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How can we measure the slowing down of healthy and ischemic stroke individuals?

F. Nazarimehr[a], F. Shahbodaghy[a], B. Hatef [b], and K. Rajagopal[c,1,*]

a. *Department of Biomedical Engineering, Amirkabir University of Technology, Tehran, 15875-4413, Iran.*
b. *Neuroscience Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran.*
c. *Nonlinear Systems and Applications, Faculty of Electrical and Electronics Engineering, Ton Duc Thang University, Ho Chi Minh City, Vietnam.*

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Abstract. Recently, resilience has attracted much attention in the study of biological systems. The goal of this paper is to investigate the slowness in ischemic stroke patients. A Trier Social Stress Test (TSST) is used to reveal the slowness of the biological system. The slowness of dynamics is calculated for the Electrocardiogram (ECG) of healthy individuals and patients with ischemic stroke. The ECG is investigated in four stages: before stress, directly after stress, 20 minutes after stress, and 40 minutes after stress. Ten healthy individuals and nine ischemic stroke patients are studied. Six early warning indicators based on slowness and variability are used in this study. The indicators are applied to the ECG beat-to-beat (RR) interval of individuals in four stages. Also, the results were normalized with the rest state of each individual. Heart rate variations were studied as another measure of the slowness of the dynamics. The results reveal that there is no significant difference in the slowness of healthy and patient cases. So, in this case, resilience cannot be used in predicting health problems.

1. Introduction

Ischemic stroke is one of the most dangerous diseases in the world, which causes many deaths [1]. Many kinds of research have been undertaken on strokes [2], depression being one of its consequences [3]. It has been claimed that mood disorder patients have more physiological reactions to stress [4]. Stress events can cause activation of the Sympathetic Adrenal Medullary, and the activation of the autonomic nervous system can be indicated in heart rate variations [5,6]. In other words, the activation of the Sympathetic Adrenal Medullary increases heart rate and blood pressure. Ischemic stroke is a huge source of stress and can change the autonomic nervous system. So, heart rate variations are an essential measure that is different in healthy and stroke patients [7]. Further, the variations of heart rate in response to acute stress can help the prediction of mood-disorders in post-stroke patients [8]. Many studies have been undertaken on the prediction of heart failure [9]. Prediction of successful defibrillation in cases of ventricular fibrillation has been discussed in [10], and classification of heart failure using heart rate variability has been studied in [11].

Prediction of critical transitions in dynamical systems is crucial. Such transitions can cause considerable changes to unwanted/desired states. Near

1. *Present address: Center for Nonlinear Systems, Chennai Institute of Technology, Chennai, India.*
*. *Corresponding author.*
E-mail addresses: fahimenazarimehr@yahoo.com (F. Nazarimehr); fshahbodaghy@aut.ac.ir (F. Shahbodaghy); boshrahatef@yahoo.com (B. Hatef); karthikeyan.rajagopal@citchennai.net (K. Rajagopal)

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bifurcations, the system returns more slowly to its stable attractor from a disturbance. It is called critical slowing down [12,13]. The system's dynamics can approach the bifurcation points through various parameter changes [14,15]. Many indicators of bifurcation points have been proposed based on the slowness of dynamics [16]. Autocorrelation (AC) with lag-1 and variance are some of the well-known early warning signals. Classic early warning indicators were designed to predict the bifurcation points of type period-one dynamics. However, some new early warning indicators have been proposed recently to predict various bifurcations [17]. The Lyapunov Exponent (LE) is one of the early warning indicators which predicts bifurcation points using its dynamical properties [18]. Some modifications of classical predictors have been designed to indicate various bifurcations [19].

The slowness before bifurcation points has been studied to predict many chronic disorders before an acute attack [20]. Recently, the flood of data collected using wearable electronics helps researchers deal with the resilience of physiology [21]. Resilience means the ability of the system to return to a normal attractor after a perturbation [21]. Critical slowing down can be used as a predictor to detect if the system has lost resilience [12]. Many kinds of research have been undertaken on resilience to indicate health problems [22]. Studies show that the biological system's capacity to return to its normal functioning after perturbation (resilience) is related to the risk of mortality and morbidity. In other words, decreasing resilience increases the risk of mortality [21]. In [23], clinical depression was predicted by the slowness of mood change. In [24], the rising correlation and variance of self-reported mood and physical well-being were used to predict frailty. The rapid dynamics of postural balance have been studied as an indicator of healthy aging [25].

