Poincaré plot gives a visual contact to the RR data by representing qualitatively with graphic means the kind of RR variations included in the recording. The plots were also analysed quantitatively. This quantitative method of analysis is based on the notion of different temporal effects of changes in the vagal and sympathetic modulation of the heart rate on the subsequent RR intervals without a requirement for a stationary quality of the data. Computerised analysis entails fitting an ellipse to the plot, with its center coinciding with the center point of the markings. The line defined as axis 2 shows the slope of the longitudinal axis, whereas axis 1 defines the transverse slope, which is perpendicular to axis 2. In the computerised analysis, the Poincaré plot is first turned 45° clockwise, and the standard deviation of the plot data is then computed around the horizontal axis (axis 2), which passes through the data center (SD1). SD1 shows the instantaneous beat-to-beat variability of the data. The standard deviation of continuous long-term R-R intervals is quantified by turning the plot 45° counterclockwise (SD2) and by computing the data points around the horizontal axis (axis 1), which passes through the center of the data. SD2 shows the continuous long-term RR interval variability. In addition, the SD1/SD2 ratio was computed. The parameters quantified on the plot are shown in Figure 1.

5.2.2. Approximate entropy analysis

Approximate entropy analysis was used to measure the complexity of time series data. It quantifies the regularity or predictability of data and has been developed for time series. This method can be used to classify complex systems that include both deterministic chaotic and stochastic processes. Approximate entropy measures the logarithmic likelihood that runs of patterns that are close to each other will remain close in the next incremental comparisons. A greater likelihood of remaining close (high regularity) produces smaller approximate entropy values, and conversely, random data produce higher values. Two input variables, m and r, must be fixed to compute approximate entropy, and m = 2 and r = 20% of the standard deviation of the data sets have been recommended for time series, based on previous findings of good statistical validity. The details of this method have been described by Pincus (1991). These values were also used in the present study. Different r values were first tested, however. With high r values too much detailed system information was lost, which made the time series misleadingly regular. Too low r values, on the contrary, did not keep the effect of signal noise at minimum, and therefore the recommended input variables were used.

5.2.3. Detrended fluctuation analysis

The detrended fluctuation analysis technique was used to quantify the fractal-like scaling properties of RR interval data. This method is a modified root-mean-square analysis of random walk, which quantifies the presence or absence of fractal correlation properties and has been validated for time series (Peng et al. 1995). In this method, the root-mean-square fluctuation of integrated and detrended time series is measured at each observation window and plotted against the size of the observation window on a log-log scale. Heart rate correlations were defined particularly for short-term (< 11 beats, α), but also for long-term correlations of RR interval data. In this method, a fractal-like signal (1/f signal spectrum) results in an exponent value 1 ($\alpha = 1.0$). White Gaussian noise (totally random signal) results in a value 0.5 ($\alpha = 0.5$), and a Brownian noise signal ($1/f^2$ signal spectrum) with a spectrum of rapidly decreasing power in the higher frequencies results in an exponent value 1.5. $\alpha = 0.5$ corresponds to a time series where interbeat behaviour is random. $\alpha = 0 - 0.5$ correspond to time series where large and small values are more likely to alternate, whereas at α values of $0.5 - 1.0$ a long interbeat interval is more likely to be followed by a long interval and vice versa.

5.2.4. Power-law relationship analysis

The power-law relationship of RR interval variability was calculated from the frequency range of 10^{-4} to 10^{-2} Hz. The point power spectrum was logarithmically smoothed in the frequency domain and the power integrated into bins spaced 0.0167 log (Hz) apart. A robust line- fitting algorithm of log (power) on log (frequency) was then applied to the power spectrum between 10^{-4} to 10^{-2} Hz and the slope of this line was calculated (β). The robust algorithm minimises the absolute deviations of data points from a linear model instead of the squared fitting error, thus reducing the adverse effect of occasional outlier points in the spectrum. This specific frequency band is chosen on the basis of previous observations regarding the linear relationship between log (power) and log (frequency) in this frequency band in human heart rate time series data. Only recordings with > 12 hours of analysed data were used for the power-law relationship analysis. The details of this method have been described previously (Saul et al. 1987, Bigger et al. 1996). The slope of this power-law relationship of heart rate variability computed over the ultra low and very low frequency oscillations is a spectral measure different from the traditional measures of heart rate variability, because it does not reflect the magnitude of heart rate variability, but the distribution of spectral characteristics of RR interval oscillations.

5.3. Signal behaviour tests

A series of simulations with artificially generated data and real RR signals were performed to test the behaviour of dynamical measures (I,III,IV). 1) Artificial white Gaussian noise, noise with a spectrum compatible with the inverse power law (1/f noise) and noise with a spectrum compatible with the $1/f^2$ noise were generated, and values of dynamical variables were calculated for these, using different input variables and epoch sizes. The artificial signals described above were also randomly shuffled by interchanging the sample positions pairwise 500 times. Similar shuffling was performed on real RR interval data. 2) In addition, artificial signals with different spectral characteristics were generated in order to simulate real RR signals. The relative powers of the very low and high frequency spectral bands were varied systematically to see how this affected the dynamical variables. Also, the power ratio of very low and high frequency components of a real RR signal was varied by digital filtering techniques. 3) Artificial noise with different power spectral properties was added to real RR data. The amount of frequency powers and the width of the frequency bands were varied. 4) Finally, two types of base noise were added to a real RR signal in different signal to noise ratios. The first type was additive white Gaussian noise and the second additive quantization type of noise generated by recording constant RR intervals with an electronic device (Lionheart Multiparameter Stimulator) via the usual Holter measurement procedure. The quantization effect occurs due to the limited sampling accuracy of RR intervals. The standard deviation of additive white Gaussian noise and quantization noise was 5 ms. The standard deviation of the real RR signal was increased from 40 ms to 80 ms in 10 ms steps. Thus, a signal-noise ratio of 8 to 16 was tested in the experiments.

