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Review

Chaos in the cardiovascular system: an update

Claus D. Wagner, Pontus B. Persson*

Institut für Physiologie der Humboldt-Universität zu Berlin (Charité), Tucholskystraße 2, D-10117 Berlin, Germany

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Abstract

Rhythmic changes of blood pressure, heart rate, and other cardiovascular measures have drawn the attention of several investigators, since these oscillations can shed light onto the activity of the underlying control network. The overwhelming proportion of circulatory variations, however, are not linear, i.e., they do not consist of perfectly rhythmic components. Thus, these fluctuations are more adequately analysed by non-linear techniques, most of which are adopted from chaos theory. A spotlight issue of 'Cardivascular Research' (Vol. 31, 1996), focused on chaos in the cardiovascular system. This current review outlines today's understanding of this field by presenting the major discoveries and developments which have taken place since then.

Keywords: Heart rate variability; Non-linear dynamics; Risk stratification; Vasomotion

1. Introduction

Two years ago the 'Spotlight Issue on Chaos in the Cardiovascular System' appeared [Cardiovascular Research, volume 31, 1996], in which a selection of topics related to chaos in heart and circulation were highlighted. Since then, new studies have deepened our insight and broadened our understanding regarding the nature of chaotic behaviour.

The purpose of this article is to update those topics which have been affected most by the newest trends in this field. Hence, the recent developments of cardiac chaos were chosen as a major focus. Another emphasis was placed on mechanisms responsible for chaotic behaviour observed in vasomotion and risk stratification. A brief outline of the methods used to identify chaos is found at the end of this review.

2. Cardiac chaos

Heart rate (HR) is not constant but varies considerably, even in the absence of physical or mental stress. A power spectrum of HR reveals at least two frequency ranges [47,53], in which power can accumulate. It is discussed controversially, whether modification of the power of these ranges occurs by influencing either sympathetic [low frequency range, (LF) 0.04–0.15 Hz] or vagal [high frequency range (HF) 0.15–0.4 Hz] traffic to the heart [10,70]. Beside these more or less periodic components, HR reveals a broad, noise-like variability over a large frequency span [36]. It seems that this irregular variability, which accounts for the largest proportion of HRV, is due to non-linearities in the control network.

Several authors have quantified non-linear measures in order to test their feasibility to identify changes in autonomic nervous outflow. Yeragani et al. compared fractal dimensions of HR time series with HF and LF powers, and found positive correlations of these measures with sympathetic and vagal activity [76]. Others found that non-linear components of HRV are drastically reduced by cholinergic blockade, but not by β-adrenergic blockade [86,87], a similar observation has been made after vagal denervation in neonatal swine [40], and in patients suffering from congestive heart failure [6]. In another study, Hagerman and colleagues disrupted the autonomic nervous activity to the heart with propranolol and atropine and found a reduction in the largest Lyapunov exponent [26]. This confirms the potential value of using measures of non-linear dynamics as a tool for evaluating autonomic nervous

*Corresponding author.

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outflow to the heart. Interestingly, Hagerman et al. could not totally eliminate the non-linear structures in HRV in their experiments using combined blockade. Thus they concluded that other mechanisms like circulating hormones, preload, or afterload contribute to the non-linearity observed. However, respiration does not seem to contribute to this effect, since no evidence was found for a non-linear input from the respiration into the cardiovascular centres [32].

It is intriguing, that marked changes in non-linear properties are observed throughout early human development [43,51]. This seems to reflect changing control complexity during autonomic nervous system maturation [40]. A distinct non-linearity was not observed in preterm infants [69], which indicates that complex heart rhythms mainly develop during the final weeks of gestation [50]. Attempts have been made to use non-linear measures to identify children at risk, however, with differing results. Largest Lyapunov exponents of infants suffering from bronchopulmonary dysplasia, for instance, showed no differences compared with a control group [44,51]. On the other hand, a symbolic dynamics approach applied to premature babies at high risk for Sudden Infant Death Syndrome revealed significant differences to controls [45].

