# Autonomic control is a source of dynamical chaos in the cardiovascular system

Cite as: Chaos **29**, 121101 (2019); https://doi.org/10.1063/1.5134833 Submitted: 06 November 2019 . Accepted: 22 November 2019 . Published Online: 11 December 2019

A. S. Karavaev 🝺, Yu. M. Ishbulatov ២, V. I. Ponomarenko ២, B. P. Bezruchko ២, A. R. Kiselev ២, and M. D. Prokhorov ២







ENTER CODE **50DEC19** AT CHECKOUT

Chaos 29, 121101 (2019); https://doi.org/10.1063/1.5134833 © 2019 Author(s).

#### ARTICLE

# Autonomic control is a source of dynamical chaos in the cardiovascular system

Cite as: Chaos **29**, 121101 (2019); doi: 10.1063/1.5134833 Submitted: 6 November 2019 · Accepted: 22 November 2019 · Published Online: 11 December 2019



A. S. Karavaev,<sup>1,2,3</sup> (D) Yu. M. Ishbulatov,<sup>1,2</sup> (D) V. I. Ponomarenko,<sup>1,3</sup> (D) B. P. Bezruchko,<sup>1,3</sup> (D) A. R. Kiselev,<sup>2,3</sup> (D) and M. D. Prokhorov<sup>1</sup> (D)

## AFFILIATIONS

<sup>1</sup>Saratov Branch of the Institute of Radio Engineering and Electronics of Russian Academy of Sciences, Zelyonaya Street, 38, Saratov 410019, Russia

<sup>2</sup>Department of Innovative Cardiological Information Technology, Institute of Cardiological Research, Saratov State Medical University, B. Kazachaya Street, 112, Saratov 410012, Russia

<sup>3</sup>Department of Dynamic Modeling and Biomedical Engineering, Saratov State University, Astrakhanskaya Street, 83, Saratov 410012, Russia

# ABSTRACT

The origin of complex irregular dynamics in a cardiovascular system is still being actively debated. Some hypotheses suggest the crucial role of stochastic modulation of cardiovascular parameters, while others argue for the importance of cardiac pacemakers' chaotic deterministic dynamics. In the present study, we estimate the largest Lyapunov exponent and the correlation dimension for the 4-h experimental interbeat intervals and the chaotic signals generated by the mathematical model of the cardiovascular system. We study the complexity of the mathematical model for such cases as the autonomic blockade, the exclusion of all the stochastic components, and the absence of variability of respiration. The obtained results suggest that the complexity of the heart rate variability is largely due to the chaotic dynamics in the loops of autonomic control of circulation.

Published under license by AIP Publishing. https://doi.org/10.1063/1.5134833

The origin of the complexity in heart rate dynamics is an intriguing issue that has been discussed for over 20 years. The particular importance of this problem is emphasized by well-known experimental studies, which showed that the degree of complexity of heart rate variability (HRV) can be used as an indicator of cardiovascular health. Usually, a high irregularity of the heart rhythm is typical for healthy subjects, and in patients with diseases of the cardiovascular system (CVS), the complexity of the dynamics of the heart rhythm decreases. A number of hypotheses have been proposed to explain this phenomenon. Some of them explain the complex irregular dynamics of the heart rhythm by stochastic influences of various nature. According to other hypotheses, the origin of complexity in the dynamics of the cardiovascular system is the process of respiration. The role of autonomic control in the complex dynamics of the cardiovascular system is still being discussed. To study the origin of the complex dynamics of the cardiovascular system, we analyzed both the long experimental records of the intervals between heart beats of healthy subjects and the signals from the mathematical model of cardiovascular system that we proposed earlier. We revealed that the irregularity in heart rate variability originates not only from the stochastic influence but also from the chaotic dynamics of autonomic control of heart rate. The obtained results allow us to better understand the operation of cardiovascular system and the origin of its irregular dynamics. The results can be potentially useful for medical diagnostics of the state of the cardiovascular system.

#### INTRODUCTION

The study aims to investigate complex nonlinear dynamics of cardiovascular system (CVS) that manifests itself in heart rate and arterial pressure (AP) irregularity. Some investigators suggest that irregular dynamics of heart rate variability (HRV) and AP signals can be attributed solely to stochastic interference in CVS (Turcott *et al.*, 1996; Kaplan *et al.*, 1990; Kanters *et al.*, 1994). Suggested origins of interference are, for example, stochastic modulation of CVS parameters (Ivanov *et al.*, 1998) or "central" dynamical noise (Bunde *et al.*, 2000; Togo *et al.*, 2001). However, many researchers inclined to see the origin of CVS irregularity in nonlinear dynamics and development of relatively low-dimensional deterministic chaos (Glass *et al.*, 1988; Pool, 1989; Barahona *et al.*, 1996).

Meanwhile, many researchers have reported the presence of complex dynamics in CVS signals of healthy subjects and patients without cardiac tissue impairments. The origin of such behavior and the preferred method of quantification of complex CVS dynamics are heavily debated. Active discussion is held around the role of respiration in forming of complex dynamics (Wessel et al., 2009). Some researchers assume that the autonomic control of circulation can be the source of chaotic dynamics (Wagner et al., 1998; Porta et al., 2017). Ernst (2017) and a number of other authors suggest that complex CVS dynamics is caused mostly by the influence from higher brain center onto autonomic control. Clemson et al. (2014) hypothesize that the combination of previously mentioned factors is necessary. The revealing of origins of irregularity in CVS signals is important for understanding the process of blood circulation and applications in clinical medicine (Wessel et al., 2009; Pavlov et al., 2000; Goldberger, 1996).

