Changes in Cerebral Hemodynamics in Patients with Hypertension and Post-Covid

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Abstract: The study results are based on the data of examination of 73 patients with controlled hypertension of the II stage. The 1st study group consisted of patients with hypertension and history of Covid-19 infection (36 patients), the 2nd group – patients with hypertension was the control group. All patients were examined using ultrasound duplex scanning of head and neck vessels. The state of cerebrovascular reserve was studied according to the method of Lelyuk – the morphofunctional state of the middle cerebral artery in hypo- and hyperventilation. The vasomotor reactivity index was calculated. Statistical analysis methods were in accordance with generally accepted international standards. Thickening of the intimal media complex of the carotid arteries during ultrasound scanning of head and neck vessels was observed in 73 (100%) patients (intimal media complex more than 0.9 mm) in the area of maximum visual thickening. The vasomotor reactivity index in patients of the 1st study group was 35.4 (11.0; 49.2), in patients of the 2nd group – 46.7 (26.8; 76.4), which is a statistically significant difference, p=0.002, including the distribution of mean values and their descriptions in terms of the median and interquartile range Me (25%; 75%). Thus, patients with controlled hypertension and the history of Covid-19 infection were shown to have impaired cerebral blood flow, which was manifested by a decrease in the vasomotor reactivity index. When examining the main arteries of the head and neck, the vasomotor reactivity index should be determined to assess the state of cerebral hemodynamics and develop treatment measures.

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Introduction

The respiratory system is known to be at the forefront of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection. Regardless of its tropism to lung tissue, the SARS-CoV-2 virus attacks various organs and systems of the human body, including cardiovascular, neurocognitive, neurological, gastrointestinal, hepatic, metabolic and mental and resolve multi-organ dysfunction (McMichael et al., 2020). Concomitant illnesses will increase the risk of Covid-19 and increase mortality (Verity et al., 2020). Based on retrospective studies, approximately 50% of patients with Covid-19 have more than one comorbidity, and with severe infection, the number of such patients increases to 72% (Ruan et al., 2020). Database analysis of 5,700 patients with Covid-19 (mid-century 63 years), hospitalized in up to 12 hospitals in New York, showing that 88% of patients had one or more comorbidities: arterial hypertension (AH) increased 56.6% of patients have ischemic heart disease – in 11.1%, obesity – in 41.7% and diabetes – in 33.8% (Richardson et al., 2020). Among patients who died from Covid-19, comorbidity that worsened the prognosis was significantly more common (1.9 times). The presence of 2 concomitant diseases increased the risk of death by 9.5 times for patients with one disease. Viral infection can destabilize the cardiovascular system and increase the occurrence of new cardiovascular complications, which significantly increases the risk of death in Covid-19. In SARS-CoV-2-infected patients with concomitant cardiovascular diseases, mortality increased by 2.4 times (Guan et al., 2020a). Cardiovascular tissues or cells expressing angiotensin-converting enzyme 2 receptors (ACE-2 receptors) are potentially at risk of infection by SARS-CoV-2 (Zhang et al., 2020). In patients at high risk for developing cardiovascular disease (CVD), loss of ACE-2 due to receptor internalization caused by SARS-CoV-2, will worsen CVD. A decrease in the expression of ACE-2 receptors in the vascular wall contributes to the development of endothelial dysfunction and inflammation, especially with concomitant diseases such as atherosclerosis and diabetes (South et al., 2020). Factors associated with increased disease severity include comorbidities such as hypertension, diabetes, and coronary artery disease. Hypertension is one of the most important factors of poor prognosis in patients with Covid-19. The global prevalence of hypertension in 2019 among adults 30–79 years of age was 34% among men and 32% among women. Despite the high prevalence of hypertension, the level of awareness of existing hypertension, effective treatment and control of blood pressure was low in 2018–2019, and has worsened further during the Covid-19 pandemic (Guan et al., 2020b; Inciardi et al., 2020; Wang et al., 2020a; Wu and McGoogan, 2020; Wu et al., 2020; Zhou et al., 2020).