In this paper, a Trier Social Stress Test (TSST) is used to study the resilience of healthy and ischemic stroke individuals. The electrocardiogram (ECG) of individuals is used to study early warning indicators of the ECG beat-to-beat (RR) intervals. They are discussed in four stages: before stress, directly after stress, 20 minutes after stress, and 40 minutes after stress. Also, heart rate variations are studied as a measure of the slowness of dynamics. Preliminaries of the paper are discussed in Section 2. In Section 3, the results of the study of slowness are investigated. The conclusion of this paper is described in Section 4.

2. Preliminaries

Recently, the study of resilience in the indication of regime change has become an interesting topic. The human body has the ability to regulate vital parameters such as blood pressure and glucose levels. Some stressors can push the dynamical systems through a regime shift [21]. By decreasing the resilience of the system, the probability of mortality and morbidity increases [21]. Various tests were designed to show the resilience before the regime shifts of biological systems. Slow recovery after exercise was studied in [26], which shows that cases with slowness have higher risk of ischemic stroke. Also, [27] has shown that the slow recovery of blood pressure after standing up raises the possibility of syncope. In this paper, the results of recovering heart rate variations after a stressed condition are studied in two healthy and ischemic stroke cases.

2.1. Test design and data collection

The TSST is used in this paper, which includes severe stress. The age of studied cases is 18 to 70 years, and patient cases had an ischemic stroke more than one year before the study. The ECG of the subjects was collected at four intervals, before stress, directly after stress, 20 minutes after stress, and 40 minutes after stress. In the TSST process, the individuals have a speech prepared for 5 minutes. They entered the test room and gave a speech for 3 minutes about their work and family. The test is followed by a 12 minute math portion, and the examiners ask them to subtract 13 from 1022, sequentially. If an individual makes a mistake, they are informed by the examiners that the answer is incorrect and they start again from 1022. This test is used to investigate the slowness of ECG dynamics in various cases [8]. The clinical trial assignment is IRCT20171128037666N1.

2.2. Early warning indicators

Various early warning indicators have been proposed to show the slowness of dynamics. Six indicators are used in this paper, one of which is AC. Near a bifurcation point, the slowness of the system dynamics causes an increase in short-term memory. So, AC is increased before a bifurcation point [13]. Standard Deviation (SD) is another indicator that is increased before a bifurcation point due to rising variability [28]. Long-term memory can also be quantified using the HE [29]. The LE is another indicator of bifurcation points, which approaches zero near the bifurcation points [17,18]. A Correlation Dimension (CD) is a fractal dimension which can predict bifurcation points [22,30]. Kurtosis (K) is another tipping point indicator that predicts bifurcation points using the increasing of the tailedness of probability distribution for the data near the bifurcation points [31].

3. Results

The TSST is used in this paper to study the slowness of heart rate dynamics. The RR intervals of heart rate for

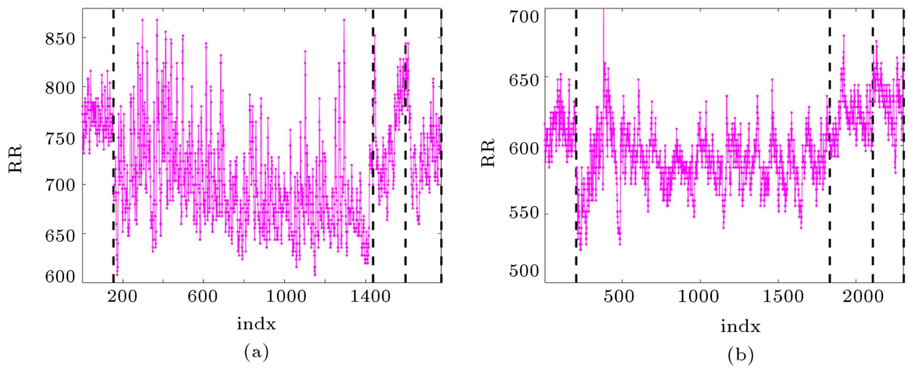

Figure 1. The ECG beat-to-beat (RR) intervals of heart rate for two (a) healthy and (b) patient cases. During the test, the individuals undertook a math exam, which caused stress to their bodies and minds. So, their heart rate increased, which caused a decreasing of the RR intervals. Then, the body system endeavours to return the individual's condition to its normal state.

two healthy and patient cases are presented in (a) and (b) of Figure 1, respectively. The ECG is collected in four intervals, which are separated by dashed lines. The first 2 minutes are collected before the stress. Then, 14 minutes of the ECG is collected directly after the stress. The third interval is 2 minutes, which is collected 20 minutes after stress, and the fourth is 2 minutes, which is collected 40 minutes after stress. In healthy and patient individuals, the RR intervals decrease during the stressor and return to their normal state after removing the stress.

