Original article

Synchronization of autonomic control loops of blood circulation in patients with COVID-19

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Abstract: This study *aims* to investigate the strength of synchronization between the autonomic control loops of the cardiovascular system (CVS) in patients with COronaVIrus Disease 2019 (COVID-19).
Methods — We calculated the total percent of phase synchronization index (S index) between the loops of autonomic control of heart rate and vascular tone in two sample groups: healthy individuals and COVID-19 patients.
Results — The group-average value of the S index in COVID-19 patients is lower comparing to healthy individuals, the Mann-Whitney U-test confirmed that the differences are statistically significant.
Conclusion — Obtained results suggest that the decreased value of the S index reflects the presence of a viral disease, and the S index is a promising basis for non-invasive screening diagnostics of viral diseases, particularly of COVID-19.

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Introduction

The challenge posed to the world by the COronaVIrus Disease 2019 (COVID-19) pandemic has forced researchers to look into early diagnostics of viral diseases. Development of the methods for early non-invasive screening allows for more efficient and selective use of accurate laboratory methods, and timely isolation of sick patients. Such approaches can significantly reduce the burden on laboratories during epidemics and pandemics, and increase effectiveness of anti-epidemic measures.

A promising direction is to monitor autonomic control of blood circulation. Several well-known works revealed that severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) influences the dynamics of the circulatory system by secreting the angiotensin-converting enzyme 2 (ACE2) [1-3]. The cellular entry point for SARS-CoV-2 is ACE2, which is a component of the renin-angiotensin system (RAS) and is involved in regulation of the cardiovascular system (CVS) [1].

The review article by Huijing Xia and Eric Lazartigues provided data on the interaction of ACE2 and the autonomic nervous system. Changes in the volume of ACE2 secretion significantly affect the autonomic control of blood circulation, modulate the work of the sympathetic and parasympathetic loops, cause changes in long-term and short-term control of blood pressure, prevent or causes the development of hypertension [4].

It was also shown that COVID-19 was noticeably more severe in patients with cardiovascular diseases, which may be was due to increased secretion of ACE2 in these patients compared to healthy people [5-6]. On the other hand, in COVID-19 patients with no detected CVS pathologies, secretion of the ACE2 was also increased, which was, presumably, associated with the activity of the SARS-CoV-2 virus [7].

A variety of methods can be used to diagnose the condition of CVS autonomic control including linear approaches based on statistical and spectral analysis of RR-intervals [8-9], as well as nonlinear approaches that consider the components of the CVS as interacting generators of complex-shaped signals [10-12].

Several studies have shown that such methods were promising tools for COVID-19 diagnosis. For example, work [9] investigated the spectral and time-domain indices of RR-intervals, as well as the standard deviation of RR-intervals (SDNN index). In that paper, it was established that decreased activity of sympathetic control and increased activity of parasympathetic control correlated with a worse prognosis of the natural history in patients with COVID-19. The properties of HVR signals change during the early stages of

COVID-19, as was proven in [10] by fitting a nonlinear model to each subject, HRV was monitored before and after the first positive test for COVID-19.

Another work has shown a statistically significant difference between healthy subjects and COVID-19patients, by applying the sample entropy to integrated transformed probability signals (heart rate and systolic blood pressure signals), common symbolic dynamics entropy, and copula parameters, however, only the cross-entropy indexes calculated from HRV and systolic pressure signals showed a statistically significant difference between serious and mild cases of COVID-19. This result contributed to the hypothesis that severity of COVID-19 is associated with RAS disorder and encourages further research.

At the same time, no studies reported a detailed analysis of phase dynamics of autonomic control of CVS during COVID-19. As part of our previous work, we paid great attention to the development of methods for studying not only individual activity of the autonomic control loops but also their coupling [11, 12]. The phase analysis of CVS was shown to be a promising tool for clinical practice, in particular, for correcting the therapy in patients with hypertension and after myocardial infarction [13-15]. We showed that the total percentage of phase synchronization index (S index) was a sensitive index of CVS status [16, 17] and was an index for specific pathologies [13-15].

