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HEART RATE VARIABILITY IN PATIENTS WITH MODERATE AND SEVERE COVID-19

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The study of heart rate variability (HRV) in COVID-19 is of undoubted interest, as it allows one to judge about disturbances in the work of the cardiovascular system, as well as about shifts in the state of autonomic regulation of physiological functions. Both of these systems are targets for viral damage.

The aim. To investigate how HRV changes in seriously ill COVID-19 depending on the severity of the disease, as well as to determine the prognostic role of ROC analysis in predicting the outcome of the pathological process. Materials and methods. observations were carried out on 29 patients of moderate severity (age 58.7 ± 6.5 years), and 55 seriously ill (59.4 ± 9.2 years) COVID-19. The control group consisted of 69 people (mean age 62.5 ± 9.6). HRV was studied using the Rehovot Dynamic Light Scattering apparatus (Israel) and using an original algorithmic approach. Statistical processing was performed using the R language version 3.6.2. To assess the relationship between the studied indicators, the Pearson correlation method was applied. To calculate the threshold values for survival and mortality, which have predictive value, an ROC analysis was performed. Results. In patients with COVID-19, HRV parameters significantly decreased. There were no significant differences in the studied values between groups of different severity. The data obtained indicate a violation of the activity of both the sympathetic and parasympathetic divisions of the autonomic nervous system. ROC analysis of HRV did not provide a predictive model for COVID-19 with a high probability of an outcome. Conclusion. In patients with moderate and severe COVID-19, the main indicators of HRV are significantly reduced. Using ROC analysis of HRV, no significant predictors of favorable and fatal outcomes were found in patients with COVID-19.

Keywords: COVID-19, microcirculation, heart rate variability.

It is known that the method of studying heart rate variability (HRV) is subtly responsive to the action of stress stimuli, as well as to any changes in the body of a healthy and sick person. At the same time, HRV in different courses of COVID-19 has practically not been studied. Elucidation of this issue is extremely

important not only for theory, but also for practical medicine, because it quite accurately allows us to judge changes in the work of both the cardiovascular system and regulatory mechanisms that ensure a balance in the activity of the sympathetic and parasympathetic divisions of the autonomic nervous system. (ANS) under stress, as well as a wide variety of pathological conditions [22, 26].

The list of target organs affected by the SARS-Cov-2 virus is not limited to the respiratory tract. Alteration of the cardiovascular and central nervous systems is essential in the pathogenesis of the new coronavirus infection. It has now been established that cardiovascular manifestations in patients with COVID-19 include myocardial damage, arrhythmias, cardiac arrest, heart failure, and bleeding disorders [7,8]. They have a fairly widespread character and a protracted course. Moreover, the mechanism of heart damage in patients with COVID-19 includes direct damage to myocardial cells mediated by

angiotensin-converting enzyme 2 (ACE2) receptors, as well as systemic inflammation, which causes indirect damage to myocytes [21]. Moreover, patients with COVID-19, whose disease is fatal, always suffer from cardiopulmonary complications [25].

A. Izcovich et al. [19], having analyzed 207 studies by various authors, identified the main factors that provide valuable predictive information about mortality and / or severe disease in patients with COVID-19. Among them, a significant part was associated with lesions of the cardiovascular system, cerebrovascular diseases, chronic obstructive pulmonary disease, cardiac arrhythmia, arterial hypertension, diabetes, dyslipidemia, respiratory failure, etc. Moreover, a decrease in HRV often correlates with an increase in the concentration of C-reactive protein (CRP). There is no doubt that HRV in COVID-19 is primarily influenced by the inflammatory process caused in response to viral invasion. According to the

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authors, "... a short-term intermittent HRV analysis in patients with COVID-19 can provide potential value for the prognosis of the disease."

The mechanisms of heart damage in COVID-19 are not well established, but likely include increased stress due to respiratory failure and hypoxemia, direct myocardial damage caused by SARS-CoV-2, and indirect damage from a systemic inflammatory response. But most likely, the complex of all the listed factors influences the function of the heart [5].

Considering the presented data, it seems promising to study HRV shifts in patients with moderate and severe COVID-19.

Clinical characteristics of patients and research methods.