Much research shows that before a dynamical system bifurcation, the system dynamic is slower. It means that by adding perturbation to the system near the bifurcation points, the system returns to its attractor more slowly. Many studies have endeavoured to investigate this slowness in mathematical and biological systems. Le et al. [26] have shown that the risk of ischemic stroke is higher in patients with a slower rise of blood pressure after exercise. In this section, any slowness in the dynamics of heart rate variations of patients with ischemic stroke has been investigated. The slowness of dynamics is quantified using the early warning indicators of the previous section. The results are compared in four stages: before stress, during stress, 20 minutes after stress, and 40 minutes after stress. It is assumed that in patient cases, the system's dynamic should be slower at recovery intervals. To visualize the results, a pair of early warning indicators are shown in a two-dimensional space. The results of healthy individuals are shown using stars, and patients are shown using squares. Figure 2 presents the SD versus AC of the individuals in four stages. Near a bifurcation point, the AC and SD increase. The results show that in the recovery stages 3 and 4, the slowing down indicators do not show any significant differences in the slowness of healthy and patient cases. However, the slowness results after perturbation should be discussed in stages 3 and 4, but the SD of stage 1 shows more differences in healthy and patient cases.

In the second test, the results of the LE and HE are studied. Figure 3 presents that the two indicators cannot differentiate between healthy and patient cases in the four stages.

As another test, results of the CD and kurtosis are discussed in Figure 4. The CD and kurtosis do not differentiate between the healthy and patient cases.

Until now, the test results show that slowness and variability are not higher in ischemic stroke cases than in healthy cases. To normalize each indicator for each person, the variation of indicators after the stressor is considered related to their rest state. So, the percentages of no changes in the indicators are calculated as follows:

$$P_{In_{13}} = \left(1 - \frac{|In_{s1} - In_{s3}|}{In_{s1}}\right) * 100, \tag{1}$$

$$P_{In_{14}} = \left(1 - \frac{|In_{s1} - In_{s4}|}{In_{s1}}\right) * 100, \tag{2}$$

where In_{s1} is the indicator in stage 1, In_{s3} is the indicator in stage 3, and In_{s4} is the indicator in stage 4. So, $P_{In_{13}}$ displays the similarity of indicator value in stages 1 and 3, while $P_{In_{14}}$ shows the similarity of indicator value in stages 1 and 4. The normalized indicators are used to show the slowness of each person in comparison with their rest state. Figure 5 presents $P_{In_{14}}(1-4)$ versus $P_{In_{13}}(1-3)$ for various indicators. The results show that the similarity of indicators before and after stress is not significantly different in healthy and patient cases.

As another test, the variation of heart rate at various stages is studied instead of RR intervals. The Heart Rate (HR) increases in stage 2 and decreases to its normal state after the stressor. (a) and (b) of Figure 6 show the HR of healthy and patient cases for the four stages. The results display that the HR of any

