Significance of using a nonlinear analysis technique, the Lyapunov exponent, on the understanding of the dynamics of the cardiorespiratory system in rats

Tamer ZEREN[1],*, Mustafa ÖZBEK[2], Necip KUTLU[2], Mahmut AKILLI[3]
[1]Department of Biophysics, Faculty of Medicine, Celal Bayar University, Manisa, Turkey
[2]Department of Physiology, Faculty of Medicine, Celal Bayar University, Manisa, Turkey
[3]Department of Physics, Faculty of Science, İstanbul University, İstanbul, Turkey

Background/aim: Pneumocardiography (PNCG) is the recording method of cardiac-induced tracheal air flow and pressure pulsations in the respiratory airways. PNCG signals reflect both the lung and heart actions and could be accurately recorded in spontaneously breathing anesthetized rats. Nonlinear analysis methods, including the Lyapunov exponent, can be used to explain the biological dynamics of systems such as the cardiorespiratory system.

Materials and methods: In this study, we recorded tracheal air flow signals, including PNCG signals, from 3 representative anesthetized rats and analyzed the nonlinear behavior of these complex signals using Lyapunov exponents.

Results: Lyapunov exponents may also be used to determine the normal and pathological structure of biological systems. If the signals have at least one positive Lyapunov exponent, the signals reflect chaotic activity, as seen in PNCG signals in rats; the largest Lyapunov exponents of the signals of the healthy rats were greater than zero in this study.

Conclusion: A method was proposed to determine the diagnostic and prognostic values of the cardiorespiratory system of rats using the arrangement of the PNCG and Lyapunov exponents, which may be monitored as vitality indicators.

Key words: Cardiorespiratory system, pneumocardiography, cardioventilatory coupling, nonlinear analysis, Lyapunov exponent, vitality indicator

1. Introduction

The dynamic behavior and properties of autonomous physiological systems can provide an understanding of the human body (1) while additionally providing simulation and mechanical models to predict behaviors of physiological systems. One such autonomous physiological system is the cardiorespiratory system, whose function requires harmony from the time-dependent dynamic changes between the heart and lungs. This harmony is investigated as a complex system with sensitive physiological parameters. The cardiac signals superposed on respiratory curves, including pneumocardiography (PNCG) signals (2), are known as air flow changes, which appear in the respiratory tract in relation with cardiac rhythms. These pulses are usually used to evaluate the effectiveness of the cardiac and respiratory relationship (3).

In nonlinear dynamic system studies, the Lyapunov exponent is a quantitative measurement method of a parameter's sensitive dependence on initial conditions and provides a quantitative indication of the chaotic level of a system. If physiological signals have at least one positive Lyapunov exponent, they reflect an unstable and unpredictable system and are used to define deterministic chaos (4). The Lyapunov exponent defines the average rate of divergence of 2 neighboring trajectories of chaotic signals in phase space. If the Lyapunov exponent is zero or negative, trajectories are on a stable attractor. Contrarily, a positive exponent means that the trajectories are on a chaotic attractor (5,6). An increased Lyapunov exponent implies increased sensitivity to initial conditions and characterizes unpredictable variations (7). Basically, sensitivity to initial conditions is a primary characteristic of chaotic systems and is quantified by the Lyapunov exponent for dynamic systems.

Since the cardiorespiratory system has been considered as a nonlinear dynamical system (8), its trajectories can be investigated in phase spaces (9) using PNCG signals. This investigation could lead us to determine the chaotic dynamics of the cardiorespiratory system, such as the

* Correspondence: tamerzeren@yahoo.com

delay time and the embedding dimension using the autocorrelation function (10) and the false nearest-neighbor methods (11). In addition to these methods, the Lyapunov exponent might be the most valuable method with its quantitative measurement features.

The chaotic dynamics of respiratory systems have been determined by different nonlinear analyses methods. The noise titration technique (12), automatic classification of signals method (13), combined nonlinear methods (14), approximate entropy method (15), and Lyapunov exponents (16) have been successfully applied to the analysis of respiratory volume.