A lot of studies are dedicated to the development of chaotic dynamics in heart itself. It was shown that the chaotic behavior of the heart is due to spiral waves and activity patterns caused by disturbances in mechanical and conductive properties of cardiac tissue. Most commonly, aforementioned disturbances are symptoms of pathologic processes and associated with acute arrhythmia. Such phenomena were extensively studied in human and animal studies and in mathematical models and biological models, such as isolated heart (Bittihn *et al.*, 2017; Krogh-Madsen *et al.*, 2017; Gomes *et al.*, 2017; Guevara *et al.*, 1981).

It was shown that the degree of CVS complexity correlates with the physiological condition (Valente et al., 2018; Porta et al., 2017; Dimitriev et al., 2016; Shiogai et al., 2010; Anishchenko et al., 1993). It can be applied in medical diagnostics and treatment of various diseases (Lerma et al., 2017; Denton et al., 1990; Ivanov et al., 1999). However, the problem is yet to be solved, despite a long history of the debates. Some researchers are skeptical about the validity of nonlinear complexity measures estimated from experimental data since real CVS signals are noisy and typically short. Aforementioned problems lead to large errors in the estimation of complexity measures and complicate the interpretation of the results (Valente et al., 2018; Tan et al., 2013; Bezerianos et al., 1995; Glass et al., 1990). A promising way of solving these issues is to study the signals from mathematical models of CVS. However, reliable results can be obtained only from models that are developed from the first principles, simulate the structure of real CVS, and have physically meaningful parameters.

To model the complex dynamics of a healthy CVS, we decided to focus on autonomic control of circulation. Cavalcanti and Belardinelli (1996) proposed the CVS model in the form of three differential equations with delay to represent autonomic control. They demonstrated that with an increase in delay time, the Hopf bifurcation occurs and stable focus goes into limit cycle. Further increase in delay time leads to a cascade of period-doubling bifurcations and chaotic dynamics. However, this model cannot be applied to the problem under study since the parameters of the model are nonphysiological that was criticized by Vielle (2005).

Based on the study of Seidel and Herzel (1998), Kotani *et al.* (2005) proposed the CVS model with physiological parameters and the ability to exhibit stable oscillations and chaotic dynamics. However, in this model (Kotani *et al.*, 2005), the loops of autonomic control of mean arterial pressure and heart rate are represented by

nonautonomous linear relaxation oscillators with delay. This simplification makes it impossible to simulate some experimentally observed phenomena (Karavaev *et al.*, 2009; 2018), in particular, the synchronization between the autonomic control loops and respiration with linearly increasing frequency. The importance of cardiorespiratory coupling was reported in Wessel *et al.* (2009), Schäfer *et al.* (1998; 1999), and Hramov *et al.* (2007). Other known experimental studies (Ringwood *et al.*, 2001; Burgess *et al.*, 1997) argue for the nonlinear and self-exciting nature of circulation autonomic control.

We have proposed a modified mathematical CVS model based on Kotani *et al.* (2005) that takes into account the nonlinear properties of autonomic control. The modified model demonstrates better agreement with the experimental data and explains the experimentally observed nonlinear phenomena (Karavaev *et al.*, 2016; Ishbulatov *et al.*, 2017).

This study aims to provide a quantitative analysis of CVS complex nonlinear dynamics and investigate its origins through a comparison between the signals of the CVS mathematical model and the 4-h experimental records of interbeat intervals.

# **EXPERIMENTAL DATA**

To study the complex dynamics of CVS, we analyze 4-h experimental electrocardiogram (ECG) records of five healthy subjects (four males and one female, ages 20-25 years). All the subjects signed a written consent. The experimental studies were performed in accordance with the Declaration of Helsinki and approved by the local research Ethics Committee of the Saratov Research Institute of Cardiology (Saratov, Russia). All experimental signals were recorded using the standard electroencephalograph analyzer EEGA-21/26 "Encephalan-131-03" (Medicom MTD Ltd., Taganrog, Russia) (http://medicom-mtd.com/en/products/eega.html). The signals were recorded from 2 p.m. to 6 p.m. at rest, when the subjects were lying in a quiet, dimly lit room with temperature control, at least 2 h after the last meal. The subjects were breathing spontaneously. All signals were sampled at 250 Hz and digitized at 14 bits. The record of respiration was used to control evenness of breathing. Sections of the records containing artifacts were carefully excluded from the analysis.

Heart rate variability (HRV) was measured from the experimental data as it is recommended in Task Force of the European Society of Cardiology and the North American Society of Pacing Electrophysiology (1996); sequences of RR intervals, i.e., the series of time intervals between the two successive R peaks in ECG. Then, the RR intervals were interpolated via cubic  $\beta$ -splines, resampled at 5 Hz, and filtered with the 0.05–0.40 Hz bandpass filter to extract the signals of heart rate and vascular tone autonomic control. We use these signals throughout the paper for the analysis. The parameters of the experimental data are presented in Table I.