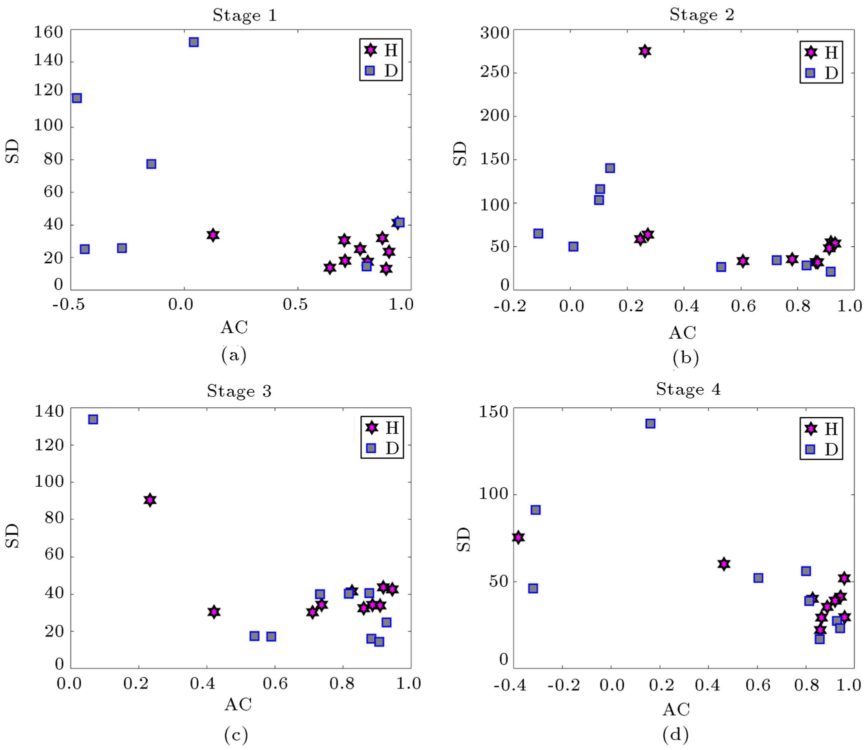

Figure 2. The Standard Deviation (SD) and Autocorrelation (AC) of the individuals: (a) Before stress, (b) directly after stress, (c) 20 minutes after stress, and (d) 40 minutes after stress. The results of healthy individuals are shown using stars, and patients are shown using squares. The slowness results after perturbation should be discussed in stages 3 and 4, but the SD of stage 1 shows more differences between healthy and patient cases.

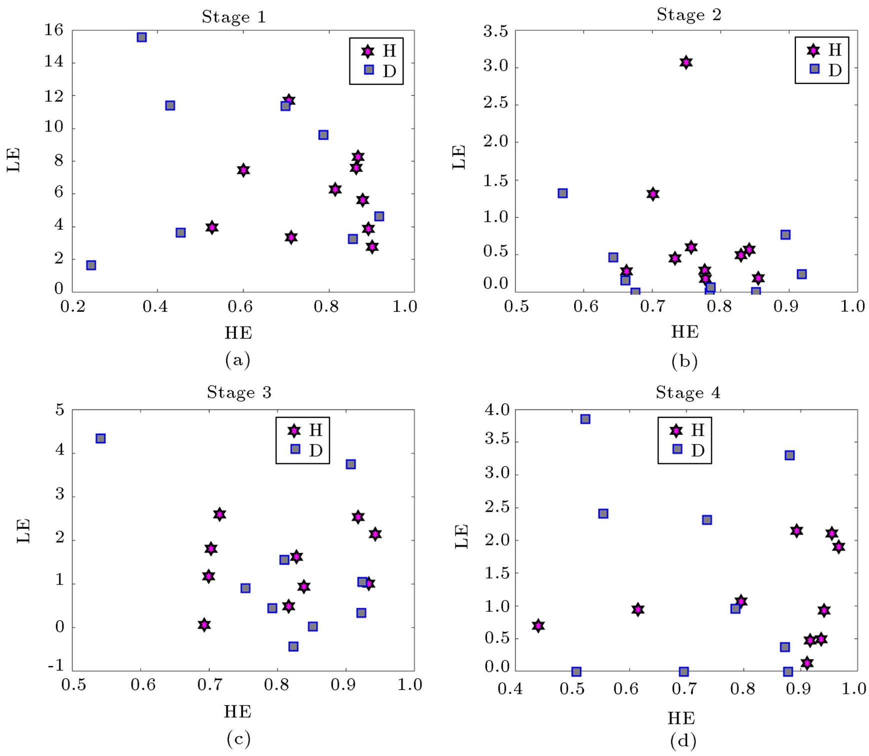

Figure 3. The Lyapunov Exponent (LE) and Hurst Exponent (HE) of the individuals: (a) Before stress, (b) directly after stress, (c) 20 minutes after stress, and (d) 40 minutes after stress. The results of healthy individuals are shown using stars, and patients are shown using squares. The two indicators do not show any differentiation between healthy and patient cases in the four stages.