In the last decades, significant attention has been given to the nonlinear dynamics of body temperature (17), blood volume, blood flow and blood oxygenation signals (18), neurophysiologic (19) and electrocardiographic signals (20), heart rate (21), arterial pressure fluctuations (22), and human menstrual cycles (23) using nonlinear techniques related to Lyapunov exponents.

Positive Lyapunov exponents and nonlinear fractal dimensions had been found in arterial blood pressure time series (24). The Lyapunov exponent was positive in ocular aberration dynamics of the human eye (25). Recent studies have indicated that nonlinear methods could be valuable to understand neuronal dynamics. In one study, an epileptic seizure was detected from EEG signals using nonlinear time series analysis techniques (26) as well as independent component analysis (27).

Recently, the embedding parameters including the delay times and the embedding dimensions of PNCG signals were obtained at the Celal Bayar University Faculty of Medicine in order to investigate the dynamic features of the cardiorespiratory system of small laboratory rats

(28). The Lyapunov exponents of the PNCG signals from the time series were also presented (29,30) and they were reconsidered in two graduate theses (31,32). In this study, we would like to renew the Lyapunov exponents (29–32) as given in the Table to interpret the diagnostic and prognostic features of the cardiorespiratory system.

This paper has been organized as follows: in Section 2, we present the experimental preparations, protocol, and recording system of PNCG signals. The time series results and attractors of PNCG signals (28–32) were respectively plotted and tabulated. The data are also represented in Figures 1–3 in Section 3 in order to obtain more information about the diagnostic and prognostic properties of the pathologic behaviors of the cardiorespiratory system. In Section 4, we consider the role of the Lyapunov exponents to determine physiological and pathological conditions of the cardiorespiratory system. We conclude with how these results could lead us to construct an electrical circuit model for the cardiorespiratory system and show the application possibility of q-statistical models.

2. Materials and methods

2.1. Study protocol and experimental applications
Tracheal air flow signals were recorded in spontaneously breathing anesthetized rats. Male Sprague Dawley rats were used to obtain PNCG signals. Their weights varied between 0.27 and 0.33 kg. The rats received humane care in pursuance of the Guidelines of Care and Use of Laboratory Animals for Research designed by the National Medical Research Society. During the experiment, the rats were fed a standard laboratory diet and drinking water was available ad libitum.

Table. Nonlinear analysis of the tracheal air flow signals including PNCG signals of rat 1, rat 2, and rat 3.

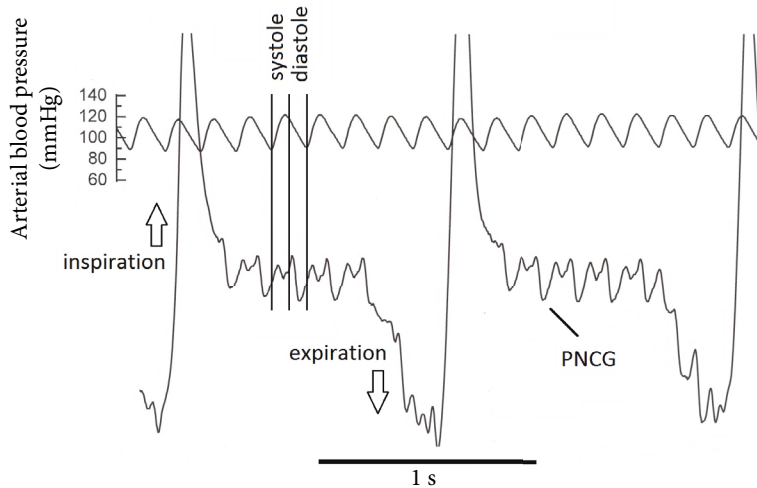|	Delay times (τ)	Embedding dimensions (m)	Lyapunov exponents ($\lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5$)	Fractal dimensions (D_c)
Rat 1	33	4	0.100842 −0.010083 −0.12731 −0.446907	0.865
Rat 2	31	4	0.103975 0.000221 −0.135505 −0.499214	0.883
Rat 3	40	5	0.182774 0.0166 −0.0833 −0.3333 −0.925	0.807