Therefore, this work aims to study the degree of synchronization of the autonomic control loops of circulation in COVID-19 patients.
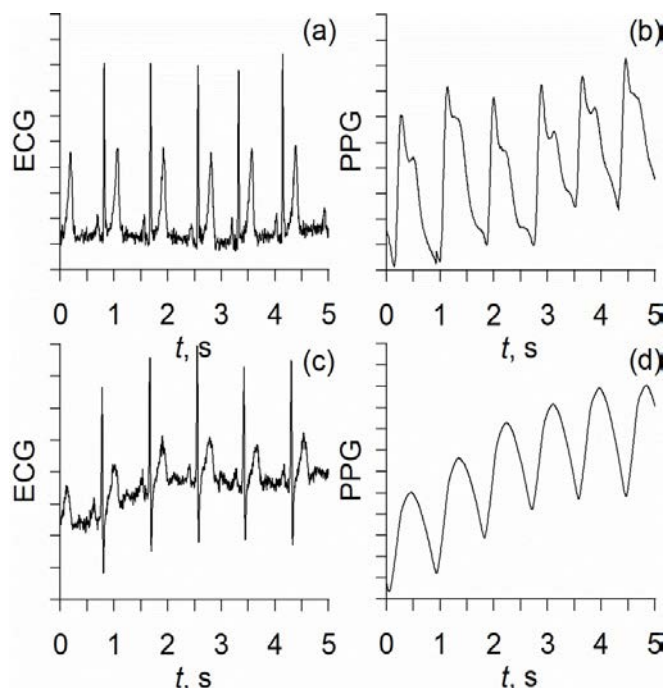

Figure 1. Typical examples of experimental data: (a) – ECG and (b) – PPG from healthy people, (c) – ECG from COVID-19 patients, and (d) – PPG from the COVID-19 patients.

Material and Methods

Signal recording

Selected COVID-19 patients match the following inclusion criteria: absence of somatic pathologies; laboratory-confirmed case of COVID-19; All subjects involved in the study gave informed consent to medical intervention and processing of their personal data. The study included 32 healthy volunteers (age 17 to 23, 22 women and 10 men) and 32 patients with COVID-19 (age 25 to 68, 14 women and 18 men). All COVID-19 patients had a mild case of the disease and did not require oxygen support.

We carried out simultaneous registration of electrocardiographic (ECG) and photoplethysmographic (PPG) signals (signal of blood filling, recorded using an optical sensor with active backlight and reflected light setup). The signals were recorded using a standard polygraph EEGA-21/26 "Encephalan-131-03" (Medikom MTD Ltd, Taganrog, Russia). The bandpass filter was set to 0.05–100 Hz and the sampling rate was set to 250 Hz at 14-bit resolution. ECG signals were recorded in the I standard lead (differential signal from the wrists of two hands) and PPG signals were recorded from the earlobe [18]. The PPG signals were recorded using a reflected green light sensor (550 nm) [19].

The experimental signals were recorded at rest in a horizontal position. The length of each recording was 20 minutes. *Figure* 1 shows typical examples of experimental signals.

Signal processing

HRV signals were estimated from ECG signals by calculating the sequence of interbeat intervals (RR-intervals). The obtained signals were interpolated using cubic β-splines, as recommended in [8], resulting in equidistant time series of RR-intervals with a sampling frequency of 5 Hz.

As the next step of the signals processing, we detected the intervals of phase synchronization between the LF-oscillations in RR-intervals and PPG signals using a technique proposed in [20]. To introduce a phase of LF-oscillations in the experimental signals, we filtered the experimental signals using a bandpass filter (0.06-0.14 Hz) and obtained the $\xi(t)$ signals. This technique was actively used to study the signals of various nature [21]. The signal $\xi(t)$ was a complex function of time, which is defined as follows:

$$\xi(t) = s(t) + i\tilde{s}(t) = A(t)e^{i\varphi(t)}, \quad (1)$$

where $s(t)$ was an HRV or PPG signal, $A(t)$ and $\varphi(t)$ were, respectively, the amplitude and phase of the analytical signal and the function $\tilde{s}(t)$ was the Hilbert transform of $s(t)$,