It is important to take into account possible functional and pathological disorders that are observed in patients who have had Covid:

- functional disorders of vital systems of the body can persist for a long time after the elimination of an acute infectious-inflammatory process and the resolution of viral pneumonia;
- functional and pathological disorders of varying severity can occur in patients with any course of Covid-19;
- patients with severe/extremely severe forms of Covid-19 experience the most pronounced negative changes due to the consequences of intensive care (intensive care aftereffects syndrome – ICU syndrome) and stay in the intensive care unit (ICU);
- consequences of staying in the ICU: forced immobilization (bed rest), polyneuromyopathy and polyneuropathy of critical illness, myopathy, post-intubation dysphagia, stiffness and contractures of the joints;
- with general muscle weakness, loss of muscle mass and muscle strength (peripheral muscle dysfunction), physical inactivity and decreased physical performance;
- weakness of the respiratory muscles, primarily muscle concussion, with the possible development of atrophy of the diaphragm, which leads to its dysfunction;
- dysfunction of the cardiovascular system, instability of hemodynamic parameters;
- risk of thrombosis and thromboembolism;
- insufficient control of cardiovascular risk factors;
- nutritional deficiency, violation of a nutritious and balanced diet;
- sleep and consciousness disorders (other cognitive disorders);
- psycho-emotional disorders (depression, anxiety disorders, which make up about 60% of all mental disorders) (Bubnova et al., 2020).

It is precisely because of the extensive damage to the body's systems that recommended instrumental and laboratory tests have long been known, such as:

- electrocardiography (ECG), according to indications – daily ECG monitoring;
- echocardiography (EchoCG);
- assessment of external respiration function using spirography;
- assessment of the SpO_2 level of blood oxygen saturation – pulse oximetry;

- computed tomography (CT) scan data over time;
- clinical blood test with determination of the rate of erythrocyte subsidence, assessment of the number of platelets;
- coagulogram (international normalized ratio, activated partial thromboplastin time) and D-dimer level;
- biochemical blood test with determination of blood potassium and sodium levels, transaminases, total protein, albumin (if possible), C-reactive protein, glucose, creatinine with calculation of glomerular filtration rate using the CKD-EPI formula;
- general urine analysis and assessment of daily protein loss according to indications;
- to assess hypoxia tolerance, it is recommended to use Genchi and Stange functional tests;
- to assess exercise tolerance, a six-minute walk test with assessment of blood saturation dynamics during the test;
- cardiopulmonary loading testing on a treadmill or bicycle ergometer if necessary, preferably also with an assessment of the dynamics of blood saturation.

But the proposed methods for studying post-Covid patients are not sufficient to control the possible above-listed functional and pathological conditions that can develop after suffering from the corona virus. Namely, it is not enough to control the risks of damage from the cardiovascular system; as noted above, hypertension is the most significant risk factor for a negative prognosis. Therefore, in our study, we additionally conducted an ultrasound examination of the cerebrovascular reserve during transcranial Doppler sonography with the determination of the vasomotor reactivity index (VMRI) in patients with hypertension and post-Covid (Sonkaya et al., 2021).

The aim of the study

To determine the level of the brain's cerebral reserve for studying its state in patients with controlled hypertension and post-Covid.