Figure 1. Simultaneous record of arterial blood pressure pulsations (upper trace) and breathing pattern (lower trace), including the pneumocardiography (PNCG) signals. Upper trace: The systolic and diastolic arterial blood pressures are determined as maximal and minimal values (120 and 90 mmHg), respectively, but the periods of both systole and diastole are approximately estimated according to the shape of arterial blood pressure signals. Lower trace: The PNCG signals are manifested between the air flow signals of inspiration and expiration periods. The PNCG signals are also air flows signals reflecting changes in blood flow direction between thorax and abdomen, due to the heart's actions.
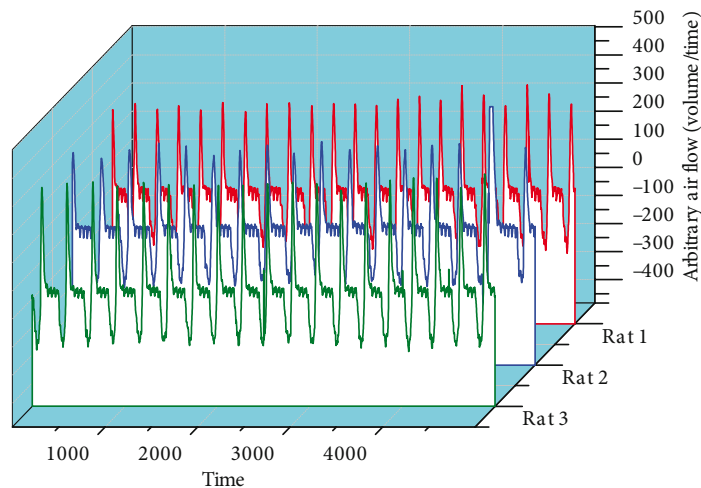

Figure 2. Time series of the tracheal air flow signals including PNCG signals of rat 1, rat 2, and rat 3. These are the row data used to calculate the Lyapunov exponents.

An intraperitoneal administration of pentobarbital sodium was used for the anesthetizing of rats. The primary dose of pentobarbital sodium was 50 mg/kg, and additional doses were between 5 and 7.5 mg/kg. Following the pentobarbital application, the anesthetized rats were placed horizontally on an operating table. All applications were performed under spontaneous respiration. Initially, we performed the tracheotomy with a metal cannula to keep the airway free and to prevent resistance in the airway. The arterial blood pressure was recorded from the catheterized right femoral artery. The body temperature of the rats was kept at around 36.5 °C with the help of a warmed operation table.

For the electrolyte requirements of the rats, 2 mL of saline was intraarterially injected after the operational preparation. Signals were recorded 30 min after the injection. The rats were sacrificed using an overdose of pentobarbital at the end of the experiment. The experimental procedures involved in this study were approved by the local animal ethics committee of Celal Bayar University, Manisa, Turkey.
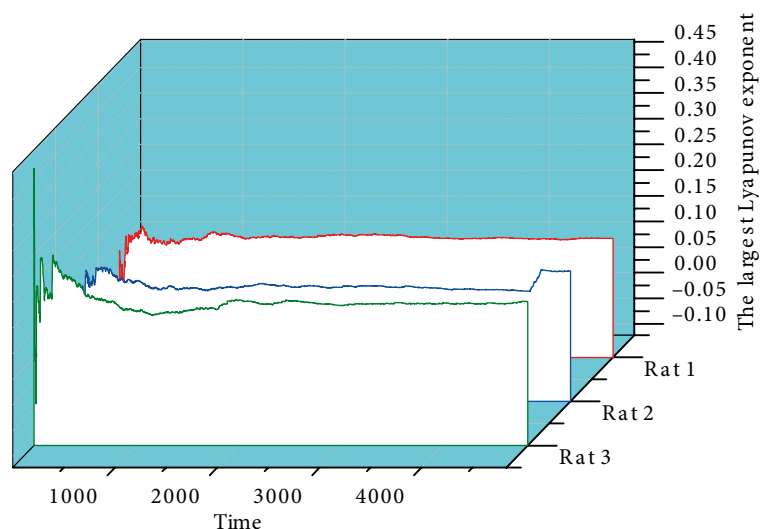
Figure 3. The largest Lyapunov exponents, $\lambda_a = 0.100842$, $\lambda_b = 0.103975$, and $\lambda_c = 0.182774$, for the time series of the tracheal air flow signals including PNCG signals of rat 1, rat 2, and rat 3 in Figure 2. The positivity of these values points out the chaotic behavior of the series and may reflect the normal physiological condition.