$$\tilde{s}(t) = \frac{1}{\pi}\mathrm{P.\,V.}\int_{-\infty}^{+\infty}\frac{s(\tau)}{t-\tau}d\tau, \quad (2)$$

where P.V. means that the integral was taken in the sense of the Cauchy principal value. Phase $\varphi(t)$ was then introduced as

$$\varphi(t) = \arctan\frac{\tilde{s}(t)}{s(t)}, \quad (3)$$

Then we calculated the phase difference

$$\Delta\varphi = \varphi_1 - \varphi_2, \quad (4)$$

where φ_1 was the phase of LF-oscillations was the RR-intervals signal and φ_2 was the phase of LF-oscillations in the PPG signal.

Linear approximation of the phase difference $\Delta\varphi$ in a moving window was carried out to detect the intervals of phase synchronization. The intervals of $\Delta\varphi$ signal approximated by a close to a horizontal line (which means that $|\Delta\varphi| <$ const) were considered to correspond to the intervals of phase synchronization (4).

To quantify the frequency of the synchronous intervals we calculated the total percentage of phase synchronization index (S index). S index is a ratio of the total lengths d_k of the intervals of synchronization to the total length T of a signal:

$$S = \frac{\sum_{k=1}^{N} d_k}{T} \times 100\%, \quad (5)$$

where k is a counting number of a synchronization interval and N is the total number of intervals. The S index represents the relative time that loops of autonomic control exist in the regime of phase synchronization.

Results

The S indices were calculated for healthy volunteers and COVID-19 patients. Individual values of the S indices are shown in *Figure* 2.

The maximum value of the S index among the healthy volunteers was 67%, and 56% among the COVID-19 patients; the minimum values of the S index were 9% and 19%, respectively. Fig. 2 shows that the values of the S indices tend to be lower in COVID-19 patients in comparison to the healthy volunteers. The results of the statistical analysis are presented in *Figure* 3.

The results shown in *Figure* 3 demonstrate that the mean values of the S index in COVID-19 patients are lower in comparison to healthy volunteers. The Mann-Whitney U-test allows us to reveal a significant difference in S values in groups of healthy people and patients: $U_{emp.}$=227, $U_{0.05}$=415.0. The Mann-Whitney U-test confirmed that the difference in the group-average S indices is statistically significant at p≤0.05.

Discussion

The main finding of the study was that the S index, which corresponds to the frequency of phase synchronization intervals between the loops of autonomic control, was lower in COVID-19 patients comparing to healthy volunteers. The Mann-Whitney U-test confirmed that the difference between the group-averaged values of the S index was statistically significant.

We observed the decrease of the S index in COVID-19 patients, despite the known results of other researchers that suggested activation of sympathetic control due to ACE2 expression [4, 6]. It may indicate that the reaction of autonomic control to viral infections is more complex than was previously assumed: the presence of the virus increased the activity of the sympathetic control loops and, at the same time, decreased the strengths of their coupling. This result requires additional research.

The question about the specificity of obtained results is relevant. According to the results from [23], infection by different types of viruses can increase the concentration of ACE2. Additionally, similar effects can be caused by some pathologies affecting RAS (diabetes, kidney disease) [23], some pathologies of the cardiological [5] and gynecological profile [24-25], as well as changes in the physical condition [16], as was shown in our previous studies.
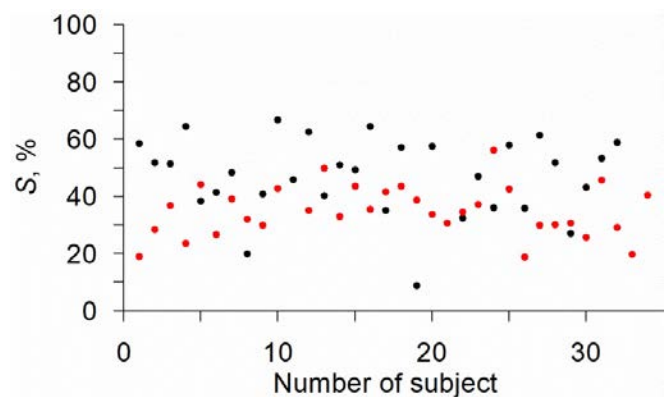