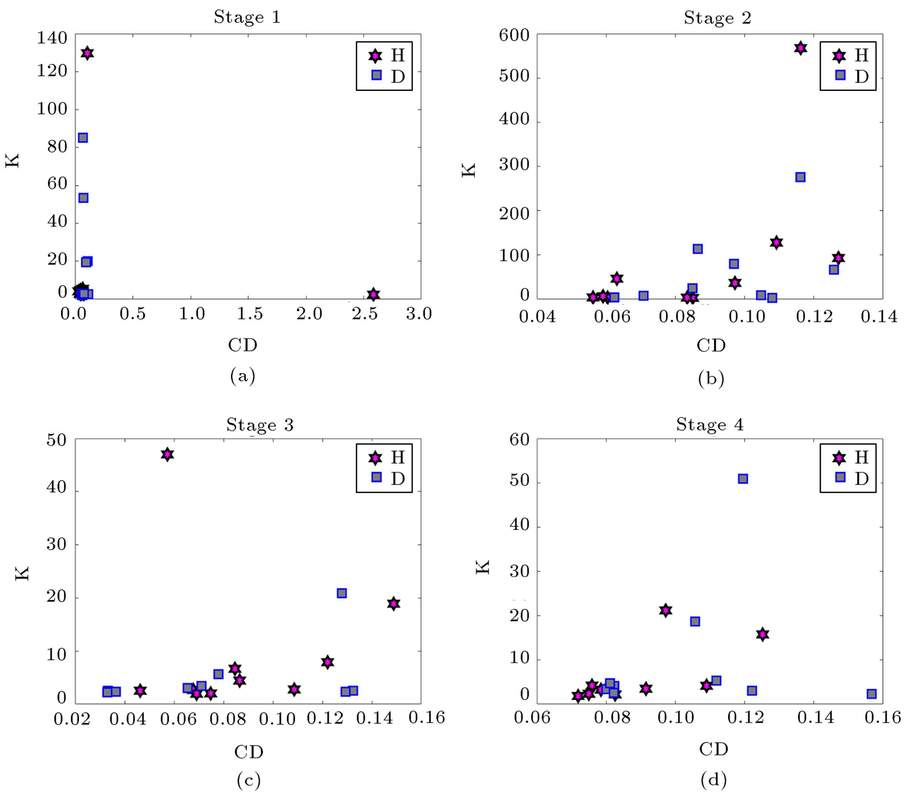

Figure 4. The kurtosis and Correlation Demension (CD) of the individuals: (a) Before stress, (b) directly after stress, (c) 20 minutes after stress, and (d) 40 minutes after stress. The results of healthy individuals are shown using stars, and patients are shown using squares. The CD and kurtosis do not differentiate between healthy and patient cases.