#### MATHEMATICAL MODEL

The mathematical model proposed by us in Karavaev *et al.* (2016) is based on the Kotani *et al.* (2005) and Seidel *et al.* (1998) models. The model simulates the following processes: main heart rate, baroreflectory control of heart rate and heart contractility, and forming of arterial pressure (AP) during the cardiac contraction and

**TABLE I.** Parameters of the experimental data.

Signal type	RR intervals
Length (h)	4
Number of patients	5
Age (years)	20-25
Resampling frequency (Hz)	5
Resolution (bits)	14
Filtration band (Hz)	0.05 - 0.40

cardiac filling phases. The model also simulates the influence of respiration on the aforementioned processes. The structure of the model is presented in Fig. 1.

The model consists of four first-order differential equations with a time delay. To model the respiration, we used a sinusoidal signal with stochastic modulation of frequency (see the supplementary material). We introduced the stochastic component [see Eq. (1) in the supplementary material] to simulate the processes excluded from the model, namely, the dynamical noise of central origin (Bunde *et al.*, 2000; Togo *et al.*, 2001) and low-frequency (LF) CVS humoral control. The detailed description of the model is given in the supplementary material.

# METHODS

To investigate complex chaotic dynamics of both the experimental and model cardiovascular signals, we applied several



FIG. 1. Structure of the mathematical model. Blocks indicated with solid bold red rectangles represent the heart rate sympathetic control. Blocks indicated with solid blue rectangles represent the heart rate parasympathetic control. Blocks indicated with dashed bold red rectangles represent the sympathetic control of the vascular tone.

techniques of chaos theory, namely, the estimation of fractal dimension from the correlation integral (Grassberger *et al.*, 1983) and calculation of the largest Lyapunov exponent (Rosenstein *et al.*, 1993). The analysis of the experimental and model signals involves the reconstruction of attractor from a single time series. We used the method of delays as it is recommended in Rosenstein *et al.* (1993).

The correlation dimension d was estimated from the correlation integral C(l) (Grassberger *et al.*, 1983) defined as

$$C(l) = \lim_{N \to \infty} \frac{n(l)}{N^2},$$
(1)

where n(l) is the number of points of the reconstructed attractor, for which the Euclidean distance to the nearest neighbor is smaller than *l*. The values of *l* are varied in the range of 0.1–0.3 of the standard deviation of RR intervals. *N* is the number of points used for calculation. We used N = 5000 throughout the paper. For dynamical systems,  $C(l) \sim l^d$  and *d* can be estimated as

$$d = \frac{\ln(C(l))}{\ln(l)}.$$
(2)

To estimate the largest Lyapunov exponent, we used the Rosenstein algorithm (Rosenstein *et al.*, 1993) since it can be applied to short time series. The first step of the Rosenstein algorithm is to find the nearest neighbor for each point of the reconstructed attractor. The close in time neighbors should be excluded from the analysis (Rosenstein *et al.*, 1993). For dynamical systems, the mean rate of separation of the nearest neighbors obeys the following equation:

$$\ln(L) \approx \ln(L_0) + \lambda_0 t, \tag{3}$$

where  $L_0$  is the initial distance,  $\lambda_0$  is the largest Lyapunov exponent, and *t* is the time of calculation. The time t = 0.6 s corresponds to the time of the linear law of separation of the nearest neighbors.  $\lambda_0$  is calculated as follows:

$$\lambda_0 = \frac{\langle \ln(L) \rangle}{t}.$$
 (4)

The parameter values used for the calculation of correlation dimension and the largest Lyapunov exponent are presented in Table II.

# COMPARISON OF MODEL AND EXPERIMENTAL DATA

In Fig. 2, typical time series and power spectra of RR intervals are presented for a healthy subject and the mathematical model of CVS.

The low-frequency (LF) rhythms associated with the heart rate sympathetic control are observed in the 0.05–0.15 Hz band of the model power spectrum. In the model and experimental signals, these rhythms correspond to the self-exciting dynamics of the sympathetic control of vascular tone and heart rate (Seidel *et al.*, 1998; Ringwood *et al.*, 2001). The high-frequency (HF) rhythms associated with the respiration and the parasympathetic control of heart rate are observed in the 0.15–0.40 Hz band (Task Force of the European Society of Cardiology and the North American Society of Pacing Electrophysiology, 1996). It is seen in Fig. 2(b) that HF peak in the model power spectrum agrees well with the HF peak in the power spectrum of the experimental signal. However, the width of the LF peak in the model is narrower than in the experiment.

Calculation of correlation dimension		Calculation of the largest Lyapunov exponent		
Embedding dimension	13	Embedding dimension	13	
τ (s)	0.04	$\tau$ (s)	1	
l	0.1-0.3	<i>t</i> (s)	0.6	
Window lengths (s)	1000	Window lengths (s)	1000	

**TABLE II.** Parameters of the methods for calculating the correlation dimension and the largest Lyapunov exponent.  $\tau$  is the delay used to reconstruct the embedding space with the delay method, and *l* is the maximal Euclidian distance between the nearest neighbors normalized to the standard deviation of the filtered RR intervals.