Artificial white Gaussian noise with a spectrum of the same power content at all frequencies (flat spectrum) resulted in short-term fractallike scaling exponent values between 0.5 and 0.55 (expected value $\alpha_1 = 0.5$) , approximate entropy values between 1.94 and 2.02 and a power-law slope value (β) 0, as expected. Digitally filtered noise with a spectrum compatible with the 1/f power law resulted in slightly higher (0 – 3%) short-term fractal values than expected (expected value $\alpha_1 = 1.0$) and a power-law slope value (β) –1.0, as expected. The Brownian noise signal with a $1/f^2$ signal spectrum resulted in a short term exponent value 1.5 and a power-law slope value (β) –2.0, as expected. After shuffling the filtered artificial signals and real RR interval data, the values obtained with the different measures were similar to those obtained with artificial white Gaussian noise (I,II,III,IV).

In experiments with different relative very low and high frequency powers of artificial signals, a decrease in very low frequency power invariably caused an increase in approximate entropy. A slight artificial addition of the band width high frequency power in real RR data resulted in increased approximate entropy. The larger the power increase was, the larger the increase in entropy value. Addition of white Gaussian noise to a real RR signal in different signal to noise ratios had a minor effect on approximate entropy (V).

Artificial modification of real RR interval data showed that an increase of low frequency power resulted in a subtle increase of the short term exponent value, while an increase of the high frequency component resulted in a decrease of this exponent. In

addition, an artificial addition of the band width of the high frequency power towards the direction of the very-high frequency band resulted in a significant reduction of the short-term scaling exponent.

5.4. Effects of editing

To test how data editing affects the values of dynamical measures, the data of several subjects were edited using different methods. The effect of the number of excluded beats on dynamic analysis was studied by increasing progressively the number of edited beats from the same data set. The effects of different editing methods were studied by comparing the results obtained when edited beats were alternatively deleted, replaced by the value of neighbouring RR interval or replaced by inserting new RR interval values interpolated from previous and subsequent beats.

The heart rate behaviour values did not differ between the different editing methods when < 5% of the beats were randomly edited. When 5 – 30% of the beats were randomly edited in 5% of the intervals, the short term scaling exponent value decreased progressively when the edited beat was replaced by the interval length of the neighbouring beats or when the interpolating method was used, but remained stable (< 5% error) when the editing was carried out by deleting the beats. When ectopic beats were retained in the data sets, the short term scaling exponent and power-law slope values were lower, whereas approximate entropy resulted in higher values compared to the values recorded after removal of the ectopic beats. The selection of the editing method did not affect the long range slope values of power-law relationship analysis, whereas approximate entropy was sensitive to editing method, as expected.

5.5. Electrophysiologic and angiographic examinations

Electrophysiologic testing included incremental ventricular pacing and programmed ventricular stimulation using up to 3 extrastimuli and 2 basic drive cycle lengths (600 and 400 ms) from the right ventricular apex and outflow tract. The stimulation protocol and the definition of induced arrhythmias have been described in detail previously (Huikuri et al. 1993). Left heart catheterisation was performed by the Judkins technique. Left ventricular cineangiograms were recorded in the 45 degree right anterior oblique projection, and ejection fraction was calculated by a biplane area-length method. Coronary angiograms were recorded in multiple projections, and coronary artery stenoses with > 50% luminar narrowing were considered significant.

5.6. Echocardiographic measurements

A Hewlett-Packard 77020A ultrasound colour Doppler system was used for the M-mode, two-dimensional and Doppler echocardiographic recordings, observing standard techniques and a method described previously (Airaksinen et al. 1989).

5.7. Exercise electrocardiographic measurements

The healthy subjects and the patients with stable angina pectoris performed a symptom-limited maximal exercise test on an electrically braked bicycle ergometer (I,II,III,IV). A horizontal or downsloping ST depression of > 0.1mV occurring 0.08 seconds after the J point was considered to be of ischemic origin. The criterion for an ischemic episode during the 24-hour ambulatory recording was a ≥ 1 mm horizontal or downsloping ST segment depression lasting for ≥ 1 min.

5.8. Other analysis

A clinical history and evaluation, a physical examination, chest x-ray, blood pressure and biochemical analyses were obtained by standard methods. Serum total cholesterol, high-density and low-density lipoprotein cholesterol, triglyceride and glucose were measured from overnight fasting samples by the methods described earlier (Räihä et al. 1994, 1997).

5.9. Statistics

The results are mostly given as means ± standard deviation. In the light of Kolmogorov-Smirnov tests (Z-value > 1.0), in addition to the absolute values, a logarithmic transformation to the natural base was performed on all the spectral components of heart rate variability (I,V). Student's t-test for normally distributed variables, Mann-Whitney U-test for other continuous values and chi-square test for categorical variables were used to analyse the differences between the groups (I-V). Analysis of variance followed by Bonferroni's post hoc multiple range tests was also used to compare the differences between the groups (III). The paired t-test for dependent variables was used to analyse differences one hour before a specific event and in the 24-hour average (IV). Multiple regression analysis was used to determine the best independent variable when differentiating between the patient groups (I-IV). When analysing the sensitivity, specificity and predictive accuracy of the different measures, the 90% or 95% percentile of the values obtained for healthy subjects was used as the normal range for each measure (I,III). Spearman's and Pearson's correlation coefficients were used to estimate the

correlations between the measured variables. A p-value < 0.05 was considered significant (I,II,III,IV,V). Cox proportional hazards regression analyses were used to assess the association between different risk predictors and mortality, using SPSS Windows version 6.1 (V). To find the best cut-off points for various measures of heart rate variability, the dichotomisation cut-off points that maximised the hazards ratio obtained from the Cox regression model were sought, with all-cause mortality as the end point. All the proportional hazards regression analyses were stratified using sex and age as covariates. In addition, all the variables that had a univariate association with all-cause mortality were included in the model, in order to estimate the independent power of the different variables in predicting the mortality. Kaplan-Meier estimates of the distribution of times from baseline to death were computed, and log-rank analysis was performed to compare the survival curves between the groups (V).

