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Review

Methods derived from nonlinear dynamics for analysing heart rate variability

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Methods from nonlinear dynamics (NLD) have shown new insights into heart rate (HR) variability changes under various physiological and pathological conditions, providing additional prognostic information and complementing traditional time- and frequency-domain analyses. In this review, some of the most prominent indices of nonlinear and fractal dynamics are summarized and their algorithmic implementations and applications in clinical trials are discussed. Several of those indices have been proven to be of diagnostic relevance or have contributed to risk stratification. In particular, techniques based on mono- and multifractal analyses and symbolic dynamics have been successfully applied to clinical studies. Further advances in HR variability analysis are expected through multidimensional and multivariate assessments. Today, the question is no longer about whether or not methods from NLD should be applied; however, it is relevant to ask which of the methods should be selected and under which basic and standardized conditions should they be applied.

Keywords: nonlinear dynamics; heart rate variability; fractal; chaos; cardiology

1. Introduction

The investigation of nonlinear dynamics (NLD) and the introduction of indices to quantify the complexity of fractal dynamics have challenged our view on physiological networks regulating heart rate (HR) and blood pressure, thereby enhancing our knowledge and stimulating significant and innovative research into cardiovascular dynamics.

During the last decades, methods derived from NLD have been successfully applied to many scientific disciplines, including physics, astrophysics, chemistry, economics, biology and medicine. However, the impact of deterministic nonlinear

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One contribution of 13 to a Theme Issue 'Signal processing in vital rhythms and signs'.

metrics for enhanced understanding of physiology is only partly explored to date. Some important physiological findings based on the concepts of NLD are mentioned in §§2 and 3.

Initially the theory of NLD, developed during the late 1970s and 1980s, generated interest among many researchers to explore chaotic behaviour in biological systems and apply their findings to biology and medicine. Later on, the focus of interest shifted towards explaining and accounting for nonlinearity in the cardiovascular system, which is presumably high dimensional. Currently, a major approach is to reveal and characterize the dynamics and complexity of nonlinear systems.

The embedding theorem allows one to mathematically reconstruct an entire nonlinear system from only one observed variable, since the reconstructed dynamics are (geometrically) similar to the original dynamics (Takens 1981; Kaplan & Glass 1995; Schumacher 2004).

Pioneering work performed by Glass *et al.* (Guevara *et al.* 1981; Glass & Mackey 1988) introduced nonlinear approaches into heart rhythm analysis. Period-doubling bifurcations, in which the period of a regular oscillation doubles, were predicted theoretically and observed experimentally in the heart cells of embryonic chickens. Form, qualitative change, oscillation, stability and other important biological notions found inherent expression in the new mathematical approach of NLD (Garfinkel 1983). Ritzenberg *et al.* (1984) were the first to provide evidence of nonlinear behaviour in the electrocardiogram (ECG) and arterial blood pressure traces of a dog that had been injected with noradrenaline.

Since the original reports by Wolf *et al.* (1978) and Kleiger *et al.* (1987), the analysis of spontaneous variations of beat-to-beat intervals (BBI) has become an important clinical tool, familiar to cardiologists (Lombardi *et al.* 2000).

The first approaches of the HR variability (HRV) analyses based on nonlinear fractal dynamics were performed by Goldberger & West (1987). It was suggested that self-similar (fractal) scaling may underlie the $1/f$-like spectra (Kobayashi & Musha 1982) seen in multiple systems (e.g. interbeat interval variability, daily neutrophil fluctuations). They proposed that this fractal scale invariance may provide a mechanism for the 'constrained randomness' underlying physiological variability and adaptability. Later, Goldberger *et al.* (1988) reported that patients prone to high risk of sudden cardiac death showed evidence of nonlinear HR dynamics, including abrupt spectral changes and sustained low frequency (LF) oscillations. At a later date, they suggested that a loss of complex physiological variability could occur under certain pathological conditions such as reduced HR dynamics before sudden death and ageing (Goldberger 1991).

Babloyantz & Destexhe (1988) performed the first multivariate nonlinear analysis of HRV. With the help of several independent methods for quantifying NLD, such as phase portrait, Poincaré section, correlation dimension, Lyapunov exponent and Kolmogorov entropy, the ECGs of four normal human hearts were studied qualitatively and quantitatively. They demonstrated that the variability underlying interbeat intervals is not random, but exhibits short-range correlations governed by deterministic laws.

Techniques of phase-space reconstruction and dimensional analysis were applied to HR traces obtained from scalp electrodes in 12 normal foetuses by Chaffin *et al.* (1991).

To estimate the complexity of cardiovascular dynamics, Pincus (1991) modified the original correlation dimension and Kolmogorov entropy notions (Grassberger & Procaccia 1983*a*,*b*; Eckmann & Ruelle 1985), creating the approximate entropy (ApEn). This technique was later improved and termed 'sample entropy' (SampEn) by Richman & Moorman (2000) and reduces the superimposed bias within the original method.

As a further milestone, Novak *et al.* (1993) provided evidence of a close nonlinear coupling between the respiratory and cardiovascular systems.

Peng *et al.* (1995) applied detrended fluctuation analysis (DFA) to quantify the fractal structure of the HR, which was later validated in 1999 (Mäkikallio *et al.* 1999). Also, Kurths *et al.* (1995) introduced symbolic dynamics (SDyn) to the HRV analysis and further demonstrated its power for risk stratification of sudden cardiac death based on the multivariate approaches (Voss *et al.* 1996, 1998). The method of SDyn was further developed by Porta *et al.* (2001) for application on short-term HR time series (Guzzetti *et al.* 2005; Maestri *et al.* 2006). The discovery of the multifractal nature of HR dynamics by Ivanov *et al.* (1999) showed that the heartbeat modulation is even more complex than previously suspected, requiring multiple scaling exponents for its characterization. A very promising way to quantify complexity over multiple scales was recently introduced by Costa *et al.* (2002, 2005). The apparent loss of multiscale complexity in life-threatening conditions (Norris *et al.* 2008) suggests a clinical importance of this multiscale complexity measure.