# RESULTS

Reliability of complexity indices estimated from the experimental CVS data highly depends on the algorithm of embedding space reconstruction and embedding dimension. For the reconstruction of embedding space, we used the popular delay method with delays defined as time, within which the autocorrelation function decreases by a factor of *e* (Rosenstein *et al.*, 1993). Average delay estimated from experimental data was 1.0 s. This value was used for all calculations in our paper.

The problem of choosing the embedding dimension for the signal of vascular tone autonomic control extracted from RR intervals using the bandpass filtration has not been discussed in the literature. The embedding dimension of the nonfiltered RR intervals was estimated to be 3 (Skinner et al., 1990), 4 (Dimitriev et al., 2016), and even 5 (Negoescu et al., 1993). According to the delay embedding theorem (Takens, 1981; Sauer et al., 1991), a chaotic dynamical system can be reconstructed from a sequence of observations of the state of a dynamical system if the attractor is embedded in the Euclidean space with the dimension  $D > 2D_0$ , where  $D_0$  is the box counting dimension. It has been shown that one can use the embedding dimension  $D = D_0 + 1$  for the calculation of fractal dimension (Sauer *et al.*, 1991; 1993). However, the authors noted that in this case, the selfcrossing of the phase trajectories is possible and recommended to specify the theoretical estimations with the further empirical test for each particular system. In our study, we calculate the largest Lyapunov exponent from the 4-h experimental RR intervals filtered in the bandpass 0.05-0.40 Hz for dimensions varied from 7 to 25. The obtained results are shown in Fig. 3.

As can be seen in Fig. 3(a), the increase of *D* leads to the saturation of the largest Lyapunov exponent value. With an increase of *D* from 7 to 13, the standard deviation of the largest Lyapunov exponent  $\sigma(\lambda_0)$  monotonically decreases, Fig. 3(b). For  $D \ge 13$ , the values of  $\sigma(\lambda_0)$  fluctuate around a constant value. Therefore, for further calculations, we choose the embedding dimension D = 13.

The more reliable estimation of the complexity measures requires the time series containing tens and hundreds of characteristic oscillation periods. However, the technical and ethical reasons limit the possible length of experimental signals. Moreover, in Sharma *et al.* (2009), it was noted that nonstationarity of the experimental data can have a significant effect on the complexity indices. To achieve better reliability of the results, we used 1500-s windows (150 characteristic periods of the sympathetic control loop) of the time series.

Nonstationarity and variation of the largest Lyapunov exponent were analyzed during its estimation in the windows of different lengths (200–2000 s). Typical dependence of the largest Lyapunov exponent on the length of the analyzed window is presented in Fig. 4(a). No trends can be seen in the time dependences of  $\lambda_0$  in Fig. 4(a). This result suggests the relative stationarity of  $\lambda_0$  during the 4-h study conducted in healthy resting subjects.

It is evident that the estimation of the largest Lyapunov exponent in shorter windows leads to lower values and greater variation. Figure 4(b) shows the dependence of coefficient of variation (CV) (percentage of the ratio of the mean value to the standard deviation) of  $\lambda_0$  on the length of the experimental time series used for the calculation. It is seen from Fig. 4(b) that the estimation of the largest Lyapunov exponent from the time series of greater duration is more stable. The obtained results suggest that 1000-s windows are reasonable for calculation of the largest Lyapunov exponent. Such lengths of the windows were used further in the paper.

The proposed mathematical model allows us to conduct a series of numerical simulations, in which the largest Lyapunov exponent  $\lambda_0$ and the correlation dimension *d* were calculated under a number of specific conditions (Fig. 5). The obtained results were compared with the complexity indices of CVS system in healthy subjects.

We considered the following situations:

(1) The noise of central origin is excluded from the heart rate [see Eq. (1) in the supplementary material]. The respiration is





Chaos **29**, 121101 (2019); doi: 10.1063/1.5134833 Published under license by AIP Publishing.



FIG. 3. (a) Estimation of the largest Lyapunov exponent from the 4-h experimental filtered RR intervals for different embedding dimensions *D*. Whiskers represent the standard deviation. (b) Standard deviation of the largest Lyapunov exponent for different embedding dimensions.

modeled as a sinusoidal signal with a constant frequency (see the supplementary material). This case is denoted as Model No Noise (MNN).

- (2) The model under the autonomic blockade. We excluded the parasympathetic control of heart rate [see Eq. (1) in the supplementary material] and sympathetic control of heart rate [see Eq. (1) in the supplementary material], heart contractility [see Eq. (3) in the supplementary material], and vessels tone [see Eq. (5) in the supplementary material]. This case is denoted as Model under Autonomic Blockade (MAB).
- (3) The model in which the respiration is modeled as a sinusoidal signal (see the supplementary material). This case is denoted as Model No Respiration Variability (MNRV).
- (4) The model containing experimental signal of respiration (see the supplementary material). This case is denoted as Model Experimental Respiration (MER).

The values of the largest Lyapunov exponent and the correlation dimension estimated from the experimental signals (E) are  $0.027 \pm 0.005$  (mean  $\pm$  standard deviation) and  $2.185 \pm 0.146$ , respectively, see Fig. 5. For the model signals (M), the largest Lyapunov exponent and the correlation dimension take the values  $0.029 \pm 0.002$  and  $2.234 \pm 0.023$ , respectively. These results confirm complex, irregular nature of the experimental and model CVS signals.