In healthy adults, non-linear dynamics in HR seems to represent the normal situation [28,42,56]. These are obscured under pathological circumstances, e.g., such in which the cardiovascular–respiratory interplay is impaired [30], which can also be observed in patients after heart transplantation [25]. In line with the view, that the healthy state is characterised by a certain degree of chaos, it has been found that abnormalities in autonomic system functions diminish cardiac chaos. This was recently demonstrated for congestive heart failure (CHF). In CHF patients, Poon and Merrill [57] observed an increase in non-chaotic HR fluctuations, which alternate with chaotic short-term variations. The reduction in HRV complexity in CHF went parallel to a decrease in parasympathetic nervous system activity [6,48,72]. This supports the above mentioned hypothesis, that part of HRV complexity arises from cardiac vagal activity. Further support of chaos being inherent to the physiological control of heart rate is provided by Narayanan et al. [46]. They discovered unstable periodic orbits (UPO) in RR time series. Periodic orbits reflect the deterministic dynamics of the underlying system, but the UPOs are unstable, which means that they have a positive Lyapunov exponent and are therefore typical for chaotic systems. (A similar approach, however, was used by Le Pape et al. [38], who did not identify UPOs in mice electrocardiograms).

Many authors have addressed the question, whether ventricular fibrillation is chaotic or just some form of noise [16,33,81]. It is known by high-resolution mappings, that re-entrant electrical arrhythmias are a cause for the transition from orderly beating to fibrillation. Ventricular fibrillation consists of propagating wavefronts which traverse the myocardium. As the high-resolution mappings have revealed, there exist local spatio-temporal correlations, that become weaker correlated during fibrillation [82]. This observation may indicate that a deterministic mechanism generates fibrillation [3,17,81]. Although the underlying processes are not completely random, it remains unclear whether they represent a form of deterministic chaos. Garfinkel et al. recently studied the spatio-temporal dynamics in thin sheets of human and canine ventricular tissue [15]. The authors induced re-entry by application of the potassium channel opener cromakalim. The resulting period-1 re-entrant tachycardia spontaneously changed into period-2 behaviour. This is an example for a so called period doubling and constitutes a major route to chaos [52] (see also Fig. 1). In another experimental setup by this group, this transition was achieved by an external pacing

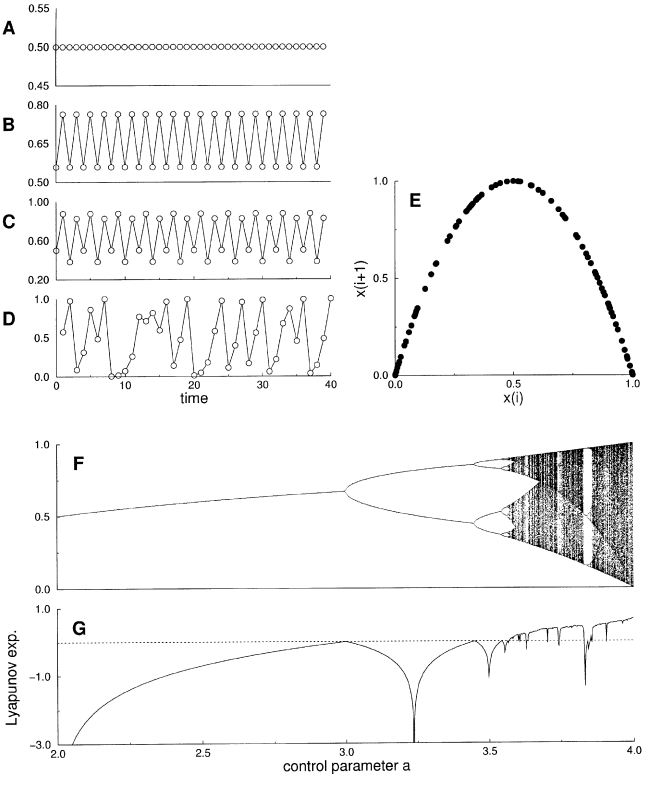

Fig. 1. The logistic equation $x_{i+1}=ax_i(1-x_i)$ with different values of bifurcation parameter a. Subsequent iterations x_i for increasing a give rise to the period-doubling route to chaos. (A) $a=2.0$ (period-1 orbit), (B) $a=3.1$ (period-2), (C) $a=3.5$ (period-4), and (D) $a=4.0$ (chaotic trajectory). When a is increased from 2 to 4, the system undergoes period-doubling bifurcations, i.e., the system switches to higher periodicities at certain parameter values. The right side (E) shows a plot of x_i versus its predecessor x_{i+1} for $a=4.0$. The parabolic shape reflects the quadratic relation between x_{i+1} and x_i. One hundred points are plotted. (F) A plot of subsequent iterations x_i as a function of the parameter a clearly shows the period-doubling bifurcations. In (G), the largest Lyapunov exponent λ is plotted as a function of a. The Lyapunov exponent is a marker for a system's sensitivity on initial conditions and is negative for periodic evolution (for $a<3.57$) and positive for chaotic motion. Note the periodic windows in the chaotic range (3.57, 4) where λ becomes negative.

stimulus. In both cases, the period-2 behaviour became amplitude and period modulated, and finally switched to a highly aperiodic fibrillation-like behaviour.