To investigate the interactions and couplings between HR and respiration and HR and blood pressure, respectively, a variety of methods from NLD have been developed and applied (e.g. Parati *et al.* 1988; Pompe *et al.* 1998; Baumert *et al.* 2002; Schwab *et al.* 2006). The methodological wealth within this subarea of research deserves a separate review and shall not be further discussed within this contribution.

Various attempts have been made to employ nonlinear approaches to model parts of the cardiovascular system (Vinet *et al.* 1990; Christini *et al.* 1995; Amaral *et al.* 1999; Gomes *et al.* 2000; Lin & Hughson 2001; Tulppo *et al.* 2005; Baselli *et al.* 2006; Khoo 2008). Again, this topic cannot be discussed in detail within this paper.

This review focuses on the significance of NLD in cardiovascular variability analysis, to explore dynamic and structural features of cardiovascular regulation and its clinical relevance. Some of the most commonly used HRV indices, derived from NLD with proven relevance to clinical research, will be summarized and important features relating to their practical applications discussed.

2. Indices of HRV derived from NLD

During the 1980s, there was much anticipation that many of the complicated systems observed in nature could be described by a few nonlinear coupled modes. The properties of those systems could then be characterized by fractal dimensions, Lyapunov exponents or Kolmogorov–Sinai entropy. However, currently it is evident that such a low dimensionality is exhibited only by rather coherent phenomena. Physiological data, as discussed here, have a much more complex structure (figure 1). Considering the variety of factors

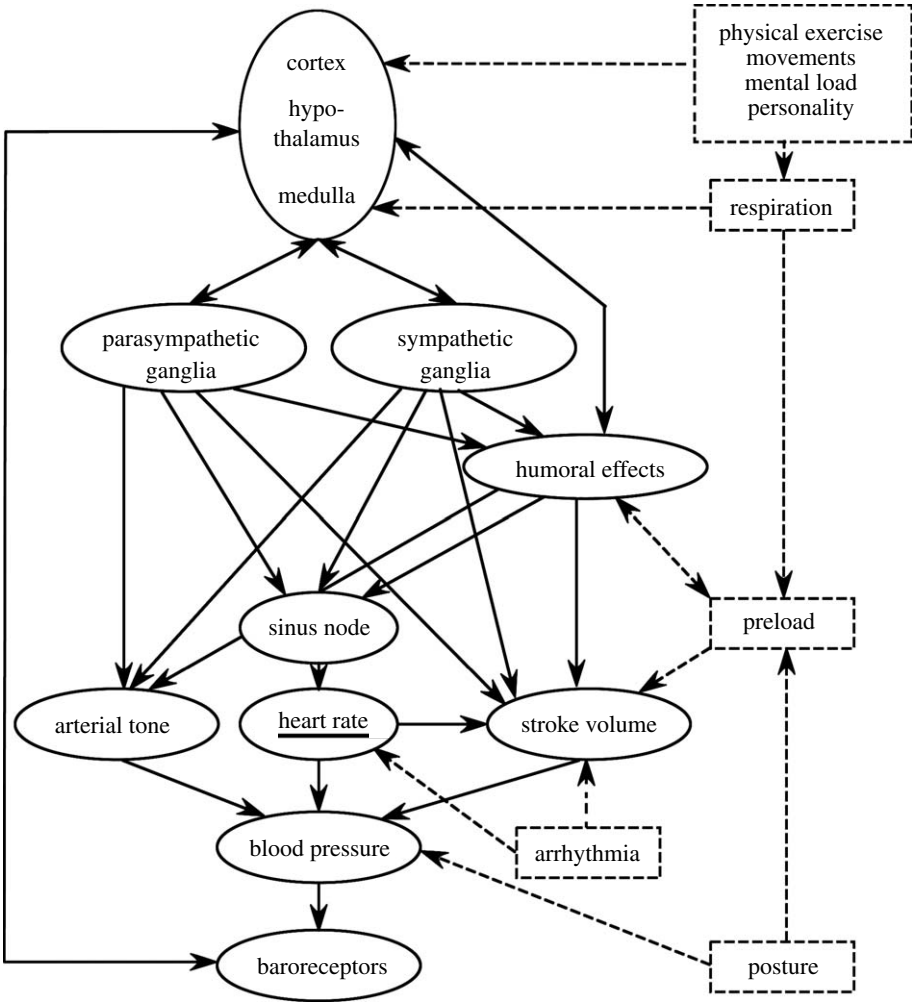

Figure 1. A simplified model of HR regulation (adapted from Hejjel & Gál 2001). Additional factors influencing considerably the HR are shown within the dashed boxes.

influencing HR, e.g. respiration or mental load (within dashed boxes in figure 1), it becomes apparent that HR regulation is one of the most complex systems in humans.

This simplified model of HR regulation (adapted from Hejjel & Gál 2001) shows the sinus node, generating the heartbeat as the primary physiological pacemaker that is innervated by sympathetic and parasympathetic efferents and affected by several humoral factors. The sinus node acts as the final summing element of sympathetically and parasympathetically mediated stimuli and their relation is reflected in the actual interbeat interval. The regulatory subsystems result in a scale-invariant cardiac control across different time scales, showing long-range correlations with a typical scaling behaviour. Therefore, to extract the relevant properties of NLD systems, classical linear signal analysis methods are often inadequate. Most physiological systems, such as HR generation, exhibit a very complex behaviour, which is far from a simple periodicity. Such

a complexity within the obtained biosignals (here, the HR time series) is caused by different components of the intrinsic system's dynamics and especially by the nonlinear interplay of different physiological control loops as illustrated in figure 1.

Possible sources proposed for the nonlinear behaviour of biological systems and different degrees of biological complexity are as follows.

