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Analysis of the coupling of autonomic regulatory loops of blood circulation in patients with Covid and cardiovascular pathologies

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ABSTRACT

The work aims to study the features of autonomic control of the cardiovascular system in two groups of patients with Covid-19: with and without arterial hypertension. A total of 15 pairs of 20-minute electrocardiogram and photoplethysmogram signals were registrated in each group. We used the methods of spectral analysis, as well as the previously proposed method for assessing the phase synchronization of 0.1-Hz rhythms of signals of autonomic control of heart rate and blood pressure. The data of patients with chronic arterial hypertension showed a lower level of synchronization than patients without it. This is probably due to the peculiarities of autonomic control of the cardiovascular system in patients with chronic arterial hypertension.

Keywords: autonomic control system, phase synchronization, Covid-19, photoplethysmogram, RR-intervals

1. INTRODUCTION

Cardiovascular diseases are the leading cause of death in all developed countries of the world [1]. Insufficient knowledge of the cardiovascular system (CVS) and the elements of its regulation, and the lack of efficient methods for early and rapid diagnosis of pathological changes, are significant problems in the fight against these diseases. Most of the existing and widely used methods for diagnosing the state of organs and body systems are based on the study of morphological manifestations of pathologies [2]. In turn, the diagnosis of functional disorders is a new and promising direction in the development of medicine since the study of deviations in the functional collective interaction of systems will prevent the further occurrence of pathological changes in organs. The analysis of the state of autonomous control of blood circulation has proven to be promising in clinical diagnostics as a sensitive marker of the development of pathologies of various organs and systems at early stages [3-8].

It should be noted that the signals of the activity of the autonomic control of blood circulation can be easily obtained non-invasively from the signals of the cardiovascular system, for example, the sequence of RR-intervals, arterial pressure oscillations according to the signals of the photoplethysmogram and the finapress [3,9,10]

The dangerous consequences of the spreading COVID-19 pandemic forced many researchers to focus on this problem. This stage of the work was a collection of the results of studying the effect of Covid-19 on the autonomic regulation of the cardiovascular system and hypotheses about the reasons for this effect. The review algorithm was chosen in accordance with the recommendation [11]. The search for publications by topic was carried out in the WoS database using the keywords "Covid-19" and "autonomic" [12].

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Currently, much attention is focused on the study of organs and systems that are affected by the evolution of a viral infection or react to the entry of the virus and can potentially act as a marker of the developmental pathology in the early stages before the indication of obvious clinical symptoms.

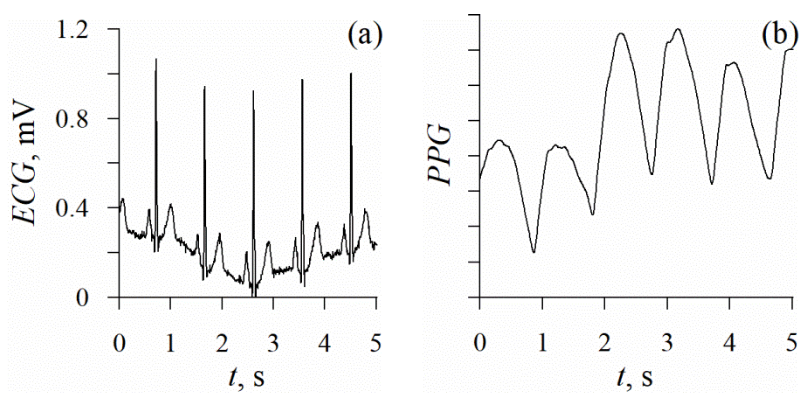
Some significant results have been obtained in this direction, which testifies to the significant impact of Covid-19 on the elements of autonomic blood circulation control. In particular, there are several hypotheses about the reasons for the influence of Covid-19 on the autonomic control of blood circulation.

One of the popular concepts is based on altering the secretion of the angiotensin-converting enzyme 2 (ACE2) [13-15]. The cellular entry point for SARS-CoV-2 is ACE2, which is a component of the renin-angiotensin system (RAS) regulation and is involved in the regulation of the cardiovascular system [16]. On the one hand, there are wellestablished relationships between RAS activation and autonomic dysfunction in cardio-metabolic diseases such as hypertension, heart failure, and diabetes [17]. In these conditions often a positive feedback loop exists between RAS activation and tonic increases in efferent sympathetic nerve activity, wherein increases in sympathetic activity can stimulate activation of RAS which in turn can further upregulate sympathetic activity [17]. On the other hand, the wide expression of ACE2 in nerve tissues and the neurotrophic nature of SARS-CoV-2 might render the cardiac nerve fibers a target [14,18].