The transition mechanisms that these authors observed [15], was from periodicity (tachycardia-flutter) to chaos, (fibrillation) via a quasi-periodic route. To further elucidate the transition pattern, as well as to determine the role of ventricular tissue mass in fibrillation, Kim et al. successively reduced tissue mass by sequential cutting [34]. They found that the number of wave fronts decreased with decreasing tissue mass and that there is a critical tissue mass essential for maintenance of fibrillation. Parallel to the reduction of tissue mass, the Kolmogorov entropy, a measure of dynamical complexity, also decreased [34]. With these experiments, the authors were able to resolve more distinctly the region between periodicity (regular arrhythmias) and chaos (fibrillation). Together with the study of Garfinkel et al. [15], these experiments strongly support the hypothesis that fibrillation is indeed chaos, reached by the perioddoubling route [67]. Taken together, there are studies showing that the healthy cardiovascular system is on the verge to chaos. Circulatory disorders can be manifested by a decrease in chaos (as in CHF), or by a greater magnitude of this form of non-linear dynamics (e.g., fibrillation).

3. Vascular chaos

Rhythmic changes in diameter (or resistance [64]) of blood vessels is a commonly observed physiological phenomenon, which occurs in small arteries and arterioles [14]. Although a great amount of resistance variability is accounted for by almost periodic changes, Yamashiro et al. suggested a relaxation oscillator (pacemaker) behaviour responsible for vasomotion [84]. Indeed, the dynamics of vasomotion may be chaotic. Tsuda and colleagues investigated pulsations in a finger's capillary vessels [71] and found the largest and the second largest Lyapunov exponents to be positive and, hence, the system was classified as chaotic. In order to rule out the possibility that chaos in vasomotion might simply be a secondary effect (i.e., the chaotic motion observed in the capillary vessels originates from RR-interval variability (cardiac chaos), the authors made simultaneous measurements of heart beat. In fact, heart rate did reveal deterministic chaos, but its topology differed from that of the capillaries. Since the peripheral vessels are under control of the autonomic nervous system, Tsuda et al. interpreted their results in terms of a non-linear modulation by the nervous system [71]. Other studies, on isolated mesenteric and femoral rat arteries [66] and hindlimb skeletal muscle of anaesthetized rabbits [59], however, indicate that the local pacemaker cells or paracrine factors are responsible for inducing vasomotion.

Thus, Griffith and Edwards investigated vasomotion in isolated rabbit ear resistance arteries, which were elicited by application of histamine [19]. They described an irregular rhythmicity. The transition from regular (or periodic) behaviour to chaos took place via three possible ways: first, a period-doubling route to chaos; second, a quasi-periodic route to chaos; and third, intermittency, a state, where the system is arrested between almost periodic motion and chaos [24]. These chaotic fluctuations were not abolished by endothelium denudation, suggesting vascular smooth muscle cells as the source of the oscillations (with correlation dimensions between 2 and 4).

This interpretation was supported by a further series of experiments, in which it was shown that vascular smooth muscle Ca^{2+} fluxes can create aperiodic vasomotion [20,22]. Two major frequency components in the perfusion pressure spectrum were selectively blocked pharmacologically with calcium antagonists: a fast subsystem (5–20 s) was inhibited by verapamil (inhibiting voltage-dependent Ca^{2+} influx; inhibition of voltage-dependent K^+ channels or the Ca^{2+}–ATPase extrusion pump, however, had no effect on the form and complexity of vasomotion [13]), whereas a slow subsystem (1–5 min) was attenuated by ryanodine, suppressing Ca^{2+}-induced Ca^{2+} release from the sarcoplasmic reticulum [35]. Thus, a plausible reason for this form of vascular chaos is the coupling between both oscillators [23], i.e., cytosolic [Ca^{2+}]. It was finally shown, that this form of vasomotion (chaos, quasi-periodicity, and mixed-mode responses) can be described in terms of iterative circle maps; a model for the dynamics of coupled non-linear oscillators [9].