— Different subsystems (control loops) acting in a network with feedback interactions to help constantly adapt the system to its physiological needs and requirements.
— In the case of a pathophysiological process and ageing, the adaptation of a subsystem to changed basic conditions/needs of the total system (e.g. changing of the operational points).
— In the case of severe pathophysiological developments, the compensation of a disturbed or failing subsystem by one or more other interacting subsystems.

This leads to the objective of quantifying the complexity of physiological dynamics with the help of different indices. However, there is no general accepted definition for complexity. In the analysis of signals from biological systems, the term or concept of complexity is mostly used with regard to their dynamical and/or structural expression, including important features such as nonlinearity, time irreversibility, fractality and long-range correlations. Complex physiological signals are typically non-stationary, but not random.

Prominent nonlinear measures, with emphasis on their main properties and applicability, will be discussed for the families A–D (table 1).

(*a*) *Family A: fractal measures*

Concept: to assess self-affinity of heartbeat fluctuations over multiple time scales.

(i) *Power-law correlation* (*scaling exponent* β)

Kobayashi & Musha (1982) first reported the frequency dependence of the power spectrum of RR-interval fluctuations. The slope of the regression line of the log(power) versus log(frequency) relation ($1/f$), usually calculated in the 10^{-4}–10^{-2} Hz frequency range corresponds to the negative scaling exponent β and provides an index for long-term scaling characteristics (Saul *et al.* 1987). This broadband spectrum, characterizing mainly slow HR fluctuations indicates a fractal-like process with a long-term dependence (Lombardi 2000). Saul *et al.* (1987) found that β is similar to -1 in healthy young men. Bigger *et al.* (1996) reported an altered regression line ($\beta \approx -1.15$) in patients after MI.

Limitations: stationarity, periodicity and the need for large datasets are required; artefacts and patient movement influence spectral components.

(ii) *Detrended fluctuation analysis* (*indices* $\alpha 1$ *and* $\alpha 2$)

This method is based on a modified random walk analysis and was introduced and applied to physiological time series by Peng *et al.* (1995). It quantifies the presence or absence of fractal correlation properties in non-stationary time-series data. DFA usually involves the estimation of a short-term fractal scaling

Table 1. Summary of some important features of the selected nonlinear indices. (F, family of nonlinear measures; for abbreviation of indices, see §2.)

F	descriptor	indices	short term	long term	correlated partly with
A	power-law correlation	scaling exponent β		X	frequency components: (UVLF, VLF, LF)
A	detrended fluctuation analysis	$\alpha 1$ (short term)	X		LFn, HFn, LF/HF, HF/P, LF/(HF+LF), SD1/SD2
		$\alpha 2$ (long term)		X	LF, VLF/(HF+LF)
A	multifractal analysis	$D(h)$ with local exponent h	X	X	not yet known
B	approximate entropy	ApEn	X		indexes describing vagal modulation of heart rate (rmssd, pNN50, HF power)
B	sample entropy	SampEn	X		negatively with LFn and LF/HF; natural logarithm (ln) of the total power; ln LF and ln LF/HF
B	multiscale entropy	MSE	X		not yet known
B	compression entropy	CE	X	X	sdNN, rmssd, wpsum02, plvar, forbwords
C	symbolic dynamics	Shannon and Rényi entropies, forbidden words, wpsum02, wpsum13, phvar, plvar, 0V, 1V, 2LV, 2UV, 0V%, 1V%, 2LV%, 2UV%	X	X	cvNN, sdNN, rmssd, pNN50, SD2
D	Poincaré plot	SD1 (short term), SD2 (long term), SD1/SD2	X	X	SD1: rmssd, mainly with HF, lesser with LF; SD2: sdNN, LF and HF power

exponent $\alpha 1$ over the range of $4 \leq n \leq 16$ heartbeats and a long-term scaling exponent $\alpha 2$ over the range of $16 \leq n \leq 64$ heartbeats (Peng *et al.* 1995). DFA was developed to quantify the fluctuations on multi-length scales. The self-similarity occurring over a large range of time scales can be defined for a selected time scale with this method (Mäkikallio *et al.* 1999). Healthy subjects revealed a scaling exponent of approximately 1, indicating fractal-like behaviour. Patients with cardiovascular disease showed reduced scaling exponents, suggesting a loss of fractal-like HR dynamics ($\alpha 1 < 0.85$, Mäkikallio *et al.* 1999; $\alpha 1 < 0.75$, Huikuri *et al.* 2000).

Limitations: at least 8000 data points should be used; monofractal method; normal-to-normal interbeat intervals are required; dependency on editing ectopic beats.

(iii) *Multifractal analysis*

Multifractal analysis describes signals that are more complex than those fully characterized by a monofractal model. Ivanov *et al.* (1999) demonstrated that healthy HRV is even more complex than previously suspected and requires a multifractal representation, using a large number of local scaling exponents to fully characterize the scaling properties. Multifractality in heartbeat dynamics indicates the involvement of coupled cascades of feedback loops in a system operating far from equilibrium. Ivanov *et al.* (1999) found a loss in HRV multifractality in patients suffering from congestive heart failure (CHF).

Limitations: requires many local and theoretically infinite exponents to fully characterize their scaling properties.

(*b*) *Family B: entropy measures*

Concept: to assess the regularity/irregularity or randomness of heartbeat fluctuations.

(i) *Approximate entropy/sample entropy*

The ApEn represents a simple index for the overall complexity and predictability of time series (Pincus 1991). ApEn quantifies the likelihood that runs of patterns, which are close, remain similar for subsequent incremental comparisons (Ho *et al.* 1997). High values of ApEn indicate high irregularity and complexity in time-series data. For healthy subjects, ApEn values range from approximately 1.0 to 1.2 and for post-infarction patients ApEn values are approximately 1.2 (Mäkikallio *et al.* 1996; Ho *et al.* 1997).

Limitations of ApEn: stationarity and noise-free data are required; inherent bias exists; counting self-matches; dependency on the record length; lacks relative consistency; evaluates regularity on one scale only; outliers (missed beat detections, artefacts) may affect the entropy values.