2.2. Recordings and analysis of signals

In this experiment carried out in the physiology laboratory, an innovated instrument of the miniature Fleisch pneumotachograph was used to record the tracheal air flow signals, including PNCG signals. This pneumotachograph was calibrated at body temperature as suggested by Kreit and Sciurba (33). During the studies, the resistance of the tube did not need to be controlled due to the open side of the instrument. The tracheal cannula was bound to the instrument over the record of these signals. The Pneu01 differential pressure transducer (WPI, Berlin, Germany) was used to measure the airflow rate. The signals of the Pneu01 transducer were respectively amplified by the TBM-4 multichannel transducer amplifier (WPI) and a multichannel differential amplifier (INH-Verstärker, Science Products GmbH, Hofheim, Germany). Both BLPR blood pressure transducer and the TBM-4 (WPI) were used to record the femoral artery pressure (Figure 1).

We then calculated the Lyapunov exponents of the PNCG signals using the Nonlinear Dynamics Toolbox of the Applied Chaos Laboratory, including the Eckmann and Ruelle method.

3. Results

Figure 1 shows the results of the simultaneous recording of blood pressure (upper) and respiratory airflow rate (lower) signals. The heart rate and respiratory frequency were 360 min^{-1} and 46 min^{-1}, respectively. The remarkable synchronization between blood pressure pulsation and small air flow signals indicated that these are heart beat-induced air flow signals, the so-called PNCG signal. As shown in Figure 1, PNCG signal was manifested between

expiration and inspiration signals, but it was not observed if the respiratory flow changed rapidly.

In the recent work of our collaborative group, the tracheal air flow signals, including PNCG signals, of 3 representative rats from 16 experimental rats were analyzed to construct phase spaces by using the delay times (τ) and the embedding dimensions (m) for $\tau_a = 33$, $m_a = 4$; $\tau_b = 31$, $m_b = 4$; and $\tau_c = 40$, $m_c = 5$ (28). In this study, the chaotic attractors (9) were also investigated from a time series of reconstructed phase space of the cardiorespiratory system, and we renewed the Lyapunov exponents for the rats given in the studies published by Yalcin and Akdeniz, Uzel, and Akıllı (29–32). The data, extracted using the Nonlinear Dynamics Toolbox from the Applied Chaos Laboratory, in addition to the Eckmann and Ruelle method (4), are shown in Figure 3:

i) Lyapunov exponents for the signals of rat 1 given in Figure 3: $\lambda_1 = 0.100842$ (largest), $\lambda_2 = -0.010083$, $\lambda_3 = -0.12731$, and $\lambda_4 = -0.446907$.

ii) Lyapunov exponents for the signals of rat 2 given in Figure 3: $\lambda_1 = 0.103975$ (largest), $\lambda_2 = 0.000221$, $\lambda_3 = -0.135505$, and $\lambda_4 = -0.4992140$.

iii) Lyapunov exponents for the signals of rat 3 given in Figure 3: $\lambda_1 = 0.182774$ (largest), $\lambda_2 = 0.0166$, $\lambda_3 = -0.0833$, $\lambda_4 = -0.3333$, and $\lambda_5 = -0.925$.

All these results are also shown in the Table for comparing the Lyapunov exponents.

4. Discussion

PNCG is the recording of cardiac signals superposed on respiratory curves in the external airways; PNCG signals can be obtained using a precise method (34,35). PNCG

signals have been proposed as an effective method for the evaluation of cardiac performance. In addition, these signals might be beneficial to assess respiratory conditions (36). Initially, animal experiments to measure PNCG signals were performed on large laboratory animals, such as specially ventilated dogs (34,37). In contrast, our collaborative group has developed a technique to measure PNCG in small laboratory animals (28).