These hypotheses can be used to explain the features of autonomic control of blood circulation in patients with Covid-19 and chronic arterial hypertension compared with those who were not diagnosed with any cardiovascular pathologies.

2. MATERIAL AND METHODS

In this work, experimental records of patients on outpatient treatment in a hospital with a diagnosis of Covid-19 were obtained. These patients were divided into 2 categories: patients with arterial hypertension (stages 1-2) and without it. A total of 15 pairs of electrocardiogram (ECG) and photoplethysmogram (PPG) signals were included in each group. All patients had a mild course of viral disease. They did not need oxygen support. Signals were recorded by a standard certified recorder: the psychophysiological telemetric device "Reactor-T" (Medicom-MTD, Taganrog) for 20 minutes in a calm state, lying down, with spontaneous breathing. The electrocardiogram signal was recorded in the I standard lead by the recommendations [19]. Photoplethysmogram signals were recorded with an infrared sensor [20-22]. The sampling rate was 250 Hz. Figure 1 shows typical sections of experimental signals for two studied samples.



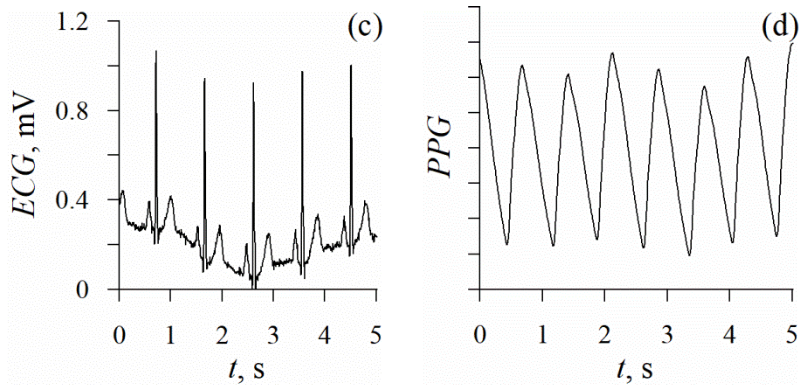


Figure 1. The examples of simultaneous experimental records of a patient with Covid-19: (a) − ECG, (b) − PPG; for a patient with Covid-19 and chronic arterial hypertension: (c) − ECG, (d) − PPG.

Studies of autonomic control of blood circulation often include analysis methods include frequency domain measures [23]. Therefore, the first step in analyzing the collected data was to obtain information on heart rate variability from the electrocardiogram signal according to the method for estimating the duration of the RR-intervals of the experimental ECG signals [23]. A new signal, a signal of a sequence of RR-intervals, was interpolated using cubic β-splines.

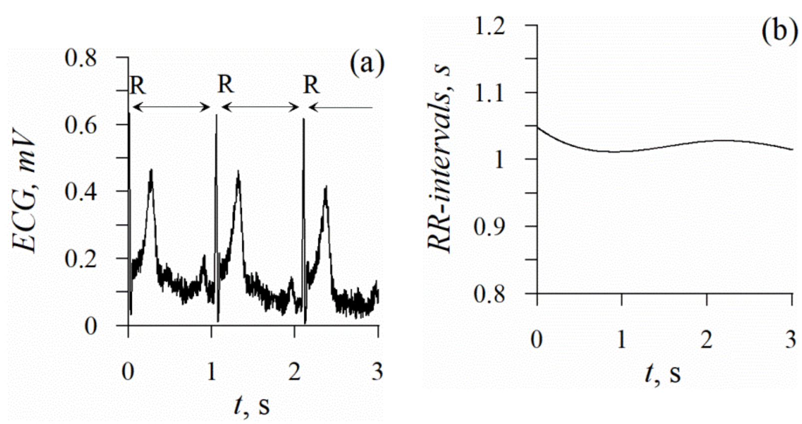


Figure 2. Examples of the experimental ECG signal (a) and the corresponding RR-intervals (b).

3. RESULTS

The study of the features of autonomic control of blood circulation in patients with Covid-19 and with or without arterial hypertension was carried out by assessing the power spectra of signals and studying the phase dynamics of signals. Spectral analysis was carried out using the Welch and Daniel method [24-25]. Figure 3 shows typical power spectra for signals of RR-intervals and PPG of patients from two samples. Visual analysis of the power spectra did not reveal significant differences between the two samples.