The model without stochastic components (MNN in Fig. 5) also demonstrates a chaotic behavior:  $\lambda_0$  is positive (0.0024  $\pm$  0.0008) and d is a noninteger and greater than 2 (2.014  $\pm$  0.004). These results suggest that irregularity of human HRV is caused by dynamical chaos in CVS that originates from the loops of autonomic control of circulation. With respect to the model of a healthy subject, the model under autonomic blockade (MAB in Fig. 5) demonstrates higher values

of the largest Lyapunov exponent ( $0.048 \pm 0.004$ ). Also, the correlation dimension is higher for the MAB model ( $2.547 \pm 0.017$ ) that agrees well with the experimental observations (Porta *et al.*, 2017), suggesting the stabilizing role of CVS autonomic control.

A number of research studies suggest that the respiration plays an important role in generation of irregular CVS dynamics (Wessel *et al.*, 2009). We investigated this hypothesis by conducting two numerical experiments: without the stochastic modulation of the respiration rate (MNRV in Fig. 5) and with the experimental signal of respiration introduced to the model (MER in Fig. 5). The obtained indices of complexity ( $\lambda_0 = 0.032 \pm 0.002$  and  $d = 2.276 \pm 0.016$  for the MNRV model and  $\lambda_0 = 0.028 \pm 0.002$  and  $d = 2.224 \pm 0.018$  for the MER model) showed no significant changes with respect to the original model (M in Fig. 5). Therefore, the obtained results do not support the hypothesis about the significance of the respiration in generation of CVS complexity that agrees well with the results from Eduardo *et al.* (2016).

# DISCUSSION

Origins and characteristics of the complex nonlinear CVS dynamics are subjects of active debates. Many questions are not solved yet despite high researcher's interest and importance of the system. The present study is aimed to solve some problems that were outlined in the earlier papers. Draghici and Taylor (2016), Tan *et al.* (2013), and others pointed out that most of the studies are conducted with 5–10 min experimental signals, which are too short for the reliable estimation of the largest Lyapunov exponent and the fractal dimension. For example, Sharma mentions in Sharma *et al.* (2009) that artifacts in experimental data can lead to an incorrect result. In Kamalesh *et al.* (1995), the nonstationarity of experimental data was mentioned to cause difficulties in estimation of the complexity measures.



**FIG. 4.** Estimation of the largest Lyapunov exponent in windows of different lengths. (a) Typical time dependences of the largest Lyapunov exponent calculated in nonoverlapping windows of the experimental time series. Dashed line, thin line, bold red line, and dotted line are plotted using 200-s, 500-s, 1000-s, and 2000-s windows, respectively. (b) Dependence of coefficient of variation of  $\lambda_0$  on the window length.

Chaos 29, 121101 (2019); doi: 10.1063/1.5134833 Published under license by AIP Publishing.





The promising approach to study CVS nonlinear dynamics is the mathematical modeling. However, an adequate mathematical model is necessary to obtain reliable results. The model should resemble the real system in structure, have physically meaningful parameters, and be capable of quantitative and qualitative simulation of experimental data and phenomena. In our model, we took into account the influence of respiration and loops of autonomic control of circulation, which can be the origin of CVS complexity (Shiogai *et al.*, 2010; Wessel *et al.*, 2009; Kaplan *et al.*, 1991).

We used the mathematical model of CVS (Karavaev *et al.*, 2016; Ishbulatov *et al.*, 2017), in which much attention is given to the CVS autonomic control loops, which are modeled using nonlinear selfexciting loops. Earlier we demonstrated that this approach resulted in better (in comparison to other models of similar complexity and structure) simulation of the spectral and statistical properties of the experimental data. Taking into account the nonlinear control loops, it is possible to simulate the synchronization between the loops of autonomic control (Karavaev *et al.*, 2016; Ishbulatov *et al.*, 2017).

From the stationary, noiseless, and long model time series, we were able to reliably estimate the widespread complexity measures, namely, the largest Lyapunov exponent and correlation dimension. Using the model, we were also able to estimate the influence of the dynamical noises and the various CVS subsystems on the complexity. To verify the model, we compared the model signals with the 4-h experimental interbeat intervals recorded from healthy subjects under resting conditions. Reliability of the complexity indices estimated from the experimental data is verified by their reproducibility for each patient and through the group of patients and good correspondence to the other experimental studies. Therefore, CVS nonstationarity seems to not affect the complexity indices in our experimental study.

In Tan *et al.* (2013), it was pointed out that CVS complexity may change after the pharmacological blockade of the CVS autonomic control. However, the experimental study by Tan *et al.* (2013) could not provide reliable confirmation. In our model, the autonomic blockade resulted in significant changes in the complexity indices (MAB in Fig. 5).

The analysis of experimental data can give positive values of the largest Lyapunov exponent and noninteger value of correlation dimension because of the stochastic factors. Therefore, some researchers (Turcott *et al.*, 1996; Kanters *et al.*, 1994; Costa *et al.*, 1999) are skeptical about the presence of the dynamical chaos in CVS. However, in the model, we eliminated all sources of dynamical noises and still obtained a positive value of the largest Lyapunov exponent and noninteger value of correlation dimension (MNN in Fig. 5).