Material and Methods

The study design was defined as an open, prospective, monocentric clinical trial in parallel groups of patients. The study results are based on the data of a comprehensive examination of 73 patients with controlled hypertension aged from 30 to 70 years (average age – 52.5 [8.4] years). The hypertension duration in the examined patients ranged from 5 to 23 years; the median was 10 (9–12) years. In 36 (49.3%) of the examined patients with hypertension had a history of Covid-19 infection, they constituted the 1st study group, the remaining 37 (50.7%) patients constituted the 2nd group – the control group. In the groups, patients were comparable in terms of gender, age, duration of hypertension and concomitant pathology. All the examinees underwent general clinical, instrumental, and laboratory diagnostics to verify the hypertension diagnosis and identify concomitant pathology.
A general clinical examination and instrumental and laboratory diagnostic methods were performed according to standard protocols for cardiac patients. Additional research methods were also performed: daily blood pressure monitoring, home and office ambulatory blood pressure monitoring, electrocardiography, sonography of the main arteries of the head and neck using ultrasound duplex scanning of the vessels of the head and neck. Using ultrasound duplex scanning of the vessels of the head and neck on the HDI-7 (Philips) device with a linear sensor with a frequency of 10–12 MHz and a sector sensor with a frequency of 2–4 MHz on the right and left anterior surfaces of the neck with the patient lying on his back, with the head turned 45° in the opposite direction from the artery being examined. The common, external carotid (ECA), internal carotid (ICA) and vertebral arteries were visualized on both sides using the standard technique. In all visualized arteries, including the ECA and ICA, the diameter of the specified vessels and such blood flow parameters as maximum systolic peak (Vps), maximum diastolic (Ved) blood flow velocity, resistance index (Ri), pulsatility index (Pi), peripheral resistance coefficient (systolic-diastolic ratio – S/D), as well as vascular elasticity were determined. In each study, the thickness of the intimal media complex (IMC) of the carotid arteries was determined (normal up to 0.9 mm) in the area of maximum visual thickening, and the quantitative and qualitative state of the ICA was assessed. The state of the cerebrovascular reserve (CVR) was studied by the morphofunctional state of the middle cerebral artery (MCA) in hypo- and hyperventilation tests according to the method of Lelyuk. First, a test was performed with holding the breath on exhalation for 20 s, after 5 min a test was performed with hyperventilation for 20 s with repeated registration of linear blood flow velocities (LBFV) in the middle cerebral artery. The vasomotor reactivity index was calculated using the formula:

$$VMRI = ([V_{apnea} – V_{hyper}]/V_0) \times 100\%$$

where: V_{apnea} is the average velocity of blood flow after holding the breath, V_0 is the initial average r velocity of blood flow, V_{hyper} is the average velocity.

The patients/participants provided written informed consent to participate in this study. The study was voluntary and anonymous, and only general data

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was collected. Confidentiality of information was protected by depersonalizing participant identifiers. Statistical analysis, including the distribution of the average values and their description depending on the nature of the distribution (determined by the Shapiro-Wilk test) in the form of an arithmetic mean (M) and a 95% confidence interval (95% CI) with a normal distribution and the median and interquartile range Me (25%; 75%) – with asymmetric; calculation of relative values; assessment of the reliability of differences in the number of variables using the Mann-Whitney criterion; rank correlation analysis using the Spearman correlation coefficient (rs), using the additional STATISTICA program (version 6.1), serial number – AGAR 909E415822FA.

Results

The analysis of the obtained data showed that patients of both groups before inclusion in the study had hypertension of the with predominant damage to the heart, as a target organ, in the form of hypertrophy of the left ventricle (LV) of the heart, in 1 group there were 33 such patients (91.7%), in 2 group – 35 (94.6%). Patients with reduced LV ejection fraction (<50%) did not participate in the study. Also, the exclusion criteria were: myocarditis, as a complication after Covid-19 and impaired repolarization in the myocardium of the left ventricle.

Patients with mild or moderate severity of Covid-19 and those who recovered more than 4 months ago took part in the study. The structure of concomitant pathology was as follows: coronary heart disease (class I–II functional class according to the Canadian classification) – 28.8% (21 patients), dyslipidemia – 79.5% (58 patients), chronic heart failure (class I and II according to NYHA) – 15.1% (11 patients), 71.2% (52 patients) were overweight or obese; chronic pyelonephritis – in 23.3% (17 patients), varicose disease of the lower extremities – in 5.5% (4 patients), manifestations of osteoarthritis of large and/or small joints – in 31.5% (23 patients), included in the study. Patients were given comprehensive information in a personal interview about the goals and points of action of drug treatment, the need for constant continuous intake of drugs. All patients were recommended a diet with a reduced content of animal fats, with an increased amount of fruits, vegetables, cereals, nuts and legumes, preference should be given to sea fish, dairy products with a low fat content or without them. Continuation of taking anticoagulants, vitamins, immunocorrectors prescribed earlier was not a reason for exclusion. Patients received complex treatment in accordance with approved national protocols for the underlying disease, personalized