The aperiodic oscillations observed in the perfused rabbit ear arteries has successfully been 'controlled'. As mentioned in the initial spotlight issue [65], control of chaos is the external maintenance of the system's dynamics within a physiological range. In this study, control was attempted by a negative feedback loop that regulated pump speed according to the difference between instantaneous perfusion pressure and a reference value [21]. Different absolute levels of perfusion pressure or flow converted irregular pressure fluctuations to periodic dynamics (i.e., stabilization of unstable period-1, period-2, and period-4 orbits), and rhythmic activity was almost completely suppressed (stabilization of an unstable steady-state). However, in approximately 40% of the cases, the dynamics remained highly irregular during external control, providing evidence that absolute levels of flow/perfusion pressure are not the sources of the intrinsic complexity observed in vasomotion. Blood pressure appears rather to play the role of a control, or bifurcation parameter, in vasomotion. Autoregulation, for instance, seems to be a mode, where aperiodic or chaotic behaviour occurs, whereas periodic haemodynamics is activated below a specific local arterial blood pressure and flow threshold (at the lower end of autoregulation) [59,60]. This characteristic was recently found in a mathematical model of an arteriolar network, where diameter oscillations shifted between

periodic, quasi-periodic, and chaotic behaviour, depending on arterial pressure level [7].

How do organisms benefit from the chaotic behaviour of vasomotion? The sensitivity of chaotic systems to initial conditions (i.e., to perturbations) allows large changes in state with minimum expenditure of energy to be brought about [61]. This cost-benefit analysis gains significance in situations, where systems frequently skip from one state to another [49]. On the other hand, perturbations can easily destabilize (unwanted) periodic or steady-state behaviour and thereby induce, rather than suppress, chaos. If the system is allowed to operate near the frontier from periodic behaviour to chaotic behaviour, only minute alterations in a single parameter are necessary to switch the system from regular to irregular behaviour [24,85], thus providing a high degree of flexibility to the control of microcirculatory blood flow. Thus, non-linear dynamics observed in systemic blood pressure [2,77–79] may be caused partly by non-linear vasomotion.

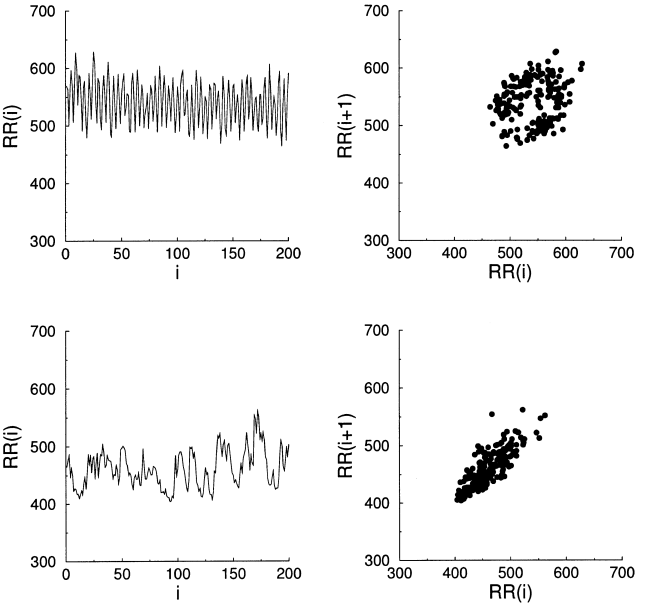

Fig. 2. Scatter plots or Lorenz plots are graphical representations for the temporal correlations within a time series. Long-term correlations are reflected in the length of the scatter plot shape, whereas short-term correlations broaden the cloud. The data are heartbeat intervals from newborns during sleep. (Top left panel) Quiet sleep, (Lower left panel) active sleep, (Right hand panels) are the matching Lorenz plots. The data is by courtesy of A. Patzak.

4. Risk stratification and non-linear dynamics

Can methods from non-linear dynamics help improve the reliability of risk stratification? This potential of non-linear HRV analysis has been demonstrated in a number of reports, focusing on risk detection and stratification in situations related to myocardial infarction (MI).