SampEn, improving ApEn, quantifies the conditional probability that two sequences of m consecutive data points that are similar to each other (within a given tolerance r) will remain similar when one consecutive point is included. Self-matches are not included in calculating the probability. Lake *et al.* (2002) described a reduction in SampEn of neonatal HR prior to the clinical diagnosis of sepsis and sepsis-like illness. The SampEn was found to be significantly reduced before the onset of atrial fibrillation (Tuzcu *et al.* 2006).

Limitations of SampEn: stationarity is required; higher pattern length requires an increased number of data points; evaluates regularity on one scale only; outliers (missed beats, artefacts) may affect the entropy values.

(ii) *Multiscale entropy*

Biological systems are likely to present structures on multiple spatio-temporal scales. Multiscale entropy (MSE) assesses multiple time scales to measure a system's complexity. The main advantage of MSE is its ability to measure complexity according to its definition 'a meaningful structural richness' and being applicable to signals of finite length (Costa *et al.* 2005). The MSE method demonstrated that healthy HRV is more complex than pathological HRV. Costa *et al.* (2002) found that pathological dynamics associated with either increased

regularity/decreased variability or with increased variability are both characterized by a reduction in complexity due to the loss of correlation properties. Costa *et al.* (2002) reported the best discrimination between pathological (CHF) and healthy HR signals on scale 5. MSE analysis revealed significantly lower SampEn values in young patients with diabetes mellitus on scale 3 (Javorka *et al.* 2008).

Limitations: stationarity is required; outliers (missed beat detections, artefacts) may affect the entropy values; the consistency of MSE will be progressively lost as the number of data points decreases.

(iii) *Compression entropy*

The entropy of a given text is defined as the smallest algorithm that is capable of generating the text (Li & Vitnyi 1997). Ziv & Lempel (1977) introduced a universal algorithm for lossless data compression (CE), using string matching on a sliding window. With some modifications, this algorithm can be applied for the analysis of heartbeat time series (Baumert *et al.* 2004, 2005). Here, the compression entropy quantifies the extent to which the data from heartbeat time series can be compressed, i.e. repetitive sequences occur. Reduced short-term fluctuations of HRV result in an increased compression. Entropy reduction appears to reflect a change in sympathetic/parasympathetic HR control (Baumert *et al.* 2005). Baumert *et al.* (2004) investigated CHF patients before the onset of ventricular tachyarrhythmia, and showed reduced CE values compared with patients during normal sinus rhythm. Truebner *et al.* (2006) found significant differences between the high- and low-risk CHF patients and Bär *et al.* (2007) found significantly reduced complexity (CE) of HR time series in patients with acute schizophrenia in comparison with healthy controls.

Limitations: dependency on sampling rate, the window length and the lookahead buffer size; integer numbers required.

(*c*) *Family C: symbolic dynamics measures*

Concept: to assess the coarse-grained dynamics of HR fluctuations based on symbolization.

(i) *Symbolic dynamics* (*entropies and probabilities*)

SDyn was introduced by Hadamard (1898) and allows a simple description of a system's dynamics with a limited amount of symbols. SDyn are suitable to describe the global short-time dynamics of beat-to-beat variability (Voss *et al.* 1993, 1996, 1998; Kurths *et al.* 1995). At first, time series were transformed into a symbol sequence of four symbols with the alphabet $A=\{0, 1, 2, 3\}$ to classify the dynamic changes within that time series. Three successive symbols from the alphabets were used to characterize the symbol strings whereby 64 different word types (bins) were obtained. The resulting histogram contains the probability distribution of each single word within a word sequence. SDyn investigates short-term fluctuations. These short-term fluctuations are mainly caused by vagal and baroreflex activities. We differentiate words consisting of alternating/constant/increasing/decreasing symbol strings reflecting especially vagal/reduced vagal (increased sympathetic)/bradycardic baroreflex/tachycardic baroreflex activity. Porta *et al.* (2001) introduced a modified procedure of SDyn. Here, the amount of

the RR intervals was limited to 300 beats. The full range of the sequences was uniformly spread on six levels (0–5), and patterns of length $L=3$ were constructed (Guzzetti *et al.* 2005). All patterns with $L=3$ were grouped, without any loss, into four families. These were: (i) patterns with zero variation—0V, (ii) patterns with one variation—1V, (iii) patterns with two like variations—2LV, and (iv) patterns with two unlike variations—2UV. The rates of occurrence of these patterns will be indicated as 0V, 1V, 2LV and 2UV% (Porta *et al.* 2007).

Limitations: detailed information will be lost; outliers (ectopic beats and noise) influence symbol strings.

(*d*) *Family D: Poincaré plot representation*

Concept: to assess the heartbeat dynamics based on a simplified phase-space embedding.

(i) *Poincaré plots* (*SD1 and SD2*)

The Poincaré plot analysis (PPA) is a quantitative visual technique, whereby the shape of the plot is categorized into functional classes (Weiss *et al.* 1994; Kamen *et al.* 1996; Brennan *et al.* 2002) and provides detailed beat-to-beat information on the behaviour of the heart. Usually, Poincaré plots are applied for a two-dimensional graphical and quantitative representation (scatter plots), where RR_n is plotted against RR_{n+1}. Most commonly, three indices are calculated from Poincaré plots: the standard deviation of the short-term RR-interval variability (minor axis of the cloud, SD1), the standard deviation of the long-term RR-interval variability (major axis of the cloud, SD2) and the axes ratio (SD1/SD2) (Kamen & Tonkin 1995; Brennan *et al.* 2002). For the healthy heart, PPA shows a cigar-shaped cloud of points oriented along the line of identity. These indices are correlated with linear indices. Laitio *et al.* (2002) showed that an increased SD1/SD2 ratio was the most powerful predictor of post-operative ischaemia. Mäkikallio (1998) found SD2 $\approx$ 125 ms in healthy subjects and SD2 $\approx$ 85 ms in post-infarction patients with ventricular tachyarrhythmia.