Our observations were carried out on 29 moderately severe patients (age 58.7 ± 6.5 years) and 55 seriously ill patients (59.4 ± 9.2 years) who received treatment at the 1st City Clinical Hospital of Chita, redesigned for the treatment of patients COVID-19, in 2020. The control group consisted of 69 people (mean age 62.5 ± 9.6 years). The groups did not differ in the frequency of concomitant diseases (diabetes mellitus, hypertension, arthritis and arthrosis, metabolic syndrome). Exclusion criteria: the presence of oncopathology, acute coronary syndrome, non-coronary myocardial damage, strokes, encephalitis, taking antiarrhythmic and cardiotropic drugs, cardiac arrhythmias, unstable hemodynamics. All our activities were carried out with the consent of the subjects and complied with ethical standards developed on the basis of the Helsinki Declaration of the World Association "Ethical Principles for Conducting Scientific Medical Research with Human Participation" as amended in 2008 and the "Rules of Clinical Practice in the Russian Federation" approved by the order of the Ministry of Health of the Russian Feder-

ation dated June 19, 2003 No. 266. The studies were approved by the decision of the local ethical committee of the Chita State Medical Academy of the Ministry of Health of the Russian Federation (protocol No. 102 dated 05/15/2020).

Standard therapy was carried out in accordance with the current version of the temporary guidelines of the Ministry of Health of the Russian Federation. "Prevention, diagnosis and treatment of new coronavirus infection COVID-19" and local treatment protocols. Antiviral and antibacterial therapy was used. Low molecular weight heparins (LMWH) were prescribed at a dose of 1 mg / kg 2 times a day or continuous intravenous infusion of unfractionated heparin (UFH) with a starting rate of 1000 U / h with subsequent correction of the injection rate based on the coagulogram parameters. Respiratory therapy included inhalation of humidified oxygen, non-invasive mechanical ventilation. Symptomatic therapy consisted of glycemic correction, administration of antipyretic drugs, nutritional support, and maintenance of water and electrolyte balance.

HRV was studied using the mDLS apparatus (Dynamic Light Scattering, Rehovot, Israel) and using an original algorithmic approach. For this purpose, a technique has been developed for the spectral decomposition of the signal into frequency components associated with hemodynamic sources of different shear rates of blood layers. To assess the characteristics of HRV, the method of photoplethysmography (PPG) was used [10, 11]. Information on the variability of RR intervals was extracted from the pulse component of the mDLS signal, and HRV indicators were calculated [10]. The measurements were made for 5 minutes.

The following time indicators were used: HR (Heart Rate) - heart rate (HR) [beats / min]; SDNN (Standard Deviation

of RR intervals) - standard deviation of all RR intervals [msec] (reflects all long-term components and circadian rhythms responsible for variability); SDSD - standard deviation of differences between adjacent intervals (represents variability in short time intervals); RMSSD (Root Mean Square of the Successive Differences) - the square root of the root mean square of the differences in RR intervals [msec] (refers to changes in the short term and reflects deviations in the tone of the autonomic nervous system, which are predominantly vagus-mediated); MAD (Median Absolute Deviation) is the absolute deviation of the median (used to assess the quality of the signal under study by the presence of outliers, ie, extreme values) [6, 14].

Frequency analysis is presented by indices: PWR - total power of oscillations in all frequency ranges; LF - power in the low frequency range (0.04-0.15 Hz), due to the activity of the sympathetic division and reflects the delay time of the baroreflex loop; HF - power in the high frequency range (0.16-0.5 Hz) is associated with respiratory movements and is mainly due to vagal activity; PWR is the sum of the low-frequency LF and high-frequency components of the HF; LF / HF - power ratio (reflects the overall sympatho-vagus balance).

Statistical processing was performed using the R language version 3.6.2. To assess the mutual relationship between the studied indicators, the Pearson correlation method was used (the choice of the method was due to the distribution of groups reliably close to normal). The quantitative characteristics of the traits were represented by the median (Me, Q2 - the second quartile), the first and third quartiles (Q1 and Q3, respectively). To calculate the threshold values of mortality that have predictive value, an ROC analysis was carried out [1]. When construct-