Figure 2. Dot plot of individual values of the S index in healthy volunteers (black) and COVID-19 patients (red).
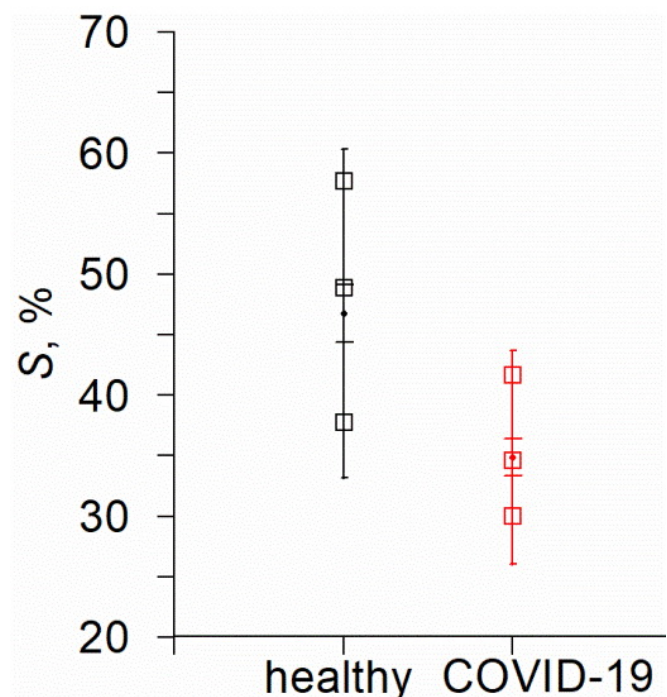

Figure 3. Distribution of the values of the *S* index estimated for healthy volunteers (black) and COVID-19 patients (red). The points show the mean values, the error bars with wide caps indicate the standard error, the error bars with narrow caps indicate the standard deviation and the open squares are the 3 quartiles.

The group-averaged values of the S index were significantly different between the groups of healthy volunteers and COVID-19 patients. However, the sensitivity and specificity of the individual classification was not high (*Figure* 3). The influence of age and sex on the individual values of the S index requires further careful study. These observations and considerations highlight the limitations of the diagnostics based on the S index.

However, despite these limitations, the S index in combination with other known methods based on spectral analysis of RR intervals [8-9] and nonlinear methods of data analysis [10-12] is a promising basis for a viral diseases screening system. The S index estimates the degree of interaction between the loops of autonomic control, and not their individual dynamics, and, therefore, statistically independent from other well-known indices and, when used in combination with them, provides additional information related to changes in the dynamics of autonomic control of circulation, increasing sensitivity and reliability of the analysis.

Conclusion

Several well-known studies have demonstrated that autonomic control of blood circulation was a sensitive index of a psychophysical state and could be used to detect various pathologies, including viral infections and COVID-19. However, the complexity of autonomic control and the irregular intervals of phase synchronization between the loops of heart rate and arterial pressure control limit the possibilities of the diagnostics indices derived from linear analysis and require the development of specialized nonlinear methods.

In this work, we compared the groups of healthy volunteers and COVID-19 patients using the previously developed index of the total percentage of phase synchronization between the autonomic control loops of CVS.

The obtained results showed that the group-averaged values of the previously proposed index were lower in COVID-19 patients in comparison to healthy volunteers. Statistical analysis of the results was encouraging and suggests that the S index reflected the presence of the viral disease. It makes this index a promising basis for non-invasive screening diagnostics of viral diseases, particularly COVID-19.

Conflict of interest
The authors declare that they have no conflict of interest.

Ethical approval
All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Design of this study was approved by the Ethics Committee of the Saratov State Medical University n.a. V.I. Razumovsky (Saratov, Russia) in 2021 and written informed consent was obtained from all subjects who participated in this study.

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