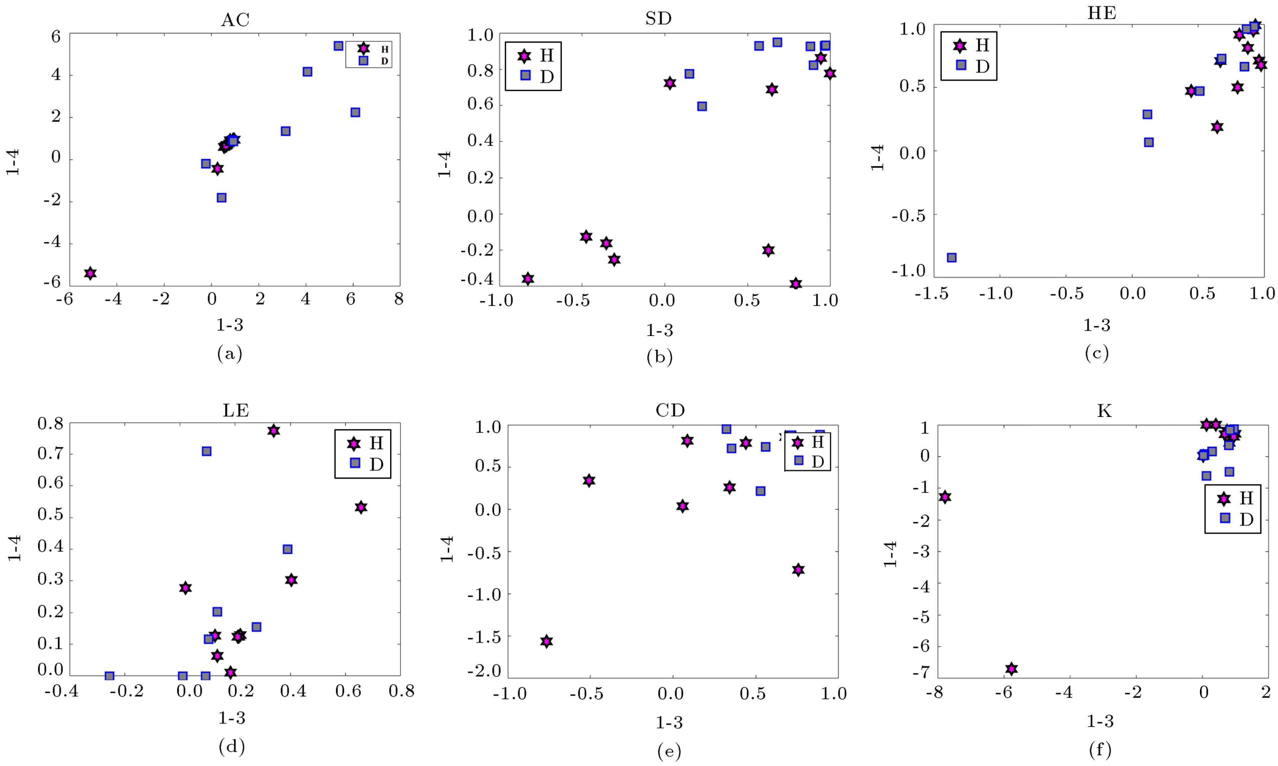

Figure 5. $P_{In_{14}}(1-4)$ versus $P_{In_{13}}(1-3)$ for (a) Autocorrelation (AC), (b) Standard Deviation (SD), (c) Hurst Exponent (HE), (d) Lyapunov Exponent (LE), (e) Correlation Dimension (CD), and (f) K. The similarity of indicators before and after stress is not significantly different between healthy and patient cases.

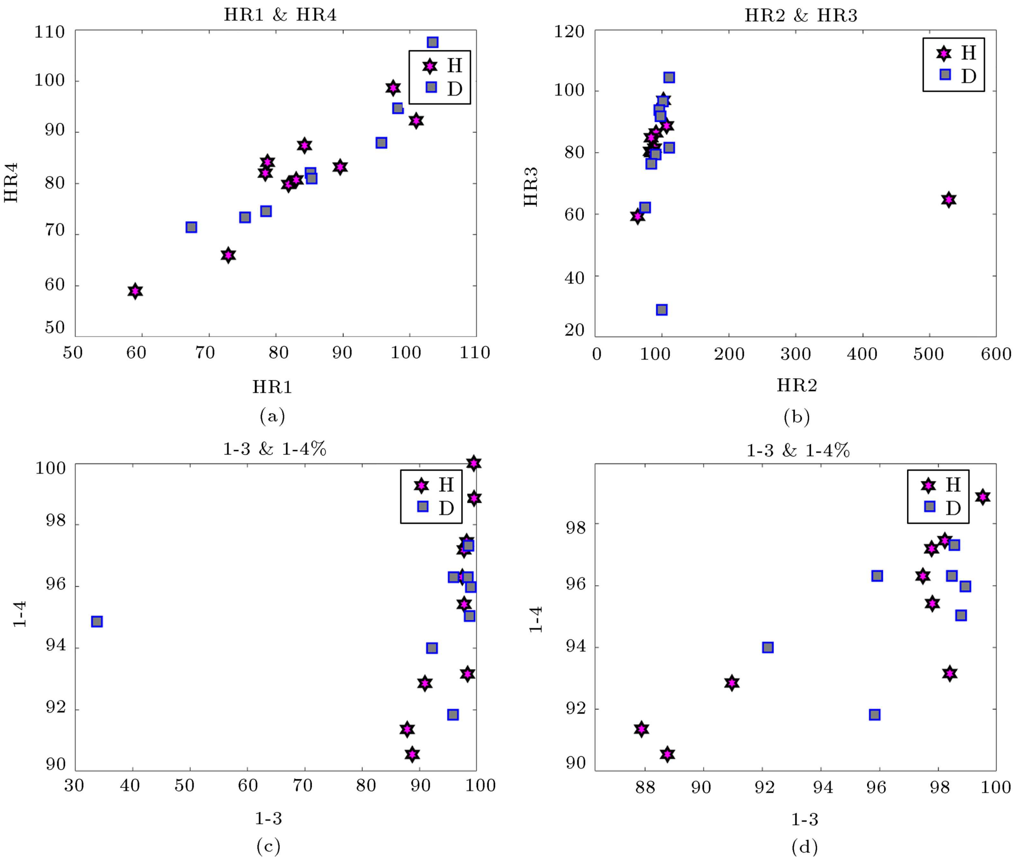

Figure 6. The Heart Rate (HR) of healthy and patient cases for the four stages: (a) HR4 vs. HR1, (b) HR3 vs. HR2, (c) the relative heart rates of 1–3 and 1–4, and (d) zoomed view of the relative heart rates of 1–3 and 1–4. The results display that the HR of any stage cannot differentiate between healthy and patient cases. Also, the relative heart rates do not show any difference between healthy and patient cases.

stage cannot differentiate healthy cases from diseased cases. The relative heart rates of 1–3 and 1–4 are shown in Figure 6(c), and their zoomed view after removing the outlier is shown in Figure 4(d). The relative heart rates do not show any difference between healthy and patient cases.

