Is the normal heart rate "chaotic" due to respiration?

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(Received 15 December 2008; accepted 22 April 2009; published online 30 June 2009)

The incidence of cardiovascular diseases increases with the growth of the human population and an aging society, leading to very high expenses in the public health system. Therefore, it is challenging to develop sophisticated methods in order to improve medical diagnostics. The question whether the normal heart rate is chaotic or not is an attempt to elucidate the underlying mechanisms of cardiovascular dynamics and therefore a highly controversial topical challenge. In this contribution we demonstrate that linear and nonlinear parameters allow us to separate completely the data sets of the three groups provided for this controversial topic in nonlinear dynamics. The question whether these time series are chaotic or not cannot be answered satisfactorily without investigating the underlying mechanisms leading to them. We give an example of the dominant influence of respiration on heart beat dynamics, which shows that observed fluctuations can be mostly explained by respiratory modulations of heart rate and blood pressure (coefficient of determination: 96%). Therefore, we recommend reformulating the following initial question: "Is the normal heart rate chaotic?" We rather ask the following: "Is the normal heart rate 'chaotic' due to respiration?"
 [DOI: 10.1063/1.3133128]

Cardiovascular diseases are the main cause of morbidity and mortality in the industrialized countries leading to very high expenses in the public health system. Therefore, it is challenging to develop sophisticated methods to improve the medical diagnostics. The question whether the normal heart rate is chaotic or not is an attempt to elucidate the underlying mechanisms of cardiovascular dynamics and therefore a highly topical challenge. Parameters of nonlinear dynamics especially from "chaos theory" are powerful tools for the description of cardiovascular dynamics; however, they should not act as paradigms; for classification tasks sometimes linear parameters can achieve similar or even better results. To understand the mechanisms of cardiovascular dynamics, however, the theory of deterministic chaos becomes more important. The initial questions of this controversial topic such as "Is the normal heart rate chaotic," however, can only be fully answered by investigating the underlying mechanisms based on multivariate approaches, which include almost all relevant influences of heart rate fluctuations. Therefore, the initial question should be reformulated: "Is the normal heart rate 'chaotic' due to external influences, e.g., respiration and/or physical, mental, as well as metabolic activity?"

Spontaneous fluctuations of cardiovascular signals had already been described more than 150 years ago.[1] It is known that the normal heart rate, the *controversial topic* to be discussed here, not only represents physiological oscillations but also reflects the complex interactions of many different control loops of the cardiovascular system and therefore sometimes looks chaotic. Due to the complexity of the sinus node activity modulation system, a predominantly nonlinear behavior has to be assumed. Nevertheless, the linear analysis of heart rate variability (HRV) has become a powerful tool for the assessment of autonomic control. HRV measurements have proven to be independent predictors of sudden cardiac death after acute myocardial infarction, chronic heart failure, or dilated cardiomyopathy.[2,3] Moreover, it has been shown that a short-term HRV analysis already yields a prognostic value in risk stratification independent of that of clinical and functional variables.[4] However, the detailed description and classification of dynamical changes using time and frequency measures are often not sufficient, especially in dynamical diseases as characterized by Mackey and Glass,[5,6] because the underlying regulatory mechanisms are still poorly understood and, therefore, the question whether the normal heart rate is chaotic or homeostatic is not yet answered satisfactorily.[7] Therefore, elucidating mechanisms for physiological interpretation is an interesting and exciting research area. For deterministic chaos, parts of the fluctuations are assumed to be intrinsic, resulting from the nonlinear control of the cardiovascular system. In contrast, homeostasis describes the physiological system as a stable state, where fluctuations arise from external disturbances. In this paper, we apply a number of linear and nonlinear parameters to the 15 data sets provided for this controversial topic in order to (i) demonstrate the ability to separate the three different groups and (ii) to tackle the question whether these time series are chaotic or not. Moreover, we give an example of cardiorespiratory modeling which demonstrates that the