The results of the numerical simulations with the MNN model and the small role of the respiration in CVS complexity (MNRV and MER models in Fig. 5) suggest that the chaotic dynamics of CVS autonomic control loops is the origin of HRV irregularity. Close correspondence between the model and experimental complexity indices argues for the adequacy of the model and allows extrapolation of the model data to the real system.

The noninteger values of the correlation dimension and small positive values of the largest Lyapunov exponent obtained in our study indicate the presence of weak dynamical chaos in the dynamics of CVS. Although the absolute values of the largest Lyapunov exponent are small, they exhibit the statistically significant changes during the physiological tests and significantly differ in healthy subjects and patients with pathologies of CVS.

In this study, we revealed the leading role of autonomic control of circulation in the development of the chaotic dynamics in CVS. The obtained results suggest that the chaotic dynamics of autonomic control provides the flexible adjustment of CVS to different external conditions and pathological changes. The complexity indices calculated from the dynamics of autonomic control of circulation contain useful information for the assessment of the state of the cardiovascular system.

We agree with the physiological interpretation of the complexity of the heart rate variability given in Task Force of the European Society of Cardiology and the North American Society of Pacing Electrophysiology (1996) and Shaffer *et al.* (2017) and support the opinion that the complexity of HRV is a reflection of the organism adaptation to changing external conditions. A chaotic system can change its properties faster and within wider ranges than a periodic system, under the same change in control parameters.

The reliable estimations of the largest Lyapunov exponent and the correlation dimension of the autonomic control dynamics required the surprisingly high embedding dimension D=13. Probably, such high value of *D* is explained by the complexity of the chaotic dynamics in the loops of autonomic control of circulation, which was modeled by delay-differential equations in a number of studies (Seidel *et al.*, 1998; Ringwood *et al.*, 2001; Kotani *et al.*, 2005).

It should be noted that mathematical modeling of biological objects is always a compromise between the completeness of the model and its complexity, which is increased critically when additional factors are introduced into the model. The proposed model proved that the introduction of the nonlinear self-exciting loops of CVS autonomic control into the model is enough for qualitative explanation and quantitative simulation of the CVS dynamical chaos. Moreover, the central noise makes a significant contribution to the complexity. Therefore, in accordance with Shiogai *et al.* (2010) and Karavaev *et al.* (2018), further development of the proposed model requires the introduction of the higher nervous activity influence on the autonomic control (Van Roon *et al.*, 2004).

#### CONCLUSION

The complexity of the CVS mathematical model has been numerically studied for a number of cases. The cases of the absence of dynamical noises of various origins, the presence of blockade of circulation autonomic control, the absence of variability in respiration rate, and the introduction of the experimental respiratory signal into the model have been considered. Calculation of the largest Lyapunov exponent and the correlation dimension have shown that chaotic dynamics of CVS autonomic control loops has a significant role in the origin of HRV irregularity. The stochastic components that model the dynamical noise of central origin also give a significant contribution to CVS complexity, resulting in higher values of the largest Lyapunov exponent and correlation dimension.

The comparison between 4-h experimental and model interbeat intervals showed good correspondence between them. It confirms the reliability of obtained estimations of the complexity indices and adequacy of the proposed model. However, further development of the model requires the introduction of the higher nervous activity influence on the autonomic control.

#### SUPPLEMENTARY MATERIAL

See the supplementary material for the detailed description of the mathematical model of cardiovascular system and the table of the model parameters.

#### ACKNOWLEDGMENTS

This work was supported by the Russian Science Foundation under Grant No. 19-12-00201.

#### REFERENCES

- Anishchenko, V. S., Saparin, P. I., and Igosheva, N. B., "Diagnostic of human being and mental condition on the basis of electrocardiogram analysis by methods of chaotic dynamics," Proc. SPIE 1981, 141–150 (1993).
- Barahona, M. and Poon, C.-S., "Detection of nonlinear dynamics in short, noisy time series," Nature 381, 215–217 (1996).
- Bezerianos, A., Bountis, T., Papaioannou, G., and Polydoropoulos, P., "Nonlinear time series analysis of electrocardiograms," Chaos **5**, 95–101 (1995).