Table 1: Echocardiographic data and sonographic characteristics of the middle cerebral artery and cerebrovascular reserve

Indicator (95% CI)	1st study group hypertension with Covid-19 (n=36)	2nd study group hypertension without Covid-19 (n=37)	Differences between groups (p)
LV hypertrophy, % patients	91.7	94.6	p>0.05
LVEF, %	67.0 (60.3–73.7)	69.0 (60.2–77.8)	p>0.05
Creatinine, μmol/l	102.5 (89.0–116.0)	97.8 (85.5–110.1)	p>0.05
LV wall thickness during diastole, cm	1.2 (0.6–1.8)	1.2 (0.8–1.6)	p>0.05
IMC, mm	1.1 (1.0–1.2)	1.0 (0.9–1.1)	p>0.05
Vps, cm/s	71.9 (66.4–77.4)	69.4 (59.6–79.2)	p>0.05
Ved, cm/s	30.2 (27.5–32.9)	29.5 (25.4–33.6)	p>0.05
Vmean, cm/s	48.4 (44.1–52.7)	47.6 (40.5–54.7)	p>0.05
Vps/Ved	2.4 (2.3–2.5)	2.3 (2.1–2.5)	p>0.05
TAMV, cm/s	46.3 (42.2–50.4)	48.6 (43.1–54.1)	p>0.05
Ri	0.5 (0.5–0.5)	0.6 (0.6–0.6)	p>0.05
Pi	0.8 (0.8–0.8)	0.8 (0.7–0.9)	p>0.05
VMRI, Me (25%; 75%)	35.4 (11.0; 49.2)	46.7 (26.8; 76.4)	p<0.05

Echocardiographic characteristics: LV – left ventricle; LVEF – left ventricle ejection fraction; sonographic characteristics: IMC – intima-media complex; Vps – peak systolic velocity; Ved – end diastolic velocity; Vmean – time-averaged mean velocity; Vps/Ved – systolic-diastolic velocity ratio; TAMV – time-averaged maximum velocity; Ri – resistance index; Pi – pulsatility index; VMRI – vasomotor reactivity index; Me – median and interquartile range; CI – confidence interval

therapy according to indications: antihypertensive drugs (ACE inhibitors/sartans, slow Ca-channel blockers, diuretics), anti-ischemic drugs; lipid-lowering therapy; antiplatelet agents; therapy for comorbid pathology) (McEvoy et al., 2024). Patients received antihypertensive treatment prescribed earlier, which did not require correction due to adequate blood pressure control.

There was no significant difference between the groups in the LV ejection fraction (LVEF) (1 group – 67.0% [95% CI 60.3–73.7%], 2 group – 69.0 [95% CI 60.2–77.8%] and in the LV wall thickness during diastole: 1 group – 1.2 cm [95% CI 0.6–1.8 cm], 2 group – 1.2 cm [95% CI 0.8–1.6 cm]), which can be seen in Table 1.

The obtained data indicate that the blood flow velocity indices in the MCA in all groups of patients with hypertension were statistically comparable ($p>0.05$). Extracranial and transcranial main vessels in patients did not have significant changes in blood flow and autoregulation disorders.

Thickening of the intimal media complex of the carotid arteries during ultrasound duplex scanning of the vessels of the head and neck was observed in 73 (100%) patients (intimal media complex more than 0.9 mm) in the area of maximum visual thickening. The vasomotor reactivity index in patients of the 1st study group was 35.4 (11.0; 49.2), in patients of the 2nd group – 46.7 (26.8; 76.4), which is a statistically significant difference, $p=0.002$ (Figure 1).