6. Results

6.1. Comparison of measures of heart rate behaviour between patients with stable angina pectoris and healthy controls

Patients with stable uncomplicated coronary artery disease had lower standard deviation of all RR intervals ($p < 0.01$) and high-frequency spectral component of heart rate variability ($p < 0.05$) than healthy controls. The mean heart rate was similar in both groups. Coronary artery disease patients also had lower approximate entropy ($p < 0.05$) than healthy controls. The short term fractal scaling exponent (α) was significantly higher in patients with coronary artery disease than in healthy controls (1.34 ± 0.15 vs. 1.11 ± 0.12, $p < 0.001$, Table 2 and Figure 1). When the groups were matched with respect to the ratio of low-to-high frequency spectral components, the short term scaling exponent value continued to be higher in coronary artery disease patients ($p < 0.001$), but approximate entropy did not differ. The short-term fractal scaling exponent differentiated coronary artery disease patients from healthy subjects better than any other variable, with a sensitivity of 78% and a specificity of 87% (I).

6.2. Comparison of measures of heart rate behaviour between postinfarction patients and healthy controls

The standard deviation of RR intervals and the very low ($p < 0.01$) and low frequency ($p < 0.001$) components in the spectral analysis of heart rate variability were lower in postinfarction patients than in healthy subjects. The high frequency band was also lower in the patient group ($p < 0.05$). However, discrete high frequency peaks were less often observed in postinfarction patients. The mean heart rates did not differ between the groups. Approximate entropy was significantly higher in postinfarction patients than in healthy subjects ($p < 0.001$, Table 2 and Figure 1), whereas neither the short term fractal-like scaling exponent nor the power-law slope differed between postinfarction patients and healthy controls. When analysed from successive segments of 4000 beats, the 24-hour

variability in approximate entropy was lower in postinfarction patients than in healthy subjects (0.27 ± 0.09 vs. 0.32 ± 0.07, $p < 0.05$). When the study groups were matched with respect to total RR interval variance (standard deviation of RR intervals in postinfarction patients 76 ± 15 msec and 76 ± 24 msec in healthy subjects, n = 30 for both), the approximate entropy value was still higher in postinfarction patients (1.24 ± 0.21) than healthy subjects (1.05 ± 0.10, $p < 0.001$, II).

Table 2. RR interval measurements

	healthy subjects (n = 45, I,II,III,IV)	uncomplicated CAD (n = 38, I)	post-MI group without arrhythmia (n = 45, II,III)	post-MI group with VT (n = 45, III)	VF group (n = 10, IV)
Mean RR interval (ms)	888 ± 117	858 ± 119	944 ± 146*	953 ± 168*	879 ± 187
SDNN (ms)	150 ± 40	131 ± 39**	106 ± 30***	90 ± 35***	77 ± 47***
SDANN (ms)	90 ± 27	77 ± 23**	75 ± 26**	63 ± 26**	73 ± 34**
HF power (ln)	5.4 ± 0.9	4.9 ± 1.0*	5.2 ± 0.9	5.2 ± 1.3	6.2 ± 1.5*
LF power (ln)	6.3 ± 0.9	6.2 ± 0.8	5.9 ± 1.0	5.3 ± 1.2**	6.0 ± 1.5
α	1.09 ± 0.13	1.34 ± 0.15***	1.06 ± 0.13	0.85 ± 0.25***	0.68 ± 0.18***
β	–1.27 ± 0.18	–1.30 ± 0.14	–1.33 ± 0.23	–1.37 ± 0.26	–1.63 ± 0.24**
SD1	21 ± 7	17 ± 9*	20 ± 10	23 ± 17	52 ± 41*
SD2	125 ± 38	111 ± 40*	104 ± 36*	85 ± 35***	86 ± 48**
SD1/SD2	0.18 ± 0.04	0.16 ± 0.04	0.21 ± 0.06	0.30 ± 0.18*	0.59 ± 0.25**
ApEn	1.03 ± 0.14	0.93 ± 0.17*	1.17 ± 0.22**	1.20 ± 0.28**	1.01 ± 0.34

Abbreviations: the values are mean ± standard deviation, α = short-term scaling exponent; β = power-law slope between 0.000 – 0.01 Hz; SD1= instantaneous heart rate variability from Poincaré plots; SD2 = continuous heart rate variability from Poincaré plots; ApEn = approximate entropy; HF = high frequency spectral component; LF = low frequency spectral component; SDNN = standard deviation of all RR intervals during the 24 hour recording; SDANN = standard deviation of RR intervals of 4000 beats segments; Mean RR = average of lengths of RR intervals; ln = logarithm to the natural base of the absolute value; MI = myocardial infarction; VT = ventricular tachycardia; VF = ventricular fibrillation CAD = coronary artery disease. * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$, significance levels for differences between healthy subjects and cardiovascular patient groups.