- Bittihn, P., Berg, S., Parlitz, U., and Luther, S., "Emergent dynamics of spatiotemporal chaos in a heterogeneous excitable medium," Chaos 27, 093931 (2017).
- Bunde, A., Havlin, S., Kantelhardt, J. V., Penzel, T., Peter, J.-H., and Voigt, K., "Correlated and uncorrelated regions in heart-rate fluctuations during sleep," Phys. Rev. Lett. 85, 3736 (2000).
- Burgess, D. E., Hundley, J. C., Brown, D. R., Li, S.-G., and Randal, D. C., "Firstorder differential-delay equation for the baroreflex predicts the 0.4-Hz blood pressure rhythm in rats," Am. J. Physiol. 273, R1878–R1884 (1997).
- Cavalcanti, S. and Belardinelli, E., "Modeling of cardiovascular variability using a differential delay equation," IEEE Trans. Biomed. Eng. 43, 982–989 (1996).
- Clemson, P. T. and Stefanovska, A., "Discerning non-autonomous dynamics," Phys. Rep. **542**, 297–368 (2014).
- Costa, M., Iveta, R., Santiago, T., Sarreira, P., Melo, J., and Ducla-Soares, E., "No evidence of chaos in the heart rate variability of normal and cardiac transplant human subjects," J. Cardiovasc. Electrophysiol. 10, 1350–1357 (1999).
- Denton, T. A., Diamond, G. A., Helfant, R. H., Khan, S., and Karagueuzian, H., "Fascinating rhythm: A primer on chaos theory and its application to cardiology," Am. Heart J. 120, 1419–1440 (1990).
- Dimitriev, D. A., Saperova, E. V., and Dimitriev, A. D., "State anxiety and nonlinear dynamics of heart rate variability in students," PLoS ONE 11, e0146131 (2016).
- Draghici, A. E. and Taylor, J. A., "The physiological basis and measurement of heart rate variability in humans," J. Physiol. Anthropol. 35, 22 (2016).
- Eduardo, L., Silva, V., Lataro, R. M., Castania, J. A., da Silva, C. A. A., Valencia, J. F., Murta, L. O., Salgado, H. C., Fazan, R., and Porta, A., "Multiscale entropy analysis of heart rate variability in heart failure, hypertensive, and sinoaortic-denervated rats: Classical and refined approaches," Am. J. Physiol. Regul. Integr. Comp. Physiol. **311**, R150–R156 (2016).
- Ernst, G., "Heart-rate variability—More than heart beats?," Front. Public Health 5, 240 (2017).
- Glass, L., "Chaos and heart rate variability," J. Cardiovasc. Electrophysiol. 10, 1358–1360 (1990).
- Glass, L. and Mackey, M. C., From Clocks to Chaos the Rhythms of Life (Princeton University Press, Princeton, NJ, 1988), p. 248.
- Goldberger, A. L., "Nonlinear dynamics for clinicians: Chaos theory, fractals, and complexity at the bedside," Lancet 347, 1312–1314 (1996).
- Gomes, J. M., dos Santos, R. W., and Cherry, E. M., "Alternans promotion in cardiac electrophysiology models by delay differential equations," Chaos 27, 093915 (2017).
- Grassberger, P. and Procaccia, I., "Measuring the strangeness of strange attractors," Physica D 9, 189–208 (1983).
- Guevara, M. R., Glass, L., and Shrier, A., "Phase locking, period doubling bifurcations and irregular dynamics in periodically stimulated cardiac cells," Science 214, 1350–1353 (1981).
- Hramov, A. E., Koronovskii, A. A., Ponomarenko, V. I., and Prokhorov, M. D., "Detection of synchronization from univariate data using wavelet transform," Phys. Rev. E 75, 056207 (2007).
- Ishbulatov, J. M., Karavaev, A. S., Ponomarenko, V. I., Kiselev, A. R., Sergeev, S. A., Seleznev, Y. P., Bezruchko, B. P., and Prokhorov, M. D., "Phase synchronization of elements of autonomic control in mathematical model of cardiovascular system," J. Nonlinear Dyn. 13, 381–397 (2017) (Russian).
- Ivanov, P. C., Amaral, L. A. N., Goldberger, A. L., Havlin, S., Rosenblum, M. G., Struzik, Z. R., and Stanley, H. E., "Multifractality in human heartbeat dynamics," Nature 399, 461–465 (1999).
- Ivanov, P. C., Amaral, L. A., Goldberger, A. L., and Stanley, H. E., "Stochastic feedback and the regulation of biological rhythms," *Europhys. Lett.* 43, 363–368 (1998).
- Kamalesh, M., Burger, A. J., Kumar, S., and Nesto, R., "Reproducibility of time and frequency domain analysis of heart rate variability in patients with chronic stable angina," Pacing Clin. Electrophysiol. 18, 1991–1994 (1995).
- Kanters, J. K., Holstein-Rathlou, N. H., and Agner, E., "Lack of evidence for low-dimensional chaos in heart rate variability," J. Cardiovasc. Electrophysiol. 5, 591–601 (1994).
- Kaplan, D. T. and Cohen, R. J., "Is fibrillation chaos?," Circ. Res. 67, 886–892 (1990).