Heart rate variability in patients with moderate and severe COVID-19

Test item	Control. n=69	Patients with moderate COVID-19. n=29	Patients with severe COVID-19.	p1	p2	p3
HR	86.6 [75-98.5]	79.4 [73.7-86.6]	83.1 [69.3-93.4]	0.33	0.44	0.74
SDNN	145 [94.9-164]	70 [36.9-95.2]	59.8 [41.6-104]	< 0.0001	< 0.0001	0.57
SDSD	113 [82.1-123]	71.3 [22.8-90.3]	57.1 [34.3-96.8]	< 0.0001	< 0.0001	0.34
RMSSD	168 [105-189]	97.5 [29.9-122]	78.9 [42.3-140]	< 0.0001	< 0.0001	0.38
MAD	72.5 [32.5-125]	35 [15-50]	25 [20-35]	0.0004	< 0.0001	0.41
PWR	6910 [3280-11100]	1140 [417-3140]	992 [563-1990]	< 0.0001	< 0.0001	0.77
LF	2260 [866-3810]	302 [126-456]	229 [102-496]	< 0.0001	< 0.0001	0.72
HF	3780 [1660-5710]	666 [98.6-1970]	577 [166-1070]	< 0.0001	< 0.0001	0.83
LF/HF	0.61 [0.463-0.795]	0.524 [0.395-1.08]	0.521 [0.352-0.983]	0.95	0.71	0.95

Note. Data representation Me [P25-P75]. Comparison of groups according to the "Wilcoxon rank sum test" criterion. p1 - control and moderate patients; p2 - control and severe patients; p3 - moderate and severe patients. Correction for multiple comparison "Hommel (1988)".

ing the ROC-curve there is a change in the value (threshold) of the investigated factor, when deciding on the possible lethality and at a given threshold, the sensitivity and specificity of prediction are calculated from the experimental data. The test cycle starts at 0% sensitivity and 100% specificity, ends at 100% sensitivity, 0% specificity. Predictive accuracy was assessed using an expert scale of indicators [17, 28]; the area under the ROC curve (Area Under Curve - AUC), which can be taken as follows: 90-100% - excellent; 80-90% is good; 70-80% is acceptable; 60-70% - weak; 50-60% - unsatisfactory [4, 15].

Results. As follows from the indicators given in the table (Table 1), the heart rate in patients with COVID-19 did not differ significantly from the norm. At the same time, SDNN, reflecting all long-term components and circadian rhythms during the recording, was significantly reduced in both the group of moderate and severe patients. The data obtained indicate that subtle adaptive responses aimed at maintaining homeostasis in the activity of the cardiovascular system are impaired in patients with COVID-19. This opinion is confirmed by a decrease in patients with COVID-19 in both study groups by almost 2 times in SDSD, RMSSD and the absolute deviation of the median - MAD. At the same time, no significant differences in the values of SDSD, RMSSD and MAD between the groups of patients with COVID-19 of different severity were found.

The data presented by us on changes in HRV in patients with COVID-19 undoubtedly reflect shifts in the balance of the sympathetic and parasympathetic divisions of the autonomic nervous system (ANS). This, in particular, is evidenced by a significant decrease in the LF index in both studied groups, due to the activity of the sympathetic division of the ANS. The data obtained indicate that patients with COVID-19 have a distinct violation of sympathetic innervation.

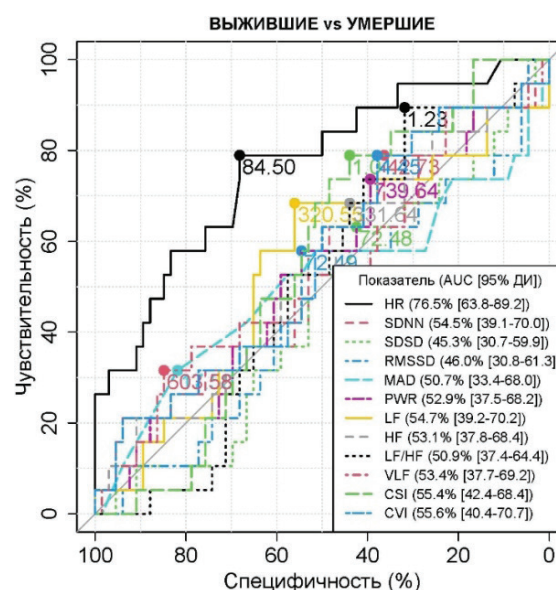
But at the same time, in such patients, there is a decrease in the HF index, associated with the function of the respiratory system and mainly due to vagal activity. Consequently, in patients with moderate and severe form of COVID-19, the activity of both sympathetic and parasympathetic divisions of the ANS is impaired. Imbalances in their balance are also indicated by a decrease in patients with moderate severity of the nonlinear sympathetic CSI index and a decrease in both degrees of severity of the course of COVID-19 in the nonlinear parasympathetic CVI index.