6.3. Comparison of measures of heart rate behaviour between postinfarction patients with and without vulnerability to ventricular tachyarrhythmia and healthy controls

There were no differences between the patients with and without vulnerability to ventricular tachycardia in the clinical characteristics, the frequency of ventricular premature depolarizations or the occurrence of nonsustained ventricular tachycardia. The mean standard deviation of all RR intervals was lower than in healthy controls, but did not differ between the groups with and without arrhythmia risk. Low frequency spectral

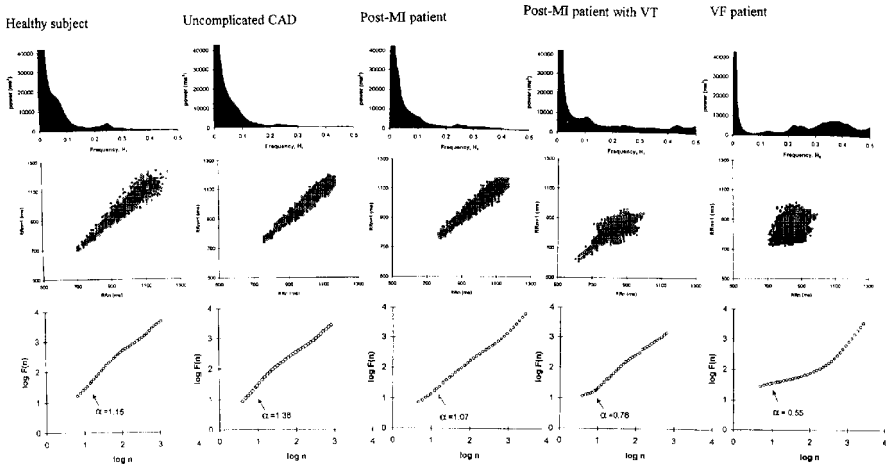
power was significantly lower in the ventricular tachycardia group than in postinfarction patients ($p < 0.01$), but high frequency spectral power did not differ. However, the shape of the high frequency spectral band was different in the ventricular tachycardia group in such a way that the high frequency band was flatter with more power distributed in the very-high frequency area (Figure 1). The short term scaling exponent (α) was significantly smaller in the arrhythmia group than in the postinfarction control group ($p < 0.001$) or in healthy controls ($p < 0.001$). Approximate entropy was significantly lower in healthy subjects than in postinfarction patients ($p < 0.001$), but did not differ between the groups with and without vulnerability to ventricular tachyarrhythmia. Nor was the power-law regression slope able to differentiate between patients with and without a risk of tachycardia. The standard deviation of long-term (SD2) continuous RR interval variability was smaller in the ventricular arrhythmia group than in the postinfarction control group ($p < 0.05$). Stepwise multiple regression analysis showed the short-term scaling exponent to be the most powerful independent predictor of vulnerability to ventricular tachycardia (III).

6.4. RR interval dynamics before spontaneous onset of ventricular fibrillation

The frequency of ventricular premature depolarizations and the occurrence of nonsustained ventricular tachycardia on the Holter recordings were significantly higher in ventricular fibrillation patients compared to arrhythmia-free postinfarction controls. The conventional measures of heart rate variability, i.e. the standard deviation of RR intervals in each segment and the standard deviation of the entire measured epoch, did not differ between the ventricular fibrillation group and the postinfarction control group. The very low and low frequency spectral components did not differ significantly between the ventricular fibrillation and control subject groups, but the high frequency spectral component was higher in ventricular fibrillation patients ($p < 0.05$). The power of the high frequency spectral component was distributed widely in the high and very high frequency areas in the ventricular fibrillation patients without any discrete respiration peak (Figure 1). Of the dynamic measures of RR interval behaviour, the short term fractal-related scaling exponent α and the power-law regression slope β showed smaller values in the ventricular fibrillation group than in the postinfarction control group ($p < 0.001$, $p < 0.01$ respectively). The instantaneous beat-to-beat RR interval variability SD1 from Poincarè plots and the SD1/SD2 ratio were higher in the ventricular fibrillation cases ($p < 0.05$, $p < 0.01$, respectively). Approximate entropy did not differ from the values observed in healthy controls. In stepwise multiple regression analysis, including the ventricular premature depolarization frequency, the occurrence of nonsustained ventricular tachycardia, two-dimensional vector analysis, detrended fluctuation analysis, power-law behaviour analysis of low frequencies and conventional time and frequency domain measures of heart rate variability, α proved to be the strongest independent predictor differentiating ventricular fibrillation patients from postinfarction controls. None of the variables changed significantly during the last hour before the spontaneous onset of

ventricular fibrillation compared to the longer period preceding ventricular fibrillation. When the last hour before ventricular fibrillation was divided into 15 minute intervals, no statistically significant changes in any variables were observed between the intervals (IV).

Fig. 1. (I,II,III,IV) Examples of power spectra, two dimensional vector analysis and detrended fluctuation analysis of fractal scaling exponents from 24-hour data in different patient populations. Healthy subject show power spectra with distinct low and high frequency peaks, a comet shape Poincarè plot and a short term scaling value ~1 in DFA analysis. Patient with uncomplicated coronary artery disease shows a clear reduction in high frequency spectral power and an increased and short term scaling value α . Patients with previous myocardial infarction show reduced low frequency spectral power. Postinfarction patient with vulnerability to tachyarrhythmia shows a flatter spectrum and a reduced short term scaling value α. Ventricular fibrillation patient shows a widened high frequency spectral band, a ball-shaped Poincarè plot of successive RR intervals and a reduced short term scaling exponent ($\alpha \sim 0.5$). Abbreviations: α = short-term scaling exponent; VF = ventricular fibrillation; VT = ventricular tachycardia; MI = myocardial infarction; CAD = coronary artery disease.



6.5. Dynamical heart rate behaviour measures as a predictor of mortality in elderly population

By the end of the 10-year follow-up 184 subjects (53%) had died and 167 (47%) were still alive. Seventy-four subjects (21%) had died of cardiac disease, 37 of cancer (11%), 25 of cerebrovascular disease (7%), and 49 (14%) of various other causes. Univariate comparison showed age, sex, history of congestive heart failure, angina pectoris, prior myocardial infarction, or cerebrovascular disease, functional class, use of cardiac medication, elevated baseline blood glucose and smoking history to be associated with all-cause mortality. Of the heart rate behaviour measures, the slope of the power-law regression line of heart rate behaviour, the standard deviation of all RR intervals, and the

very low frequency and low frequency spectral components appeared to have a univariate association with all-cause mortality. Short-term fractal-like measure was not analysed. A stepwise proportional hazards method showed both the slope of the regression line and the standard deviation of all RR intervals to possess independent predictive power with respect to all-cause mortality ($p < 0.001$ for both), whereas the very low frequency and low frequency spectral components did not enter the model as independent predictors.