- Kaplan, D. T. and Talajic, M., "Dynamics of heart rate," Chaos 1, 251 (1991).
- Karavaev, A. S., Ishbulatov, J. M., Ponomarenko, V. I., Prokhorov, M. D., Gridnev, V. I., Bezruchko, B. P., and Kiselev, A. R., "Model of human cardiovascular system with a loop of autonomic regulation of the mean arterial pressure," J. Am. Soc. Hypertens. 10, 235–243 (2016).
- Karavaev, A. S., Kiselev, A. R., Runnova, A. E., Zhuravlev, M. O., Borovkova, E. I., Prokhorov, M. D., Ponomarenko, V. I., Pchelintseva, S. V., Efremova, T. Y., Koronovskii, A. A., and Hramov, A. E., "Synchronization of infra-slow oscillations of brain potentials with respiration," Chaos 28, 081102 (2018).
- Karavaev, A. S., Prokhorov, M. D., Ponomarenko, V. I., Kiselev, A. R., Gridnev, V. I., Ruban, E. I., and Bezruchko, B. P., "Synchronization of low-frequency oscillations in the human cardiovascular system," Chaos 19, 033112 (2009).
- Kotani, K., Struzik, Z. R., Takamasu, K., Stanley, H. E., and Yamamoto, Y., "Model for complex heart rate dynamics in health and disease," Phys. Rev. E 72, 041904 (2005).
- Krogh-Madsen, T., Taylor, L. K., Skriver, A. D., Schaffer, P., and Guevara, M. R., "Regularity of beating of small clusters of embryonic chick ventricular heartcells: Experiment vs stochastic single-channel population model," Chaos 27, 093929 (2017).
- Lerma, C., Echeverría, J. C., Infante, O., Pérez-Grovas, H., and González-Gómez, H., "Sign and magnitude scaling properties of heart rate variability in patients with endstage renal failure: Are these properties useful to identify pathophysiological adaptations?," Chaos 27, 093906 (2017).
- Negoescu, R., Skinner, J. E., and Wolf, S., "Forebrain regulation of cardiac function spectral and dimensional analysis of RR and QT intervals," Integr. Physiol. Behav. Sci. 28, 331–342 (1993).
- Pavlov, A. N., Janson, N. B., Anishchenko, V. S., Gridnev, V. I., and Dovgalevsky, P. Y., "Diagnostic of cardio-vascular disease with help of largest Lyapunov exponent of RR-sequences," Chaos Soliton Fractals 11, 807 (2000).
- Pool, R., "Is It healthy to Be chaotic?," Science 243, 604-607 (1989).
- Porta, A., Bari, V., Ranuzzi, G., De Maria, B., and Baselli, G., "Assessing multiscale complexity of short heart rate variability series through a model-based linear approach," Chaos 27, 093901 (2017).
- Ringwood, J. V. and Malpas, S. C., "Slow oscillations in blood pressure via a nonlinear feedback model," Am. J. Physiol. Regul. Integr. Comp. Physiol. 280, R1105–R1115 (2001).
- Rosenstein, M. T., Collins, J. T., and De Luca, C. J., "A practical method for calculating largest Lyapunov exponents from small data sets," Physica D 65, 117–134 (1993).
- Sauer, T. and Yorke, J. A., "How many delay coordinates do you need?," Int. J. Bifurcat. Chaos 3, 737–744 (1993).
- Sauer, T., Yorke, J. A., and Casdagli, M., "Embedology," J. Stat. Phys. 65, 579–616 (1991).

- Schäfer, C., Rosenblum, M. G., Abel, H. H., and Kurths, J., "Synchronization in the human cardiorespiratory system," Phys. Rev. E 60, 857–870 (1999).
- Schäfer, C., Rosenblum, M. G., Kurths, J., and Hans-Henning, A., "Heartbeat synchronized with ventilation," Nature 392, 239–240 (1998).
- Seidel, H. and Herzel, H., "Bifurcations in a nonlinear model of the baroreceptorcardiac reflex," Physica D 115, 145–160 (1998).
- Shaffer, F. and Ginsberg, J. P., "An overview of heart rate variability metrics and norms," Front. Public Health 5, 258 (2017).
- Sharma, V., "Deterministic chaos and fractal complexity in the dynamics of cardiovascular behavior: Perspectives on a new frontier," Open Cardiovasc. Med. J. 3, 110–123 (2009).
- Shiogai, Y., Stefanovska, A., and McClintock, P. V. E., "Nonlinear dynamics of cardiovascular ageing," Phys. Rep. 488, 51–110 (2010).
- Skinner, J. E., Goldberger, A. L., Mayer-Kress, G., and Ideker, R. E., "Chaos in the heart: Implications for clinical cardiology," Nat. Biotechnol. 8, 1018–1024 (1990).
- Takens, F., "Detecting strange attractors in turbulence," in Lecture Notes in Mathematics (Springer, Berlin, 1981), Vol. 898, p. 366.
- Tan, C. O., "Heart rate variability: Are there complex patterns?," Front. Physiol. 4, 165 (2013).
- Task Force of the European Society of Cardiology and the North American Society of Pacing Electrophysiology, "Heart rate variability. Standards of measurement, physiological interpretation, and clinical use," Circulation **93**, 1043–1065 (1996).
- Togo, F. and Yamamoto, Y., "Decreased fractal component of human heart rate variability during non-REM sleep," Am. J. Physiol. Heart Circ. Physiol. 280, H17–21 (2001).
- Turcott, R. G. and Teich, M. C., "Fractal character of the electrocardiogram: Distinguishing heart-failure and normal patients," Ann. Biomed. Eng. 24, 269–293 (1996).
- Valente, M., Javorka, M., Porta, A., Bari, V., Krohova, J., Czippelova, B., Turianikova, Z., Nollo, V., and Faes, L., "Univariate and multivariate conditional entropy measures for the characterization of short-term cardiovascular complexity under physiological stress," Physiol. Meas. 39, 014002 (2018).
- Van Roon, A. M., Mulder, L. J. M., Althaus, M., and Mulder, G., "Introducing a baroreflex model for studying cardiovascular effects of mental workload," *Psychophysiology* **41**, 961–981 (2004).
- Vielle, B., "Mathematical analysis of Mayer waves," J. Math. Biol. 50, 595–606 (2005).
- Wagner, C. D. and Persson, P. B., "Chaos in the cardiovascular system: An update," Cardiovasc. Res. 40, 257–264 (1998).
- Wessel, N., Riedl, M., and Kurths, J., "Is the normal heart rate "chaotic" due to respiration?," Chaos 19, 028508 (2009).