For the analysis, the method of nonlinear dynamics was also applied, which has established itself in clinical practice as a sensitive method for assessing the state of the CVS [26]. This method estimates the degree of phase synchronization between the low-frequency components of the RR-intervals and PPG signals. The algorithm of the proposed method begins with filtering the signal with a bandpass filter in the range from 0.06 to 0.14 Hz. This step allows examining only that part of the signal traditionally associated with the sympathetic circuit of autonomic control activity. Next, using the Hilbert transform, the phases of the signals are estimated, and the phase difference is calculated. Figure 4 shows examples of phase differences for two patients from samples. The main difficulty in further calculating the phase synchronization estimate lies in the correct diagnosis of the synchronization intervals. A special algorithm using approximating straight-line estimates the slope of the phase difference curve and recognizes the synchronization intervals when this curve is close to the horizontal line. In Figure 4, the phase synchronization intervals are marked in grey. The longest phase synchronization interval in the sample of patients with Covid-19 and arterial hypertension was 103.4 seconds; in the sample of patients without chronic diseases of CVS was 95.6 seconds.

The proposed estimate of phase synchronization (total percentage of phase synchronization or index S) is the ratio of the sum of the duration of all synchronous intervals to the total length of the time series, expressed as a percentage. Table 1 shows the individual S values for each of the patients. The significance level (*p*) was calculated using AAFT surrogates (Amplitude Adjusted Fourier Transform) [27]. The table also shows the mean S ± standard deviation for each sample. In the sample of patients with chronic disease of CVS, the highest S value was 28.36%, and in the sample without hypertension, the highest S value was 55.39%. The statistical indicators for the two samples are shown graphically in Figure 5. The figure shows that the average S value for patients with Covid-19 and hypertension is lower than for patients without hypertension and amounts to 17.57% ± 4.92% versus 38.36% ± 8.87 %.

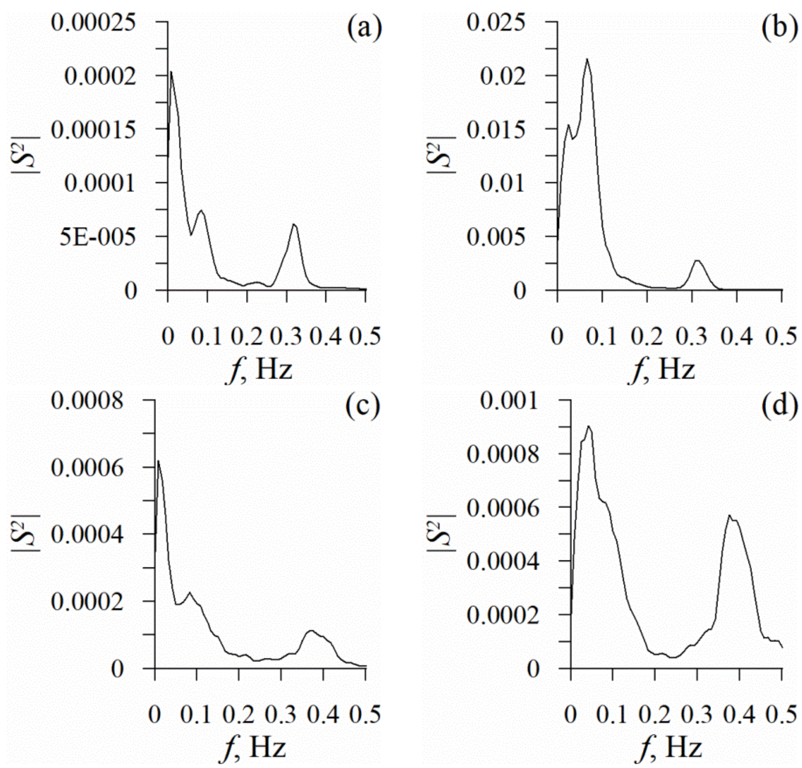


Figure 3. The examples of power spectra for a patient with Covid-19: (a) – RR-intervals, (b) – PPG; for a patient with Covid-19 and chronic arterial hypertension: (c) – RR-intervals, (d) – PPG.