In multivariate analysis, a history of previous myocardial infarction, angina pectoris, congestive heart failure and cerebrovascular disease, smoking, functional class, elevated blood glucose, standard deviation of all RR intervals < 120 msec and a slope of power-law regression < −1.50 were associated with all-cause mortality after adjustment for age and sex. When all the risk variables were included in the analysis, a steep slope of the power-law regression line (adjusted relative risk 1.74, $p < 0.001$) and a history of congestive heart failure (adjusted relative risk 1.70, $p < 0.001$, Table 3) were the only independent predictors of all-cause mortality. After the 10-year follow up in the total study population, only 19 of the 94 subjects (20%) with a power-law slope < −1.50 were alive, whereas 141 of the 211 subjects (67%) with a power-law slope ≥ −1.50 were still alive (Figure 2). After adjusting for age and sex, cardiac death was predicted by the same variables as all-cause mortality, except for smoking history, and also by the presence of ≥ 10 ventricular premature beats/hour on the 24-hour ECG recording. After adjusting for all the risk variables, cardiac death was independently associated only with a steep slope of the regression line of heart rate variability (adjusted relative risk > 2, $p < 0.001$) and a history of congestive heart failure (adjusted relative risk 1.56, $p < 0.05$). The slope of the regression line of heart rate variability was also an independent predictor of cerebrovascular death (age and sex adjusted relative risk, 1.85, $p = 0.008$), which was also predicted by a history of cerebrovascular disease. The slope of long-term heart rate variability had the best accuracy in predicting all-cause, cardiac and cerebrovascular death. The presence of frequent ventricular premature beats was specifically related to a risk cardiac of cardiac death, but had a low sensitivity (30%) compared to the sensitivity of the slope of heart rate variability (60%, V).

Table 3. Significant Predictors of All-Cause Mortality in Proportional Hazards Regression analysis

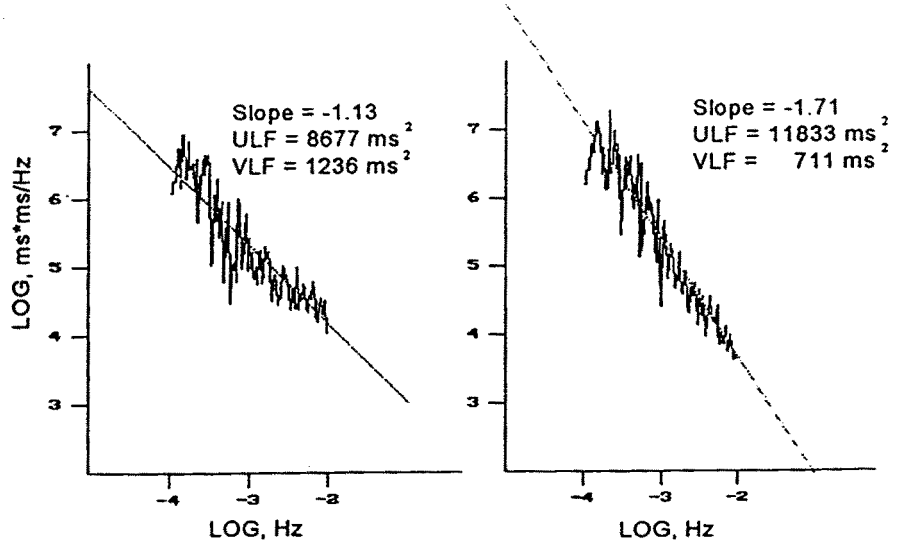
	Age and sex adjusted association with mortality			Association with mortality adjusted for all variables		
	Relative risk:	95% CI	p-value†	Relative risk:	95% CI	p-value†
Clinical and laboratory variables						
prior AMI	1.39	(1.12–1.74)	0.003	0.82	(0.58–1.14)	NS
angina pectoris	1.40	(1.1–1.67)	0.003	1.23	(0.90–1.66)	NS
CHF	1.65	(1.3–2.01)	< 0.001	1.70	(1.28–2.26)	< 0.001

Abbreviations: AMI = acute myocardial infarction; CHF = congestive heart failure; CI = confidence intervals; ECG = electrocardiography; SDNN = standard deviation of all N-N intervals; slope of HRV = power-law regression of heart rate variability. †p-values determined in multivariate Cox regression analysis. NS denotes non-significant

	Age and sex adjusted association with mortality			Association with mortality adjusted for all variables		
	Relative risk:	95% CI	p-value†	Relative risk:	95% CI	p-value†
smoking	1.42	(1.01–1.60)	0.04	1.25	(0.92–1.92)	NS
functional class 3–4	1.83	(1.46–2.29)	< 0.0001	1.24	(0.91–1.68)	NS
cardiac medication	1.69	(1.33–2.14)	< 0.0001	1.32	(0.96–1.82)	NS
CVD	1.33	(1.05–1.69)	0.02	1.40	(0.98–1.98)	NS
glucose > 6.0 mmol/l	1.27	(1.06–1.52)	0.009	1.10	(0.85–1.42)	NS
Ambulatory ECG data						
SDNN < 120 ms	1.29	(1.09–1.53)	0.003	1.16	(0.95–1.77)	NS
slope of HRV < –1.5	1.77	(1.48–2.11)	< 0.001	1.74	(1.42–2.13)	< 0.001

Abbreviations: AMI = acute myocardial infarction; CHF = congestive heart failure; CI = confidence intervals; ECG = electrocardiography; SDNN = standard deviation of all N-N intervals; slope of HRV = power-law regression of heart rate variability. †p-values determined in multivariate Cox regression analysis. NS denotes non-significant

Fig. 2. (V) Examples of power law regression slopes computed over frequencies between 10^{-2} and 10^{-4} for a 70-year-old man who was alive 10 years after the 24-hour electrocardiographic recordings (left), and a 68-year-old man who had died of myocardial infarction 22 months after the 24-hour electrocardiographic recording (right). ULF = ultra low frequency power, VLF = very low frequency power, and slope = slope of the regression line computed from the log(power) - log(frequency) plot.