Limitations: SD1, SD2 dependent on other time-domain measures.

Open source computer software versions of DFA, multifractal analysis, correlation dimension, Lyapunov exponent, SampEn and MSE analysis are available at www.physionet.org.

3. Application of methods from NLD for HRV analysis

(*a*) *HRV in healthy conditions*

Healthy HR fluctuations show a complex type of variability, embedding fractal self-similar fluctuations on time scales ranging from seconds to hours, and thus generating long-range power-law correlations (Goldberger *et al.* 2002). Results from several studies indicate that greater complexity (irregularity) appears in healthy systems. The common hypothesis is that the organism is a highly complex adaptive system, and that the complexity of its behaviour allows for the broadest range of adaptive responses due to different levels of input within a physiological range.

Table 2. Results of the group comparisons. (T1—young healthy males versus older healthy males and T2—older healthy females versus older healthy males (10 subjects in every group). Significance value: n.s., not significant; $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$; TD, time-domain indices; FD, frequency-domain indices; A, fractal measures; B, entropy measures; C, symbolic dynamics measures; D, Poincaré plot representation. For standard HRV parameters in TD and FD, see Task Force (1996); for parameters in A, B and D, see §2; for parameters in C, see Voss *et al.* (1996). CE, compression entropy; pW110, pW021 and pW321—single word type probabilities from SDyn; ‰, per mille.)

		group tests		mean value ± s.d.		
	parameter	T1	T2	young males	older males	older females
	age (years)	***	n.s.	32.43 ± 8.04	55.90 ± 5.36	56.40 ± 2.46
TD	meanNN (ms)	n.s.	n.s.	819.5 ± 120.7	894.5 ± 127.9	899.6 ± 129.1
	sdNN (ms)	n.s.	n.s.	47.2 ± 13.1	40.0 ± 9.4	43.4 ± 15.2
	rmssd (ms)	n.s.	n.s.	29.4 ± 13.8	22.2 ± 12.3	34.0 ± 17.1
FD	LF/HF (arb. units)	n.s.	n.s.	3.79 ± 2.49	3.86 ± 2.34	2.40 ± 1.57
	LFn (arb. units)	n.s.	n.s.	0.74 ± 0.13	0.71 ± 0.21	0.64 ± 0.17
	HFn (arb. units)	n.s.	n.s.	0.26 ± 0.13	0.29 ± 0.21	0.36 ± 0.17
A	$\alpha 1$ (arb. units)	n.s.	n.s.	1.02 ± 0.18	1.18 ± 0.23	1.02 ± 0.23
	$\alpha 2$ (arb. units)	n.s.	n.s.	0.90 ± 0.20	0.97 ± 0.13	0.98 ± 0.12
B	CE (arb. units)	n.s.	n.s.	0.64 ± 0.08	0.58 ± 0.06	0.60 ± 0.11
C	Shannon (bit)	*	n.s.	3.12 ± 0.32	2.73 ± 0.38	3.10 ± 0.49
	Forbword (arb. units)	n.s.	*	24.63 ± 9.52	33.80 ± 9.53	20.60 ± 14.83
	Renyi025 (bit)	n.s.	*	3.57 ± 0.27	3.30 ± 0.26	3.63 ± 0.32
	pW110 (arb. units, ‰)	*	n.s.	38.5 ± 11.1	24.0 ± 12.0	21.0 ± 12.5
	pW021 (arb. units, ‰)	n.s.	**	1.6 ± 2.2	1.6 ± 4.2	5.1 ± 5.1
D	SD1 (ms)	n.s.	n.s.	20.8 ± 9.8	22.8 ± 16.1	34.5 ± 17.1
	SD2 (ms)	n.s.	n.s.	63.3 ± 16.4	56.3 ± 12.3	61.0 ± 20.4

(i) *Age effects*

Cardiovascular structures and functions change with age, increasing the risk of developing cardiovascular disease (Oxenham & Sharpe 2003). Effects of ageing on HRV have been observed with linear as well as nonlinear complexity measures (Kaplan *et al.* 1991; Ryan *et al.* 1994), and are apparent in short-term records of 30 min. To demonstrate this ageing effect, we compared HRV of young healthy male subjects (32 ± 8 years, $n=10$) with that of older healthy male subjects (56 ± 5 years, $n=10$) under resting conditions in the supine position. HRV was quantified with indices from linear domains and NLD (see §2 for a more detailed description). Table 2 (group test T1) shows the numerical results of univariate statistics based on the Mann–Whitney U-test, and figure 2(i, ii) shows the tachograms (time series of beat-to-beat intervals) and word distributions of 64 different three-letter word types (SDyn) from a young and an older healthy male. HRV was generally reduced in the group of older subjects. In particular, the complexity indices of SDyn revealed a loss of complexity in older subjects. This is in accordance with the previous studies (Peng *et al.* 1995; Voss *et al.* 1996; Goldberger *et al.* 2002), where larger dimensions and entropies implied a greater

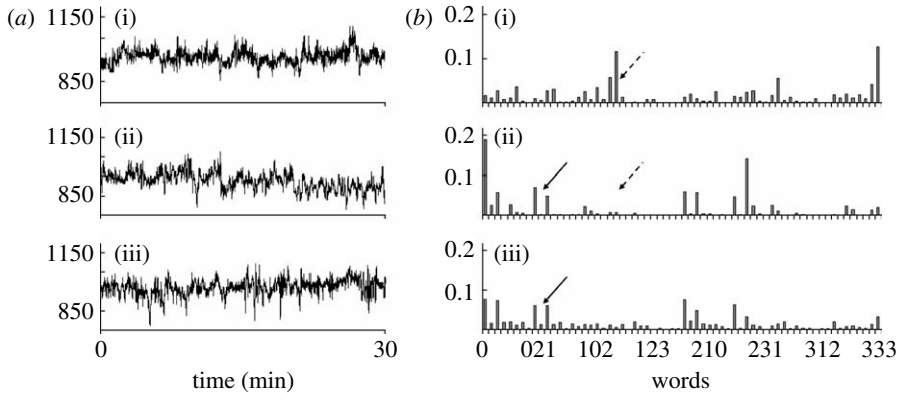

Figure 2. Examples of (*a*) tachograms (30 min; BBI, beat-to-beat intervals (ms)) and (*b*) word distributions of 64 different three-letter word types (probability; SDyn) from a (i) young healthy male, (ii) older healthy male and (iii) older healthy female. The dashed arrows indicate the most significant word distribution probability pw110 differentiating between the young and older healthy males. The solid arrows indicate the most significant word distribution probability pw021 differentiating between the older healthy males and healthy females (table 2).

complexity. Applying multifractal analysis, Shiogai (2007) demonstrated that the neurogenic control of the HR becomes more significant compared with myogenic control with ageing.