4. Discussion and conclusion

In this paper, a Trier Social Stress Test (TSST) was designed to study the slowness of the electrocardiogram (ECG) in healthy and patient cases with ischemic stroke. The slowness of the ECG after severe stress was discussed using its ECG beat-to-beat (RR) intervals and heart rate variations. Ten healthy and nine patient cases were studied. In the TSST, severe stress was applied to the individuals via having to make a speech and a mathematical problem solving portion. The individuals received a warning when they made a mistake in the math portion. The ECG of the individuals was collected in four stages: before stress, directly after stress, 20 minutes after stress, and 40 minutes after stress. During the test, the individuals were required to complete a math exam. This caused stress to their bodies and minds, so, their heart rates increased, which caused a decreasing of the RR intervals. Then, the body endeavoured to return the individual's condition to its normal state. The test was designed to reveal the resilience of individuals, which can be used to predict mood disorders.

Various early warning indicators from the viewpoint of statistics and nonlinear dynamics were used to reveal ECG dynamic slowness. Some of the indicators determined the slowness, and some have shown rising variability. The results of Standard Deviation (SD) have shown that it has more differences in stage 1 of healthy and patient cases. The results of Lyapunov Exponent (LE) and Hurst Exponent (HE) did not show any differentiation between healthy and patient cases in the four stages. Also, the Correlation Dimension (CD) and kurtosis did not differentiate between the healthy and patient cases. The study has shown that the similarity of indicators before and after stress is not significantly different in healthy and patient cases. The results of the HR of any stage cannot differentiate healthy cases from those diseased. Also, the relative heart rates did not show any difference in healthy and patient cases. In other words, the results revealed that none of the indicators supported the slowness of the ECG dynamics of patient cases compared to healthy cases. However, the stress events activate the Sympathetic Adrenal Medullary, which can be indicated in heart rate variations. The results have shown that the slowing down of the ECG was not different in healthy and patient cases, which raises some questions: Can resilience detect health problems in every biological system? What is the standard for defining a test to show the slowness of biological systems?

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Biographies

Fahimeh Nazarimehr received a BS degree in Biomedical Engineering from Shahed University, Iran, in 2012, an MS degree from Sharif University of Technology, Iran, in 2014, and a PhD in Biomedical Engineering from Amirkabir University of Technology, Iran, in 2018. Her research interests include chaos theory and its application in biological signals and systems, nonlinear dynamics, bifurcation analysis, dynamical systems in neuroscience, bio-electricity and quantitative approaches, and feature extraction and classifcation of signals.

Fatemeh Shahbodaghy began her BS degree studies in Biomedical Engineering, in 2017, at Amirkabir University of Technology, Tehran, Iran. Her research interests include neuroscience, artificial intelligence, and, especially, nonlinear and chaotic signals and systems.

Boshra Hatef obtained a PhD in physiotherapy from the medical faculty of Tarbiat Modares University, Tehran, Iran. She has researched multidisciplinary fields of neurological, electrophysiological, and biomechanical sciences in headache, low back pain, and diabetes. She is currently Assistant Professor in the neuroscience research center. Her research interests include studies regarding stress and its connection with human social interaction. She endeavours to combine the fields of several basic sciences, from biology to engineering, to investigate applicable methods for solving social problems, especially those with stress as the main risk factor.

Karthikeyan Rajagopal is presently working as a Senior Research Member and Professor in the Center for Nonlinear Dynamics of Defense in Ethiopia. He has completed his PhD in electronics and communication engineering, specializing in chaos-based secure communication engineering. His post-graduate studies involved embedded system technologies with emphasis on real-time target programming. He has over 200 international journal papers indexed in SCI and his present research areas include fractional order nonlinear systems and control, computational biology, discrete systems, time delay systems, FPGA and LabVIEW implementations of fractional order systems.