6.6. Correlations between dynamical and conventional measures of heart rate behaviour

All the time and spectral measures of heart rate variability correlated highly significantly with each other ($0.3 < r < 0.7$ for all, $n = 536$), with the exception of the ratio of low-to-high frequency components, which correlated only weakly with the other time and frequency domain measures ($-0.2 < r < 0.2$ for all). The short-term fractal-like scaling exponent and approximate entropy were not related to any single measure of heart rate variability, but correlated significantly with the ratio of low-to-high frequency spectral components ($r = 0.74$, $r = -0.49$, respectively, $p < 0.001$ for both) and with each other ($r = -0.53$, $p < 0.001$). The slope of the power-law regression line showed only a weak correlation with the time or spectral measures of heart rate variability and with the other dynamic parameters ($-0.3 < r < 0.3$ for all).

6.7. Correlations between dynamical measures of heart rate behaviour and clinical variables

No significant association was observed between the short-term scaling exponent of heart rate behaviour and the following clinical variables: age ($r = -0.2$, ns, I-V), sex, angiographic severity of coronary artery disease, functional class or left ventricular ejection fraction ($r = 0.1$, ns) (II). The slope of the power law regression line of heart rate variability showed weak correlations with age ($r = -0.16$, $p < 0.01$) and blood glucose concentration (-0.14, $p < 0.05$) and no significant correlations with the other risk variables (V).

7. Discussion

The main new finding of this research was that dynamic analysis methods derived from nonlinear dynamics of heart rate behaviour provide substantial complementary information of abnormal heart rate dynamics. Dynamical analysis of heart rate behaviour revealed abnormal patterns of RR interval dynamics which cannot be detected by the commonly employed moment statistics of heart rate variability. Fractal-like heart rate behaviour was observed in normal healthy hearts. This organising principle was found to be altered in various patient populations. The consequences of a breakdown of fractal-like organisation were shown among ventricular tachyarrhythmia patients, in whom the breakdown of the fractal-like behaviour of RR intervals predicted life-threatening ventricular arrhythmia, and also among elderly people, of whom these with a breakdown of the fractal-like behaviour of RR intervals had a significantly higher mortality rate than those with normal fractal-like heart rate behaviour.

7.1. Heart rate dynamics in patients with stable angina pectoris

The patients with stable uncomplicated coronary artery disease had a lower standard deviation of all RR intervals, as expected and already shown by other studies (Hyano et al. 1990, Airaksinen et al. 1987). The high-frequency spectral component of heart rate variability was also lower in them than in healthy controls. Reduced instantaneous and long term heart rate variability in Poincaré plots was observed in coronary artery disease patients, but their ratio remained unchanged. The patients with stable coronary artery disease also showed altered correlation properties in their RR interval dynamics, i.e. loss of normal fractal characteristics, and enhanced regularity in heart rate tracings. The short-term fractal scaling exponent was more sensitive than the other measures in detecting abnormalities in heart rate behaviour in this group of patients with stable angina pectoris. Information about the fractal organisation of heartbeat behaviour provided by previous studies has shown that healthy heartbeat dynamics have a fractal-like temporal structure, with self-similar fluctuations over a wide range of time scales (Goldberger 1996, Hausdorff et al. 1995, Goldberger 1990). This study implicated that this normal fractal

property of RR interval dynamics is altered in patients with uncomplicated coronary artery disease. This finding is partly related to changes in the spectral characteristics of heart rate behaviour. In patients with uncomplicated coronary artery disease, a significant reduction in the high frequency spectral band indicates a dominant role of the low frequency band. The loss of high frequency fluctuations corresponds to more regular (less complex) short term signal behaviour associated with a higher short-term scaling exponent and a lower approximate entropy value. The ratio of the low-to-high frequency components did correlate with the short-term fractal scaling exponent of heartbeat behaviour in this study. However, when the groups were matched with respect to the ratio of low-to-high frequency spectral components, the short term scaling exponent value was still significantly higher in patients than in the healthy subjects, confirming that dynamic analysis of heartbeat behaviour gives complementary and independent information that cannot be obtained by traditional spectral analysis techniques (I). The changes in heart rate behaviour variables in this study were not related to the clinical or angiographic severity of coronary artery disease, and none of the patients had evidence of myocardial ischemia during the recordings, suggesting that the loss of fractal correlation properties and the reduction in heartbeat complexity are not simply a consequence of end-organ damage caused by ischemic heart disease.

7.2. Heart rate dynamics in patients with prior myocardial infarction

Patients with previous myocardial infarction showed lower heart rate variability than healthy controls as analysed with time and frequency domain measures. Of the spectral measures, the low frequency spectral component was most markedly reduced, which is concurrent with the finding of a reduced low frequency component in patients with a prior myocardial infarction by Bigger et al. (1995). Neither a short term fractal-like measure or a power-law slope was able to detect changes in the heart rate behaviour of postinfarction patients, but continuous long term variability in Poincaré plots differentiated postinfarction patients from healthy controls. Despite the reduced overall RR interval variability, the approximate entropy of RR interval dynamics increased in coronary artery disease patients with a prior myocardial infarction. This was the most efficient dynamical measure for differentiating postinfarction patients from healthy subjects, implicating that the intrinsic randomness or unpredictability of RR interval dynamics increases in hearts damaged by myocardial infarction.