(ii) *Sex effects*

Under healthy conditions, sex differences in HRV have been observed across all ages (Ryan *et al.* 1994; Beckers *et al.* 2006). It has been suggested that a beneficial autonomic control of the heart in females aged less than 45 years may contribute to the lower risk of coronary heart disease and serious arrhythmias in females. We demonstrate this sex difference by comparing age-matched healthy females with the group of older healthy males investigated in the previous paragraph. Table 2 shows the numerical results for the sex comparison (group test T2), and figure 2(iii) provides an example tachogram and word distribution of 64 different three-letter word types of a representative older female. In particular, indices of SDyn indicate a higher occurrence of word types and a higher complexity of HR dynamics in women than in men (figure 2(ii) versus (iii)).

(*b*) *HRV under pathophysiological conditions*

A reduction in HR complexity was reported in patients with CHF (fractal scaling properties; Peng *et al.* 1995), myocardial infarction (MI, SDyn; Voss *et al.* 1996, 1998) and other cardiovascular diseases. Clinical research, where measures from NLD have been applied, focuses mainly on cardiology and internal medicine. In particular, those techniques have been used for HRV analysis in patients with ischaemic heart diseases (IHDs) and CHF and those threatened by severe arrhythmias. To demonstrate the power of some HRV indices derived from NLD for separating the healthy from pathological HRV, we compare three different groups of patients (dilated cardiomyopathy (DCM), ischaemic heart

Table 3. Results of the group comparisons—patients with ischaemic heart failure (IHF), dilated cardiomyopathy (DCM) and after myocardial infarction (MI) versus REF (10 subjects in every group). (Tests: T1, IHF versus REF; T2, DCM versus REF; T3, MI versus REF; significance value: n.s., not significant; $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$; TD, time-domain indices; FD, frequency-domain indices; A, fractal measures; B, entropy measure; C, symbolic dynamics measures; D, Poincaré plot representation; CE, compression entropy; for parameter definitions and units, see table 2.)

		group tests			patients (mean value ± s.d.)		
	parameter	T1	T2	T3	IHF	DCM	MI
	age	n.s.	n.s.	n.s.	54.20 ± 5.25	52.60 ± 9.14	58.25 ± 4.98
TD	meanNN	n.s.	n.s.	n.s.	920.0 ± 97.9	925.4 ± 103.9	952.7 ± 103.1
	sdNN	n.s.	n.s.	n.s.	43.3 ± 14.0	41.4 ± 18.3	38.2 ± 10.5
	rmssd	n.s.	n.s.	*	20.0 ± 7.1	25.8 ± 15.1	17.1 ± 4.3
FD	LF/HF	n.s.	n.s.	n.s.	4.52 ± 2.29	2.75 ± 2.45	3.89 ± 1.62
	LFn	n.s.	n.s.	n.s.	0.79 ± 0.09	0.64 ± 0.18	0.77 ± 0.08
	HFn	n.s.	n.s.	n.s.	0.21 ± 0.09	0.36 ± 0.18	0.23 ± 0.08
A	$\alpha 1$	n.s.	n.s.	n.s.	1.29 ± 0.15	1.17 ± 0.22	1.20 ± 0.16
	$\alpha 2$	n.s.	n.s.	n.s.	1.10 ± 0.10	1.16 ± 0.17	1.01 ± 0.15
B	CE	*	*	*	0.53 ± 0.07	0.53 ± 0.11	0.54 ± 0.05
C	Shannon	n.s.	n.s.	**	2.63 ± 0.41	2.58 ± 0.64	2.49 ± 0.30
	Forbword	n.s.	n.s.	**	33.90 ± 6.21	31.20 ± 14.65	38.63 ± 4.17
	Renyi025	n.s.	n.s.	**	3.27 ± 0.27	3.25 ± 0.60	3.10 ± 0.19
	pW321	***	*	**	0.1 ± 0.2	0.5 ± 0.7	0.1 ± 0.1
D	SD1	***	*	***	14.1 ± 5.0	18.3 ± 10.7	12.0 ± 3.2
	SD2	n.s.	n.s.	n.s.	59.5 ± 19.4	55.3 ± 24.4	52.5 ± 14.9

failure (IHF) and myocardial infarction) to that of sex- and age-matched healthy subjects (REF). The short-term indices from NLD (SDyn and compression entropy) are significantly different in all three patient groups when compared with healthy subjects (table 3). DFA shows only a trend for group differences. Although Poincaré map analysis is originally a nonlinear method, the typically extracted indices SD1 and SD2 (see §2) are more or less insensitive to nonlinear characteristics. Surprisingly, the index SD1 was able to differentiate the healthy subjects from all patients, partly in contrast to the time-domain index rmssd, which is known to be highly correlated with SD1. Figure 3 shows the tachogram, SDyn word distribution and Poincaré plot for a representative patient from each investigated group and a healthy subject. By comparing short- versus long-term recordings in risk stratification, we could demonstrate that in patients with ischaemic heart failure (low risk: survivors, $n=179$ and high risk: patients who died due to a cardiac event during a follow-up period of 2 years, $n=29$) $\alpha 1$ (DFA) differentiates both groups significantly (low risk 30 min: $\alpha 1 = 1.2 \pm 0.22$, low risk 24 hours: $\alpha 1 = 1.2 \pm 0.19$, high risk 24 hours: $\alpha 1 = 1.07 \pm 0.25$; significances: low risk 30 min versus 24 hours, n.s.; high risk and low risk: 30 min and 24 hours, both $p<0.01$). There were no significant differences in short-term versus long-term $\alpha 1$.