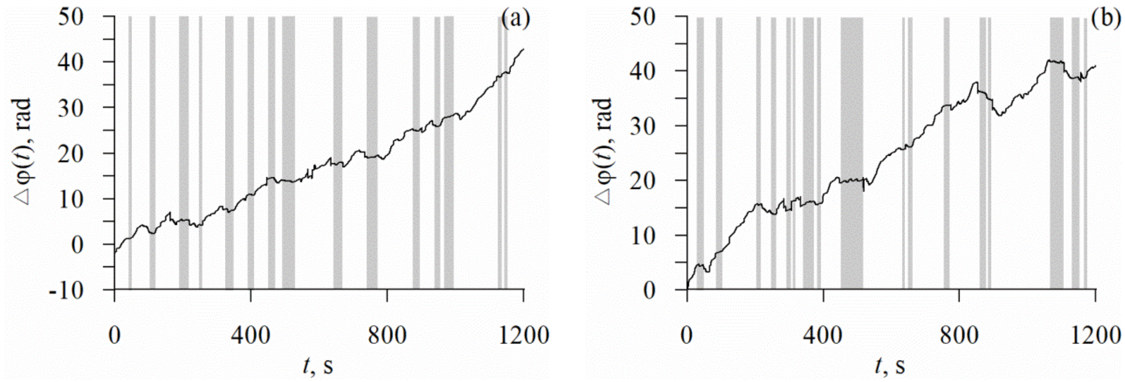


Figure 4. Comparison of the differences in instantaneous oscillation phases for patients without signs of CVS pathologies (a) and with chronic arterial hypertension (b). The values are Δφ normalized to 2π. Sections of phase synchronization are marked in gray.

Table 1. The values of the total percentage (S, %) for each subject and the statistical significance (*p*).

№		1	2	3	4	5	6	7	8
RR-PPG Covid-19	S, %	41,55	33,29	**51,49**	34,57	22,11	33,62	31,97	32,65
	p	*0,11*	*0,16*	***0,01***	*0,25*	*0,76*	*0,18*	*0,25*	*0,22*
RR-PPG Covid-19 with cardiovascular pathologies	S, %	17,73	**21,20**	13,94	**18,15**	**22,09**	13,94	11,45	**24,66**
	p	*0,09*	***0,01***	*0,28*	***0,01***	***0,01***	*0,65*	*0,91*	***0,01***
№		9	10	11	12	13	14	15	Mean±std
RR-PPG Covid-19	S, %	33,32	**55,39**	**37,44**	**52,07**	**38,34**	36,09	41,55	38,36±8,87
	p	*0,09*	***0,01***	***0,01***	***0,01***	***0,02***	*0,14*	*0,11*	–
RR-PPG Covid-19 with cardiovascular pathologies	S, %	17,88	**28,36**	12,68	15,15	15,14	19,51	11,66	17,57±4,92
	p	*0,35*	***0,01***	*0,35*	*0,40*	*0,46*	*0,12*	*0,80*	–

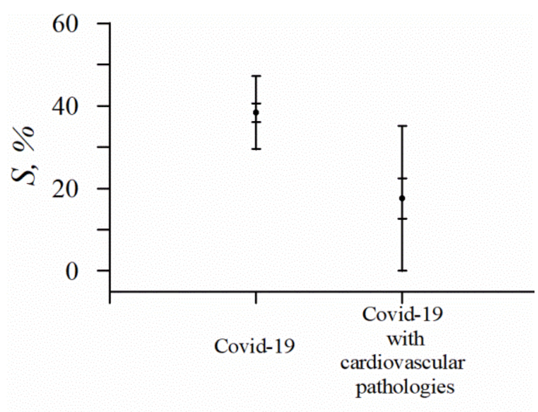


Figure 5. Statistical estimates of S for two samples of patients with Covid-19: with and without arterial hypertension. The filled circles are the mean, the first horizontal segments from them are the mean error, and the last ones are the standard deviation.

4. CONCLUSION

This work aimed to study the features of autonomic control of blood circulation during the development of a viral disease and the presence of chronic arterial hypertension. To achieve this goal, spectral analysis methods, studies of phase dynamics, and statistical analysis of the results were used.

The work revealed a lower level of phase synchronization between the circuits of autonomic control of blood circulation in patients with chronic arterial hypertension than patients without any diagnosed cardiovascular diseases. The average estimate for the first group was 17.57% ± 4.92%, for the second was 38.36% ± 8.87%. This may be due to the increased secretion of the ACE-2 protein, which is characteristic of the development of hypertension and is also a target for the penetration of the virus into the human body.

Spectral analysis of the signals did not reveal significant differences in the two samples. Apparently, the study of phase dynamics can provide new information about changes in the mechanisms of autonomic control of blood circulation during the development of the Covid-19 virus.

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