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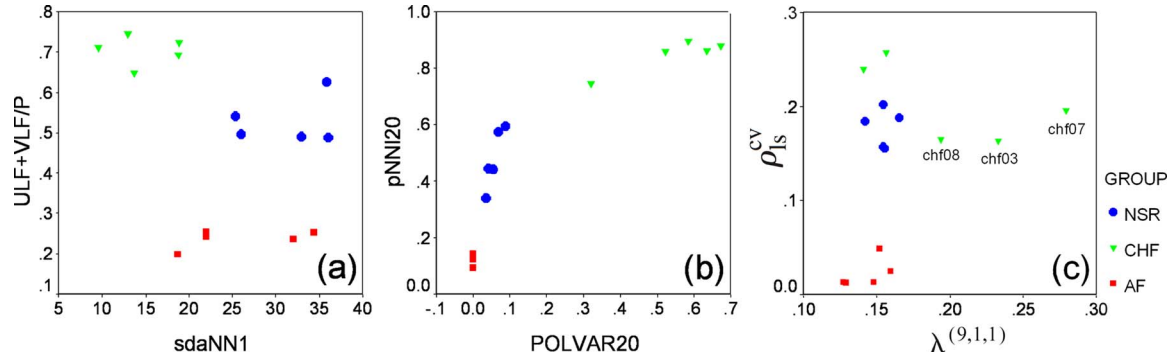

FIG. 1. (Color online) Separation of the three groups based (a) on linear parameter from time and frequency domain (the normalized ultra- and very low frequency bands ULF+VLP/P vs the standard deviation of averaged 1 min intervals sdaNN1), (b) on linear and symbolic dynamics parameters (the percentage of beat-to-beat interval differences less than 20 ms pNNI20 vs the probability of low variability less than 20 ms POLVAR20), as well as (c) on nonlinear parameters (the large-scale dimension density ρ_{ls}^{cv} vs the finite-time growth rate $\lambda^{(9,1,1)}$).

complex behavior of the heart rate is mainly caused by the respiration which influences the coupling of heart rate and blood pressure.[8] Finally, we discuss our results and pose the question whether the normal heart rate nowadays should be analyzed with or without other relevant cardiovascular signals, for instance, respiration and blood pressure.

(i) To demonstrate the classification power of linear versus nonlinear methods, we analyze 24 h data of five congestive heart failure (CHF) patients (five males, ages 59 ± 9 y), of five young healthy persons in normal sinus rhythm (NSR) (two males, ages 30 ± 10 y), as well as of five subjects suffering from atrial fibrillation (AF) selected from the Physionet database[9] for this special issue. After preprocessing, we calculate standard time and frequency domain parameters[10] as well as parameters from nonlinear dynamics which have been successfully applied to other cardiological problems recently.[11] Almost all show highly significant differences between the AF and both the NSR and the CHF groups. Moreover, with only two linear parameters we are able to separate all three groups completely [see Fig. 1(a)]. The normalized ultra- and very low frequency bands (<0.003 Hz and $0.003\ \text{Hz} < f < 0.04$ Hz, respectively) "(ULF+VLF)/P" <0.4 detects the AF patients, whereas the standard deviation of averaged 1 min intervals "sdaNN1" <20 ms uncovers the CHF subjects. An even better discrimination is achieved when using the percentage of beat-to-beat interval differences less than 20 ms "pNNI20" and the symbolic dynamics parameter "POLVAR20."[12] For POLVAR20, the absolute difference between two successive beat-to-beat intervals is symbolized ("0" if <20 ms or "1" otherwise). POLVAR20 represents the probability of the word-type "000000" occurrence and is able to detect even intermittent decreased variability. As shown in Fig. 1(b), the relation between both parameters is nonlinear, the AF patients have POLVAR20 values of approximately zero, and there is a big POLVAR20 gap around 0.2 between the NSR and the CHF groups. A further nonlinear measure is the classical correlation dimension; however, often no scaling region can be found for its calculation. Therefore, we applied the method of large-scale dimension densities ρ_{ls} which is based on a normalized Grassberger–Procaccia algorithm.[13] The algorithm leads to a suitable correction of systematic errors produced by boundary effects associated with large scales of a system. This allows for an analysis of rather short and nonstationary data. The circadian variation of the number of independent modes ρ_{ls}^{cv} enables a nearly perfect discrimination [see Fig. 1(c)] between all groups, except the CHF data 3, 7, and 8. Summarizing the classification analysis, we can state that linear as well as nonlinear parameters can separate completely the given data sets of the three groups.