Several large clinical studies have demonstrated the potential of measures based on NLD and fractal analysis. Some of them are discussed briefly in the following examples. Bigger *et al.* (1996) was the first to report the ability of

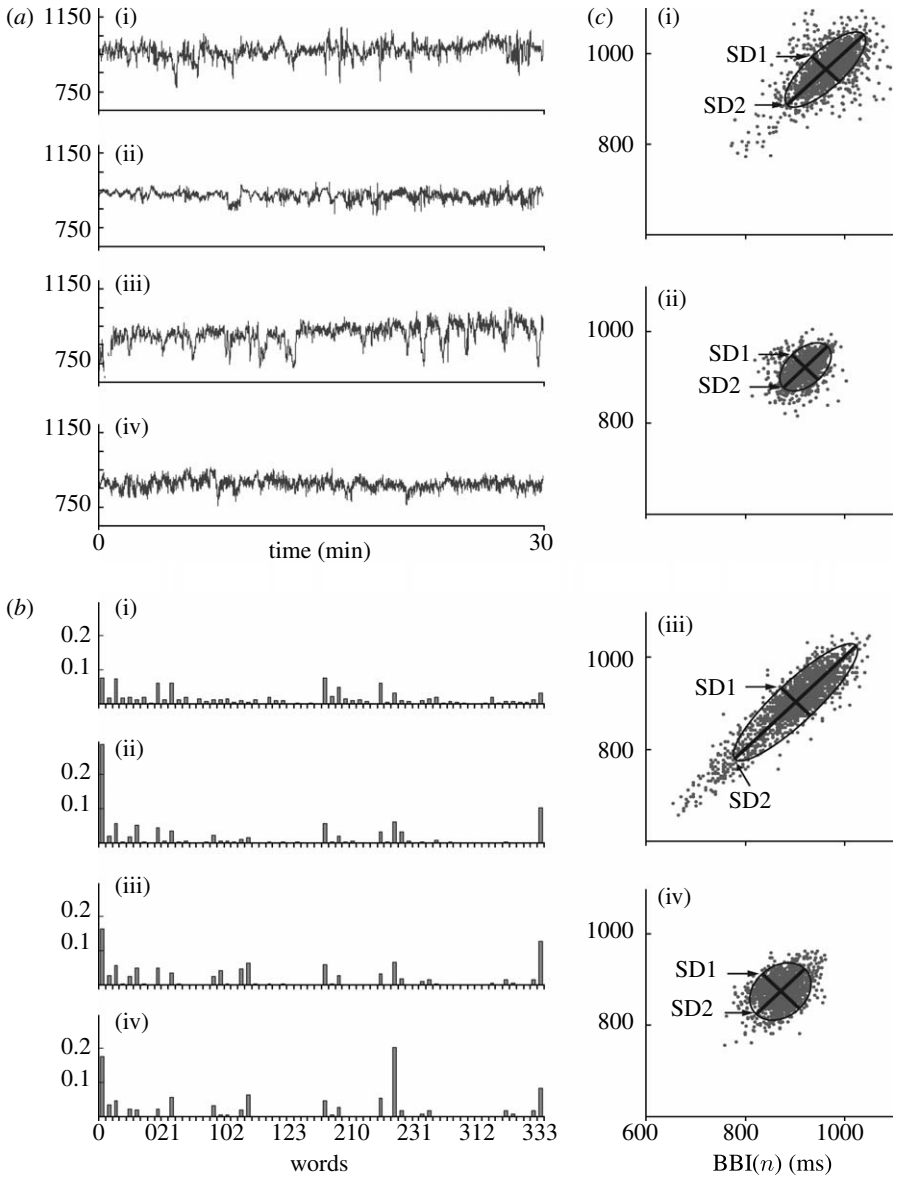

Figure 3. Examples of (*a*) tachograms (BBI (ms)), (*b*) SDyn word distributions of 64 different three-letter word types (probability) and (*c*) Poincaré plots (BBI(n+1) (ms)) for a representative patient from each investigated group and a healthy subject ((i) REF, healthy subject; (ii) DCM, dilated cardiomyopathy; (iii) IHF, ischaemic heart failure; (iv) MI, myocardial infarction); BBI, beat-to-beat intervals; SD1, standard deviation short-term variability; SD2, standard deviation long-term variability.

power spectrum based on long-term scaling indices to predict death after MI. They studied 715 patients with recent MI, 274 healthy subjects and 19 patients with heart transplants. The slope of the power-law relationship was found to be somewhat steeper (more negative) in MI and much steeper for heart transplant

patients. They demonstrated that a power-law regression coefficient below −1.372 is significantly associated with total cardiac and arrhythmic mortality. A multivariate approach (Voss *et al.* 1998), using all domains and especially SDyn, revealed the best prediction for all-cause mortality as well as for sudden arrhythmic death. In this study, 572 survivors of acute myocardial infarction were enrolled. Within the follow-up period, 43 patients died (all-cause mortality), of whom 13 died from ventricular tachycardia/ventricular fibrillation, 14 from sudden arrhythmic death, 22 from sudden death and 34 from cardiac death.

A combination of four HRV parameters from all domains (time and frequency domain, NLD) in this multivariate approach improved the diagnostic precision more than twofold. Mäkikallio *et al.* (1999) examined traditional HRV indices along with short-term fractal-like correlation properties (DFA) and power-law scaling in 159 post-MI patients with ejection fraction (EF) less than 35 per cent with 4-year follow-up. Among all of the analysed variables, reduced $\alpha 1$ (DFA) was the strongest univariate predictor of mortality in patients with depressed left ventricular function (EF less than 35%) after acute MI.