The Lyapunov exponent (λ) is a quantitative measurement method of a parameter's sensitive dependence on initial conditions, which is the primary characteristic of a chaotic system. The Lyapunov exponent is often used to discriminate between chaotic dynamics and periodic signals. The feature of the quantitative measurement provides an advantage to Lyapunov exponents for classifying the nonlinearity of the system. An increased Lyapunov exponent value reflects greater sensitivity to initial conditions and characterizes unpredictable variations, whereas low values indicate regularity (7). The largest Lyapunov exponent value, closest to 1, indicates chaotic behavior in the series. This value falls due to the relaxed situation of the brain. This suggests that when the subjects are under sound or reflexologic stimuli, the brain goes into a more relaxed state (5).

Lately, mathematical models have been created to assess the behavior of the cardiorespiratory system using pulsation analysis techniques (38). Compatible with our aim to calculate the strangeness (39), we constructed the phase space from the PNCG signals, which might be considered to be a sensitive type of cardioventilatory coupling, a transient temporal coherence between the cardiac and respiratory activity (40,41). After that reconstruction, we found the Lyapunov exponents of the PNCG signals attractors as given in Figure 3.

We previously assessed the cardiopulmonary signals from the point of view of nonlinear dynamics by the reconstruction of phase space (28). In this study, we combined the PNCG signals with a quantitative method to measure the degree of nonlinearity. Our objective was not only to obtain tracheal airflow signals but also to assess these signals in laboratory rats. For this reason, we analyzed the nonlinear features of these cardiopulmonary signals using a quantitative measure method called the Lyapunov exponent. This method could be useful to assess cardiorespiratory performance, as well as to predict progressive changes in the functions of the systems.

When researchers obtain nonlinear physiologic signals, they wonder if it is healthy for these biological systems to be chaotic (42). For this reason, the Lyapunov exponent has been investigated as a diagnostic method. Babloyantz and Destexhe concluded using Lyapunov exponents that a healthy brain is more chaotic than an epileptic brain, and there is variability loss in the brain's electrical activity during an epileptic seizure (43). The diagnostic values of

the Lyapunov exponent have also been found to be similar to a diagnosis from medical doctors in the case of typical general epilepsy (27). In another study, the Lyapunov exponent was found to be decreased for epileptic subjects compared with normal subjects (26). Lyapunov exponents have been claimed to be useful for early detection of the electroencephalographic changes (6).

On the other hand, Babloyantz and Destexhe proposed the use of the Lyapunov exponent value of cardiac activity in clinical diagnosis (44). The decrease of the Lyapunov exponent value of heart rate fluctuations and maintained arterial pressure fluctuations during hypoxia have suggested characteristic pathological change (22). The nonlinear behavior of heart rate variability (HRV) may have a diagnostic (45) and prognostic (46,47) value for patients in cardiovascular disease states and in the postoperative period of surgical myocardial revascularization (48,49). The nonlinear analysis of the HRV has also been suggested to be used for prognostic purposes in patients with stable angina pectoris (50). The decreased Lyapunov exponent and nonlinear features in heart-transplanted patients may be due to the loss of the neural modulation of heart rate (51). In addition to the Lyapunov exponent, the correlation dimension has been applied to investigate the complexity of Doppler signals and has been used as a prognostic method to determine pathological cases of the aortic valve (52). In patients suffering from chronic obstructive pulmonary disease, bronchodilator therapy and acute bronchodilation effect have increased the value of the largest Lyapunov exponent and nonlinearity (53). Recently, it was suggested that nonlinear parameters might be useful to evaluate the patient's progression in intensive care units (54). It can be expected that if the value of Lyapunov exponent falls under zero, the patient may get progressively worse.

This study shows that the Lyapunov exponent could play a significant role in the investigation of the nonlinear properties of cardiorespiratory systems. In addition, it shows the validity of modeling the cardiorespiratory systems as an electrical circuit (55,56). As Lyapunov exponent values draw closer to 0, the q-statistics investigations (57,58) of the PNCG signals in Figure 2 could give more information about cardiorespiratory systems.

This combined method of PNCG signals and Lyapunov exponent values might be useful for physiological and pharmacological studies of cardiorespiratory interactions in small laboratory animals. The effects of drugs and other substances on the cardiorespiratory system could be evaluated using the value of the Lyapunov exponent of the signals. The nonlinear parameters might be used as vitality indicators of small laboratory animals. After this study, we will continue to discuss our results to further improve the prognostic and diagnostic features of the nonlinear dynamics.

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