Apparently, these shifts in COVID-19

are complex, and, first of all, can be caused by those disorders that arise in the central nervous system itself against the background of the direct or indirect action of the virus. In particular, J Matschke et al. [23] showed that in more than half of the patients who died from COVID-19, the virus is found in the brain tissue. At the same time, traces of SARS-CoV-2 were detected in the cells of the brain stem and neurons extending from it. The most common finding is pronounced neuroinflammatory changes in the brain stem. Apparently, the virus can enter the central nervous system through the vagus nerve. In all patients, to one degree or another, the authors observed astrogliosis - an abnormal proliferation of astrocytes.

According to N Krishna et al. [20], in addition to respiratory and systemic damage to many organs and systems of the body, COVID-19 is characterized by a wide range of neurological manifestations (encephalitis, meningitis, myelitis, acute disseminated encephalomyelitis, metabolic and acute hemorrhagic necrotizing encephalopathy, cerebrovascular diseases, Guillain-Barré syndrome cranialis, vegetative dystonia and myopathy). These facts alone may indicate that the revealed changes in the balance of the sympathetic and parasympathetic divisions of the ANS may be organic in nature [9].

An essential feature of the course of the new coronavirus infection, which differs from other acute respiratory diseases, is its protracted course [12]. In the case of severe forms involving the lower respiratory tract, pathological processes can last for several weeks [16]. In these conditions of the protracted course of COVID-19 with periods of progression and relief of systemic inflammation, the body's defense systems are trying to adapt. However, in the case of a discrepancy between the regulatory capabilities of the prevalence of cell alteration, a breakdown of protective programs and adaptation processes is possible [24]. In this case, there is a decompensation of the disease and the formation of multiple organ failure. It was found that adaptation disorders are more often recorded in conditions of a low functional reserve of protective systems against the back-



The survivors vs the dead
Sensitivity (%)
Specificity (%)

ground of immunopathies and metabolic disorders of various origins [24].

The use of ROC analysis of HRV did not allow us to identify predictors of the outcome of COVID-19. Of all the studied indicators, only HR corresponded to the required significance (76.5% [63.8-89.2]), which should be regarded as an acceptable result (Fig. 1). Perhaps the low predictive value of HRV is due to the fact that the studies were carried out once.

Currently, there is no doubt that COVID-19 is a systemic disease that, in severe stages, affects all organs and systems of our body, without exception, and leads to the development of multiple organ failure. Systemic endothelial dysfunction, which develops in COVID-19, and is accompanied by a "cytokine storm", largely determines the disorders that occur in the hemostatic system [3]. It should be noted that increased aggregation of blood cells to the damaged endothelium, pronounced expression of tissue factor on the endothelium of blood vessels, heart, alveocytes and other organs and tissues, impaired fibrinolytic activity of blood, accompanied by an increase in the concentration of D-dimer, a drop in the level of natural anticoagulants, ultimately leads to the development of thrombotic micro- and macroangiopathy, which cannot but affect the damage and dysfunction of the receptor apparatus [13, 27] and, therefore, play a significant role in the imbalance of the ANS activity.

Finally, another assumption suggests itself. Of course, the nervous system cannot stand aside with such significant changes in the body that arise as a re-

sult of cell contamination with the SARS-CoV-2 virus [9]. Already with moderate forms of the course of COVID-19, both the sympathetic and parasympathetic divisions of the ANS are working at the limit. But at the same time, as our data show, the homeostatic balance will change, due to which they move to a completely new stage of interaction, which partly allows the body to adapt to significantly changed conditions of existence. It is possible that these shifts are of a temporary compensatory nature. At the same time, in severe patients, these protective adaptive shifts to ensure homeostatic reactions are clearly not enough, which ultimately leads to an imbalance in the ANS activity, thrombosis and multiple organ failure, often ending in death.

It is very likely that the deviations in the balance of sympathetic and parasympathetic influences revealed in this study, as well as a decrease in their general activity, may be early predictors of depletion of the central link in the regulation of the functioning of defense mechanisms. And the subsequently recorded pronounced deviations of the immune-inflammatory response, changes in the hemostasis and fibrinolysis systems, disturbances in ventilation-perfusion coupling in the lungs have a character dependent on the state of global dysregulation of adaptive programs [2].

Finally, it should be noted that the ROC analysis of HRV indicators failed to identify predictors of the severity of COVID-19. It is possible that failures in this direction are due to the fact that the analysis was carried out once.

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