(ii) To tackle the question whether the given time series are chaotic or not, we calculate the finite-time growth rate[14] as an analog for Lyapunov exponents in finite time. Therefore, the phase space is reconstructed by the delay embedding method.[15] Next, the evolution of each state and its nearest neighbor is analyzed during the time T. From the original distance of both states and the distance after T steps the finite-time growth rate is calculated. Here, $\lambda^{(9,1,1)}$ stands for the averaged finite-time growth rate calculated with an embedding dimension of 9 and a delay and an evolution time of 1. The higher $\lambda^{(9,1,1)}$ values of time series chf03, chf07, and chf08 [see Fig. 1(c)] demonstrate a lower predictability which, however, is caused by the relatively high number of ventricular ectopic beats in these data sets. For all data sets of all groups we get $\lambda^{(9,1,1)}$ values greater than zero, which is consistent with, but not specific for, chaos. Kaplan and Goldberger[16] already discussed the evidence of nonlinear characterizations for deterministic chaos in NSR and came to the same conclusions. In our opinion, the question as to whether these time series are chaotic or not cannot be answered reliably without investigating the underlying mechanisms leading to the observed fluctuations. Therefore, we give an example of the dominant influence of respiration on cardiac dynamics. The electrocardiogram, the continuous blood pressure (100 Hz, noninvasively via Portapres device model 2, BMI-TNO, Amsterdam, The Netherlands) and the respiration curve (via respiratory effort sensors at the chest; sampling rate of 10 Hz) were recorded for a healthy person in supine position with relaxed breathing. The beat-to-beat intervals (B_i) and systolic and diastolic blood pressures (S_i and D_i, respectively) were extracted from the blood pressure curve. The respiration on beat-to-beat basis (R_i) was extracted from the respiratory curve. A part of the B_i, D_i, and R_i time series is shown in Fig. 2. To model the dynamics of B_i and D_i, we consider a nonlinear additive autoregressive process with external inputs. To describe the fluctuations of B_i, the previous values of B_i, S_i, D_i, and R_i (lags 1–5) as well as

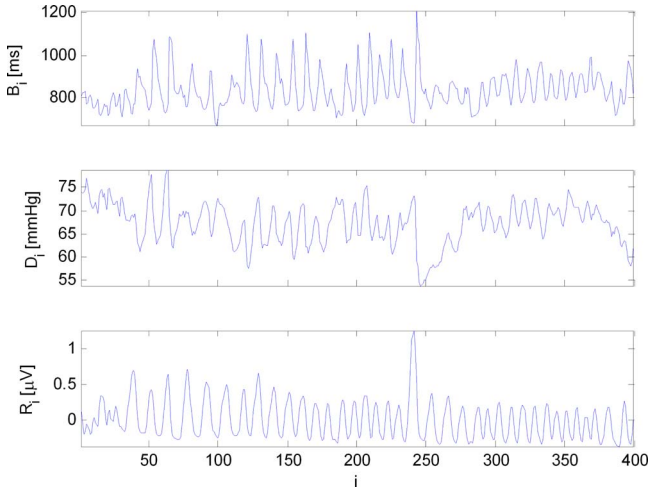

FIG. 2. (Color online) Time series of beat-to-beat interval (B_i), diastolic blood pressure (D_i), and respiration on beat-to-beat basis (R_i) of a healthy person in supine position with normal breathing.

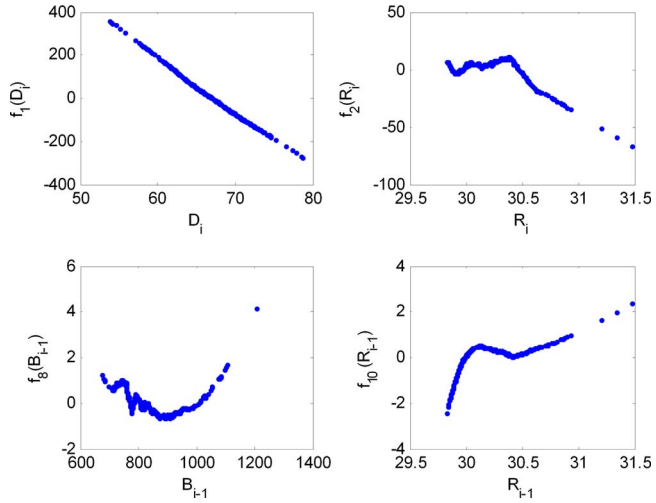

FIG. 3. (Color online) Examples of estimated weight function of the nonlinear additive autoregressive model with external input of beat-to-beat as well as diastolic blood pressure dynamics [Eqs. (1) and (2)].

the current values of S_i, D_i, and R_i are taken into account. The values of each predictor are weighted by a function f_j. The fit of the model includes the selection of relevant predictors and the estimation of their weight function, which could be nonlinear. The algorithm is an iterative nonparametric least squares routine in combination with a cross validation criterion and is called adaptive backfit.[17] The selected predictors of the fitted model of B_i are shown in Eq. (1). Since values of D_i are necessary in Eq. (1), it is also modeled considering the previous values of B_i, S_i, and R_i as well as the current value of R_i [see Eq. (2)],

$$B_i = \bar{B} + f_1(D_i) + f_2(R_i) + f_3(B_{i-1}) + f_4(D_{i-1}) + f_5(R_{i-2}) + f_6(B_{i-4}) + f_7(D_{i-5}) + \varepsilon_i, \quad (1)$$

$$D_i = \bar{D} + f_8(B_{i-1}) + f_9(D_{i-1}) + f_{10}(R_{i-1}) + f_{11}(R_{i-3}) + \mu_i. \quad (2)$$