The explanation for why the measure of approximate entropy is higher in postinfarction patients than in healthy subjects can be partly derived from changes in spectral measures.The reduction in the dominant power spectrum band, i.e very low frequency or low frequency band, in postinfarction patients results in more random behaviour of RR interval data, resulting in higher approximate entropy. This concept was confirmed by experiments with artificial signals, where decreased very low or low frequency power caused invariably higher approximate entropy values.

7.3. Heart rate dynamics in patients with vulnerability to ventricular tachyarrhythmia

Of the conventional heart rate variability measures, the standard deviation of RR intervals was lower in postinfarction patients than in healthy subjects, but it did not differentiate between patients with and without vulnerability to ventricular tachycardia. The only traditional variable able to differentiate between patients with and without arrhythmia risk was the low frequency spectral component ($p < 0.01$). Of the dynamical measures the power-law slope did not identify the patients with vulnerability to ventricular arrhythmia. Approximate entropy was higher in postinfarction patients, but was not able to differentiate between patients with and without vulnerability to ventricular tachycardia. The short term fractal correlation properties of RR interval dynamics appeared to be altered, specifically in postinfarction patients with vulnerability to ventricular tachycardia, implicating more uncorrelated short term heart rate behaviour. Conventional spectral measures were not able to differentiate between these patients equally well as the short term fractal scaling exponent.

The analysis of short term scaling subtends fluctuations mainly in the high and partly in the low frequency part of the signal spectrum. An exponent value 0.5 means that short term fluctuation is completely random. Values under 0.5 correspond to time series where long and short RR intervals are more likely to alternate (Peng et al. 1995). RR interval behaviour of this type was only observed in subjects (6 patients) with vulnerability to ventricular tachycardia. A previous study has shown alternating heart rate behaviour before ventricular tachycardia onset (Huikuri et al. 1996), and the present study extends these observations by offering a method to detect not only alternating behaviour, but also the large aperiodic abrupt temporal changes in RR intervals.

7.4. Heart rate dynamics before spontaneous onset of ventricular fibrillation

The standard deviation of RR intervals failed to predict ventricular fibrillation. Consistent with our data, Vybiral et al. (1993) have also shown that conventional analysis of heart rate variability fails to predict imminent changes in the RR intervals before the onset of ventricular fibrillation. Altered beat-to-beat RR interval dynamics were observed to precede the onset of ventricular fibrillation, however. Spectral analysis showed an increase in the high frequency component, but this spectral area was flat and widely distributed. Detrended fluctuation analysis showed that the altered beat-to-beat RR interval variability resulted from an almost random-like form of short-term RR interval behaviour rather than the fractal-like correlation properties observed in healthy subjects previously (Iyengar et al. 1996). This was visualised in Poincarè plots, which showed a ball-like or complex structure of the plots with an increase in the standard deviation of instantaneous RR interval variability (Figure 1). Skinner et al. (1994) also observed changes in the correlation dimension of RR intervals several hours before the onset of ventricular fibrillation. The present findings agree with the recent findings on heart failure

patients in whom a reduced short term scaling exponent was related to mortality (Ho et al. 1997). In addition, the long range correlation properties of RR intervals were also altered before the onset of ventricular fibrillation. The computed slope of the power-law relationship of heart rate variability was more negative in ventricular fibrillation patients, despite the absence of differences in low frequency spectral components between the groups. The slope of the power-law relationship of heart rate variability did not reflect the magnitude of heart rate variability, but rather the distribution of spectral characteristics of RR interval oscillations. The steep slope of the power-law relationship has also been shown to be associated with increased mortality in postinfarction patients (Bigger et al. 1996).

7.5. Dynamical measures of heart rate behaviour as a predictor of mortality in elderly people

Heart rate behaviour analysed by new dynamical methods turned out to be a more powerful predictor of mortality than the conventional risk markers in elderly subjects. Concurrent with the previous findings, the common risk factors, such as cholesterol, hypertension and smoking, were not powerful predictors of death, confirming that the prognostic markers applicable to younger subjects do not perform equally well among the elderly (Anderson et al. 1987, Harris et al. 1988, Mattila et al. 1988, Krumholz et al. 1994).

A previous study of a Framingham cohort showed that the traditional short-term measures of heart rate variability are able to predict all-cause mortality in elderly subjects (Tsuji et al. 1994). In our elderly population with a longer follow-up, the traditional spectral and non-spectral measures did not emerge as independent predictors of survival, because they were related to clinical risk variables. The slope of the power-law relationship of heart rate behaviour did not bear any significant relation to the other risk markers, and it remained a powerful predictor of survival after adjustment for all other variables.

The slope of the power-law behaviour of heart rate dynamics was specifically related to vascular causes of death, i.e. cardiac and cerebrovascular deaths. Heart rate variability has been previously shown to predict all-cause and cardiac mortality in patient populations with documented heart disease (Kleiger et al. 1987, Bigger et al. 1992, Bigger et al. 1996), but there has been no information on the prognostic role of heart rate variability as a predictor of cerebrovascular death. The present findings suggest that altered long-term heart rate behaviour is not only related to cardiac death, but also reflects an increased risk for any acute vascular events leading to death.