A bridge connecting linear methods in time and frequency domain with non-linear dynamics are *scatter plots*, or *Lorenz plots*, in which one RR interval is plotted against its predecessor, i.e., RR_i vs. RR_{i-1} (see Fig. 2). The same method is used to reconstruct an attractor in two dimensions (see Fig. 1). Copie and co-workers [8] showed that indices of HRV were strongly correlated with the shape of the scatter plot. The scatter plot length is correlated with long-term variability parameters, scatter plot width was closely related to short-term variability. Since scatter plots provide a geometrical representation of beat-to-beat dynamics, including the non-linear features, they may provide a tool for examining connections between physiological states and non-linear markers [8]. Hnatkova and coworkers [27] used scatter plots to distinguish between postinfarct patients who suffered an arrhythmic event during a follow-up period and those without arrhythmic complications. In this study, scatter plots were shown to provide a larger positive predictive accuracy than linear variability measures (i.e., standard deviation of all RR intervals).

Mäkikallio et al. [41] obtained a similar result in a retrospective analysis of 24-h HR data from patients with a history of myocardial infarction: the lengths of the scatter plots were significantly reduced in those patients with a propensity for ventricular tachycardia (VT). In agreement, a previous study from this group clearly demonstrated that analyzing the shape of the scatter plot pattern is a potent tool for the prediction of forthcoming VT [29]. Prior to the onset of VT, the scatter plot broadened and simultaneously, the length tended to decrease. Since the width and length of the scatter plot relates directly to short- and long-term HRV, this technique may provide insight into HR dynamics, which are not readily detected with conventional techniques (e.g., spectrum analysis).

Skinner and colleagues [62] applied the point correlation dimension algorithm (PD2), a modification of the correlation dimension, to HRV of conscious pigs during experimental MI. After coronary artery occlusion, they observed a significant decline in correlation dimension, which further decreased minutes prior to the onset of VT. Intriguingly, the second dip in PD2 was not observed in those animals, which did not experience VT. In a further study, Skinner [63] demonstrated that the mentioned decrease of PD2 prior to life-threatening VT also occurs in patients with pre-existing heart disease. In randomly selected control groups, who had no previous history of VF, but who also had non-sustained ventricular tachycardia, the PD2 values did not fall to such low levels.

Voss et al. [73,74] introduced two new methods from non-linear dynamics into HRV classification in patients after MI: symbolic dynamics and renormalized entropy. In brief, symbolic dynamics facilitates the analysis of dynamic aspects of HRV. The RR-interval series are transformed into symbol sequences, with symbols from a given symbolic alphabet (here 0, 1, 2, 3) from which words were created with a ‘word’ length of 3. Further analysis was

done using the distributions of these 'words'. The renormalized entropy, on the other hand, is a rather complex method derived from thermodynamics, which can measure the complexity of any state in relation to a reference state (for a derivation of renormalized entropy and symbolic dynamics and the definition of symbols, please refer to [74]). When methods from the three parameter domains (time, frequency, and non-linear domains) were applied individually, none of these lead to a satisfactory discrimination between patients with and without life-threatening arrhythmias. However, the non-linear methods were superior to the other means. The main result of their study was that a combined set of parameters from all three domains significantly improved the precision of high risk stratification.

The methods used for the different domains describe various aspects or characteristics of HRV [31] (e.g., a high or low HRV, periodic processes due to an autonomic regulation, or the complexity of the RR-interval series). Clearly, it would be beneficial to have a set of a few parameters covering all domains. In a recent publication, Voss and co-workers [75] introduced a set of four parameters (namely Shannon entropy, relative power in the low and very low frequency range, words from symbolic dynamics consisting of symbols '0' and '2' only, and the mean value of RR intervals from a 30-min stationary segment) and demonstrated that the multi-parametric analysis of HRV significantly increased the prediction of risk in patients who survived a MI. These promising studies indicate the potential of non-linear methods, and their combination with other tools, for identifying patients with a high cardiovascular risk.

5. The analysis of chaotic data

In this section we outline some of the most widely used techniques. The algorithms developed for the analysis of non-linear time series have been designed mainly during the past twenty years, and the majority of the present publications still make use of these approaches.

In several cases of time series analysis, only one quantity, or signal, is obtained during a recording session (e.g., an RR or blood pressure series). The goal is to recognize the major characteristics of the system by this data set. This can be a straightforward task, provided that a valid mathematical model is available. Unfortunately, this is rarely the case in cardiovascular research. When we deal with experiments in which we cannot record all the variables, the total number of degrees of freedom may not be known exactly (mathematically speaking, the number of degrees of freedom, or the dimension of the state space, is the same as the number of first-order differential equations necessary to describe the system.) Thus, prior to the investigation of characteristic quantities of the system, like fractal dimensions, entropies, or Lyapunov exponents, the phase space of the underlying dynamical system has to be reconstructed from the observed variable. This is often done by plotting the time series vs. a time delayed sequence of itself. For the choice of correct exact delay times and sufficiently high embedding dimensions of the phase space, please refer to [1,11].