The first terms $\bar{B}$ and $\bar{D}$ are the mean values of the response variable, which are included because the fitting algorithm is unique except for a constant. ε_i and μ_i represent white noise. Examples of the estimated weight function of the selected predictors are shown in Fig. 3. The coefficients of determination of both fits are 0.96 and 0.91 for the model of B_i and D_i, respectively. If in the fit of B_i only autoregressive and respiratory terms are considered, the coefficient of determination decreases to 0.88. For autoregressive terms only, without external influences, the value decreases again to 0.77. These results demonstrate that the observed unpredictability in the heart rate results from the lack of knowledge of further influences—only a small part remains unexplained in the full model. To test whether the nonlinear cardiorespiratory coupling causes deterministic chaos in the heart rate, B_i is simulated by the fitted models [Eqs. (1) and (2)] in combination of simulated respiration and the original one (Fig. 4). We see that only the complex respiratory patterns lead to complex behavior of the heart rate [Fig. 4(b)]. Additionally, the finite-time growth rates of both simulations with original and artificial respirations are calculated to be 0.12 and −0.002, respectively. The values of the original respiration and heart rate are 0.14 and 0.16, respectively. All these facts show that the complex heart rate fluctuation resulted from a modulation by breathing in this case. This complex respiratory behavior can be explained by the regulation of ventilation. The respiratory rhythm under relaxed conditions is caused by the central respiratory group of the medulla oblongata where neurons of inspiration, postinspiration, and expiration are connected in a complicated manner. Changes of the rhythm are caused by the central and peripheral chemoreflex which controls the *p*H level and the partial pressure of O_2 and CO_2 in the blood by the lung time volume.

In summary, linear and nonlinear parameters are able to separate the given data sets of the three groups completely. Parameters of chaos theory are powerful tools for the description of cardiovascular dynamics; however, they should not act as paradigms—for classification task sometimes linear parameters can achieve similar or even better results. Finding specific parameters for a concrete problem, i.e., for clinical applications, is more important than the question of

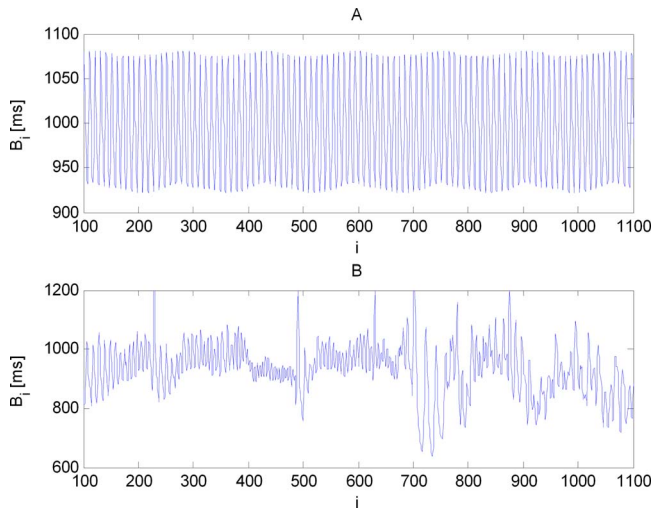

FIG. 4. (Color online) Simulation of the beat-to-beat intervals using a harmonic oscillation as (a) respiratory curve or (b) the original signal in the fitted model [Eqs. (1) and (2)]

"chaotic" origins. For the understanding of mechanisms of cardiovascular dynamics, however, the theory of deterministic chaos becomes more important. It provides fundamental mathematical concepts, such as phase space, attractors, stability, and bifurcation analysis to characterize these complex systems.[18] Specifically, these methods enable us to categorize and understand complex behavior of the cardiovascular system. But the initial questions of this controversial topic ("Is the normal heart rate chaotic?") can only be answered satisfactorily by investigating the underlying mechanisms. Our example shows that this has to be done by multivariate approaches, which include almost all relevant influences of heart rate fluctuations, e.g., respiration and/or physical, mental, as well as metabolic activity. Therefore, the initial question should be reformulated: "Is the normal heart rate 'chaotic' due to external influences?"

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