7.6. Mathematical interpretation of dynamical analysis of RR intervals

The mathematical background of the new dynamical measures of RR interval variability used in this study have been described in detail previously by Peng et al. 1995, Bigger et al. 1996 and Pincus & Goldberger 1994. Briefly, approximate entropy reflect the complexity of time series data, the power-law regression slope demonstrate the fractal-like correlation properties of RR interval data over 10^{-4} to 10^{-2} Hz, and the short term fractal-like scaling exponent indicate the correlation properties of the shorter term RR interval fluctuation. The fluctuations of a time series can also be assessed by comparing their behaviour to various types of artificially generated signals. White Gaussian noise represents time series where no correlations are found, but the data are completely random. The power-law slope (β) of a signal of this kind is 0, the short term fractal scaling exponent (α) is 0.5 and approximate entropy is ~ 2. Brown noise ($1/f^2$ noise), an integration of white noise, is characterised by the frequency spectrum of a curve rapidly decaying (power inversely proportional to frequency squared) with $\beta = -2$ and $\alpha = 1.5$. The frequency curve for a 1/f signal is smooth with fluctuations inversely proportional to frequency and with $\beta = -1$ and $\alpha = 1.0$. Approximate entropy values are higher for a 1/f signal than a $1/f^2$ signal. The 1/f signal is used as an example of a fractal-like process, which is characterised by scale-invariant self-similar long-range correlations, which generate irregular and complex fluctuations on multiple time scales.

It has been suggested that the 1/f signal properties might be an organising principle of physiological structure or function. Changes an organisation pattern of this kind may result in a less adaptable system favouring vulnerability to various pathological states (Goldberger 1996). It was shown here that a breakdown of 1/f signal properties, both in short term and in long range RR interval behaviour, occurs in subjects with vulnerability to life-threatening arrhythmias, suggesting a causal relationship between altered fractal-like signal behaviour and the onset of life-threatening arrhythmia. Since the deviations of the short-term slopes from the 1/f curve did not occur immediately before the onset of ventricular fibrillation, altered RR interval dynamics may not be a direct trigger of the onset of ventricular fibrillation, but may rather reflect changes in other regulatory systems preconditioning the heart to a life-threatening event. The importance of 1/f signal behaviour was also seen among elderly people, in whom the breakdown of this organisation pattern was a powerful predictor of cardiovascular death.

7.7. Possible pathophysiological mechanisms of abnormal short and long term heart rate dynamics

The physiological background of altered short term fractal-like behaviour is not exactly known, but one potential explanation for the altered short-term correlation properties of heart rate dynamics in patients with vulnerability to life-threatening arrhythmia might be altered sympathovagal interaction (Levy 1971). The concept of sympathoexcitation is supported by observations of more complex Poincaré plots of successive RR intervals in heart failure patients (Brouwer et al. 1996, Woo et al. 1994) with high norepinephrine

levels (Woo et al. 1994). Similar changes have also been observed upon intravenous infusion of physiological doses of norepinephrine in young healthy adults (Tulppo et al. 1998). Random, uncorrelated beat-to-beat RR interval behaviour may also reset the repolarization dynamics of the myocardium and thereby increase vulnerability to ventricular arrhythmogenesis.

The physiologic relevance of high approximate entropy of RR interval data is also open to speculation. It is possible that a higher sympathetic tone may also explain the reduction in the very low frequency spectral component and the change in beat-to-beat complexity and, consequently, the increase in approximate entropy.

The moderate correlation of the value of low-to-high frequency spectral component rates with both fractal correlation properties and approximate entropy suggests that dynamic fractal behaviour and the complexity of RR interval dynamics are related to neuroautonomic interactions.

The physiological background of altered long term heart rate behaviour (power-law slope) is not known, but the observation of significantly steeper power-law slopes in denervated hearts suggests that it is partly influenced by the autonomic input to the heart (Bigger et al. 1996).The slope has been found to be steeper in elderly subjects than in younger healthy subjects (Bigger et al. 1996, Saul et al. 1987), showing that ageing itself results in progressive changes in the long-term spectral characteristics of heart rate variability. No changes in ultra low frequency power, but a linear decline in very low frequency power have been observed upon ageing (Bigger et al. 1995), which probably also explains the steeper slope of the power-law regression line in the elderly. The altered autonomic modulation of long-term heart rate behaviour with advancing age may arise from age-related changes in various organs and body systems, which may interact with each other and thereby impair the function of the cardiovascular autonomic regulatory systems.

Abnormalities in the autonomic modulation of heart rate have been observed in various cardiovascular and cerebrovascular disorders (Huikuri 1995, Barron et al. 1994, Korpelainen et al. 1996), and it is possible that altered cardiovascular neural regulation expressed by a steep slope of long-term heart rate dynamics may be a sign of an underlying subclinical vascular disease predisposing to mortality. Another potential explanation for the prognostic role of altered long term heart rate behaviour is that it may reflect an impairment in the adaptive systems during acute perturbations, such as myocardial or cerebral ischemic events. This is supported by experimental observations, which have shown that cardiovascular autonomic regulation plays an important role in the occurrence of life-threatening arrhythmias during acute cardiac or cerebral ischemia (Schwartz et al. 1992, Hachinski et al. 1992).

8. Conclusions

1. This research showed that a dynamical analysis of heart rate behaviour derived from nonlinear mathematics can reveal abnormal patterns of RR interval dynamics which cannot be detected by commonly employed moment statistics of heart rate variability.
2. Approximate entropy showed heart rate tracings to be more predictable in patients with uncomplicated coronary artery disease, but more complex in patients with previous myocardial infarction as compared to healthy controls. This method was not able to differentiate patients with and without ventricular tachyarrhytmias.
3. A short term fractal-like scaling exponent of RR intervals showed more organised behaviour in patients with uncomplicated coronary artery disease. It was not able to differentiate patients with previous myocardial infarction from healthy controls. This measure was markedly reduced in patients with life-threatening arrhythmia and was the best variable to differentiate patients with and without ventricular arrhythmia.
4. Long term power-law slope was normal in patients with uncomplicated coronary artery disease, but significantly steeper before ventricular fibrillation, and it also predicted mortality in a general elderly population.
5. The consequences of a breakdown of fractal-like organisation were seen in ventricular tachyarrhythmia patients, in whom the breakdown of the fractal-like behaviour of RR intervals predicted life-threatening ventricular arrhythmia, and also in elderly people, among whom those with altered fractal-like behaviour of RR intervals had significantly higher mortality rates than those with normal fractal-like heart rate behaviour.

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