In the DIAMOND study, a cohort of 446 survivors of acute MI with EF less than 35 per cent was investigated and a reduction in the short-term fractal exponent $\alpha 1$ (DFA) was the most powerful predictor of all-cause mortality (Huikuri *et al.* 2000). The exponent predicted both arrhythmic and non-arrhythmic cardiac death.

Tapanainen *et al.* (2002) showed that several other HRV indices were also able to predict mortality in the univariate analysis, but in a multivariate model, after adjusting for clinical variables and left ventricular EF, $\alpha 1$ (DFA) was the most significant HRV-based contributor (comprising a set of linear indices and power spectrum $1/f$ power-law slope) to predict subsequent mortality. In a study by Stein *et al.* (2005), abnormal nonlinear HRV (short-term fractal scaling exponent, power-law slope and SD12 (Poincaré plot representation)) has been associated with mortality post-MI. The results suggest that decreased long-term HRV and increased randomness of HR are each independent risk factors for mortality post-MI. However, as with traditional HRV parameters, this relationship might be blurred by coronary artery bypass graft surgery post-MI or by diabetic autonomic neuropathy.

Guzzetti *et al.* (2000) found significantly lower normalized LF power and lower $1/f$ slope in chronic heart failure patients compared with controls. Moreover, the patients who died during the follow-up period presented further reduced LF power and steeper $1/f$ slope than the survivors. They concluded that spectral and nonlinear analyses of HRV both have prognostic relevance independent of the time-domain measures of HRV in patients with CHF.

Another study investigating 499 patients with CHF has also shown the predictive value of altered short- and long-term scaling properties for mortality (Mäkikallio *et al.* 2001). A short-term fractal scaling exponent of $\alpha 1 < 0.9$ was the strongest predictor of mortality (univariate and multivariate).

An interesting finding of that study was that the HRV indices were strong predictors of mortality in patients with mild/moderate CHF, but failed to provide independent prognostic information for severe cases of CHF.

Recently, multiscale indices of HRV have been included in clinical trials. MSE stratified 441 patients from the intensive care unit by mortality and was an independent predictor of death occurring days later (Norris *et al.* 2008).

The paper of Hu *et al.* (2008) provides an example of how concepts of NLD and fractal analysis may enhance our knowledge regarding physiological and pathophysiological regulation of HR. The authors demonstrated that scale-invariant cardiac control occurs across time scales varying from minutes to approximately 24 hours. Lesioning of the mammalian circadian pacemaker (suprachiasmatic nucleus, SCN) completely abolishes the scale-invariant pattern at time scales greater than approximately 4 hours. At time scales less than approximately 4 hours, the scale invariance was persistent after SCN lesions, but with a different pattern. This study revealed the influence of the SCN on HR fluctuations over multiple time scales, which previously could not be explained by simple pacemaker models of 24 hours rhythmicity. It was concluded that the SCN serves as a major node in the cardiac control network and imparts scale-invariant cardiac control across a wide range of time scales with the strongest effects between approximately 4 and 24 hours.

4. Summary

Methods of NLD and fractal analysis have opened up new ways to analyse HRV. Although time- and frequency-domain methods enable the quantification of HRV on different time scales, nonlinear methods provide additional information regarding the dynamics and structure of beat-to-beat time series.

In summary, we can state the following.

— There are several indices derived from NLD proven to be powerful risk stratifiers and contribute towards enhanced diagnostics of cardiovascular diseases, e.g. DFA, MSE and SDyn.
— There is a variety of other potential indices from NLD that seem promising, but have yet to be validated in further clinical trials (Maestri *et al.* 2007).
— NLD provide additional and independent information about physiological as well as pathophysiological cardiovascular regulation.
— Temporal changes in HRV and HR dynamics often depend on the baseline characteristics of the patient.

Altered HRV and HR dynamics have prognostic significance for the progression of a disease (e.g. coronary artery disease) and for mortality (e.g. after acute MI). Conversely, the HRV indices are limited in scope for differentiating between pathophysiological states or patients. However, when applied to the individual patient over a time period, these indices may prove to be clinically useful, differentiating the progression of disease. Furthermore, they might provide a valuable addition to current patient monitoring systems. Therefore, cardiovascular variability based risk stratification might be more powerful in longitudinal studies.

A further improvement in the diagnostics of cardiovascular diseases and risk stratification for arrhythmic fatal events is expected, and partly proven, by combining NLD methods of HRV analysis with additional cardiovascular signals, i.e. blood pressure and respiration. The analysis of interactions, couplings and synchronizations is also a powerful tool for research in cardiovascular regulation.

Finally, coupling models accounting for a large range of time scales and intervals are central to describing complex systems and therefore to biology (Coveney & Fowler 2005).

There are some important points that one has to consider when applying the methods from NLD.

(i) One parameter alone (independent from the domain) cannot sufficiently describe complex physiological systems, such as HR control. Therefore, multivariate approaches should be considered. NLD parameters in combination with standard linear parameters usually improve the performance of HRV analysis.
(ii) The type of underlying disease often determines the applicability of HRV indices for diagnostics or risk stratification.
(iii) There are a number of factors that might affect the results obtained by nonlinear methods and consequently have to be considered, e.g. recording duration, degree of stationarity, superimposed noise and signal pre-processing (filtering).
(iv) NLD indices are often introduced with special fixed presettings (e.g. window length, number of bins) that have been proved and optimized in various studies and have to be considered in new comparative investigations.

In conclusion, methods derived from NLD have provided new insights into the HRV changes under various physiological and pathophysiological conditions. They provide additional prognostic information and complement traditional time- and frequency-domain analyses of HRV. Today, the question is no longer about whether or not methods from NLD should be applied; however, it is relevant to ask which of the methods should be selected and under which basic and standardized conditions should they be applied.

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