The definition of dimension in daily life, i.e., for Euclidian space, is clear: a point has the dimension 0, a line or curve has dimension 1, a surface 2, and a volume 3. Mathematically speaking, a dimension gives a statistical measure of the geometry of a cloud of points and can be assigned to any arbitrary set of data points. There are several concepts of estimating dimensions, but in general they all yield common values, to which we refer to as *fractal dimension*. Unlike the common definition of dimension, strange attractors originating from chaotic systems may also reveal non-integer (fractal) dimensions. The standard algorithms for estimating the fractal dimension require very large data sets ($>10\,000$) and more importantly, they presuppose stationarity of the time series. To overcome this limitation, which would restrict possible physiological and cardiovascular application, algorithms have been developed, which operate with short and/or instationary data (for example, the pointwise correlation dimension [37,62,63]).

Lyapunov exponents measure the average local rate of divergence of neighboring trajectories in phase-space embeddings [11]. A positive Lyapunov exponent can be taken as a definition of chaos, provided the system is known to be deterministic (Fig. 1G). An early algorithm developed by Wolf et al. directly uses the rate of divergence between two nearby trajectories [83]. This algorithm works well with large data sets devoid of noise contamination, but may fail in situations of short and/or noisy data sets. Several algorithms have been developed to overcome this limitation [4,5,12,58] and may be superior for the application to cardiovascular time series.

'Entropy' refers to system randomness and predictability and allows systems to be classified by rate of information loss or generation. In other words, entropy specifies the amount of information one learns about the source of the signal x by a measurement of x (this idea was formulated by Kolmogorov and Sinai 1958–59 and is now known as KS entropy). Since the KS entropy is the sum of positive Lyapunov exponents, a non-linear system with positive entropy is intrinsically unstable. In case of large data sets, KS entropy can be estimated directly from correlation integrals [18], an alternative approach is *approximate entropy* [54,55], suitable for short data sets.

As was mentioned above, the entropy of a signal is related to the concept of forecasting the future evolution of the time series. *Non-linear forecasting* is an approach developed for making short-term predictions about the trajectories of dynamical systems. It usually compares predictions of the time series' evolution, which were assembled from another part of the time series, with the

actual evolution. The prediction error is then the normalized root-mean-square difference between predicted and actual evolution [1,39,68,80], which has been utilized to characterize the nature of the underlying dynamics (periodic, deterministic chaotic, or signals contaminated with externally induced noise).

6. Conclusions and perspectives

Methods derived from the field on non-linear dynamics, or chaos theory, have provided useful tools to characterize systems from 'life sciences'. Applications can be found throughout a wide scope of medicine, such as cardiology, physiology, and the neurosciences.

There are limitations to linear and non-linear methods, and there are several situations in which the one method is superior to the other. Linear methods are appropriate for stable linear systems, e.g., those which are characterized by a few distinct peaks in a power spectrum. Accordingly, it is not surprising, that the application of linear methods can fail in case of non-linear systems. The time series of the latter often reveal broad-band spectra instead of pronounced peaks, indicating that their dynamics stem from multivariate sources. Such dynamics are typical for most biological systems in general, and for the cardiovascular control network in particular.

However, both linear and non-linear approaches can complement each other in the analysis of a system's behaviour. Diameter changes in a small artery, for instance, are interpreted as noise by the broad-band power spectrum. The application of non-linear methods, however, shows that this process obeys deterministic rules. HRV is also, to a certain degree, describable by spectrum analysis. The aperiodic processes in HRV, which do not appear as distinct peaks, are only adequately addressed by non-linear techniques. Regarding HRV, there are indications that a reduction in complexity comes along with a decrease in vagal traffic to the heart, suggesting that a considerable amount of non-linear behaviour is promoted by this branch of the autonomic nervous system.

Finally, studies regarding the pathogenesis of myocardial infarction are promising with regard to the future prospects of non-linear dynamics in clinical use. Especially, high-risk stratification after myocardial infarction has demonstrated the advantage of combining methods from the time and frequency domain.

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