Patients with a history of Covid-19 infection had a direct correlation between creatinine levels and LVEF ($rs=0.80$, $p<0.001$), which was not observed in patients without Covid-19. Of interest is the inverse correlation between creatinine levels and VMRI ($rs=–0.60$, $p<0.001$), where a reduction in creatinine levels may be justified by the use of glucocorticoids in the treatment of Covid-19 (Wang et al., 2020b). This requires further study and scientific explanation in the future.

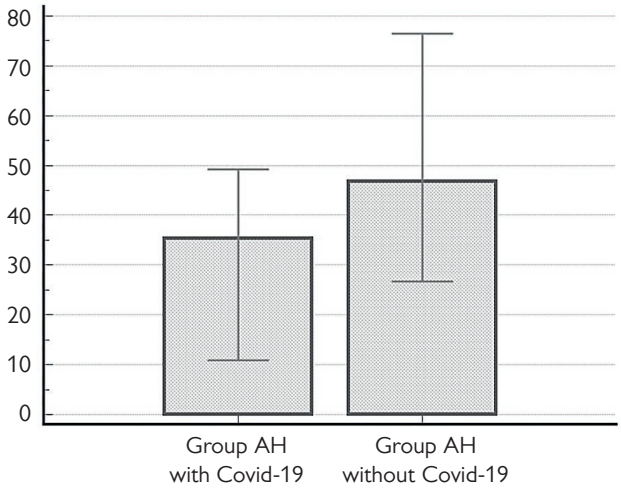

Figure 1: The vasomotor reactivity index (VMRI) in patients, median and interquartile range Me (25%; 75%). AH – arterial hypertension.

Discussion

One of the ways of implementing a negative impact on cerebral hemodynamics may be atherosclerotic and hypertensive vascular damage and deterioration of cerebral blood flow. That is why a study of the main arteries of the head and neck was conducted to determine the cerebrovascular reserve. The data obtained indicate that the blood flow velocity indicators in the middle cerebral artery in all groups of patients with arterial hypertension and hypertension with post-Covid were statistically comparable ($p>0.05$). Extracranial and intracranial main vessels did not have significant changes in cerebral blood flow and disturbances in autoregulation processes and significant structural differences. It is significant that all 73 (100%) patients with stage II hypertension had thickening of the intimamedia complex. Thickening of the IMC was independent of the presence or absence of Covid infection in the past. In the two study groups it was slightly higher than 0.9 mm, with an average of 1.0 to 1.1 mm. The results of the study revealed a significant ($p<0.002$) decrease in the VMRI in patients with hypertension and post-Covid (35.4 [11.0; 49.2]) as in patients with hypertension without post-Covid 46.7 ([26.8; 76.4]). The latter indicates a close relationship between the value of the VMRI and the presence of post-Covid in patients with hypertension; in patients with hypertension and post-Covid, there is a violation of cerebral blood flow, which was manifested in a decrease in the VMRI.

We understand the limitations of this study, associated with the small number of participants in the study groups, as well as the formation of special groups by age, gender, comorbid pathology and physiological characteristics, as well as treatment results. However, the results obtained allowed us to focus on the importance of studying the cerebrovascular reserve in patients with hypertension and post-Covid as an option for timely diagnosis and personalization of treatment along with adequate antihypertensive therapy.

Conclusion

Thus, hypertension and a history of COVID-19 disrupt adaptive changes in the cerebral vessels, which leads to increased stress on the vessel walls and impaired

protection of arterioles, capillaries and venules from potentially destructive fluctuations in blood pressure. An increase in basal cerebral blood velocity and a decrease in vasomotor reactivity rates in patients with Covid-19 can be considered as an indicator of dysfunction of cerebral hemodynamics in the central nervous system and this can be evaluated as a result of endothelial dysfunction. Autoregulation is a critical driver of both the structural and functional changes in cerebral blood flow caused by hypertension, but the pathogenic mechanisms remain poorly defined for the vital cerebrovascular regulatory mechanisms. The patients with controlled hypertension and a history of Covid-19 infection have impaired cerebral blood flow, which is manifested by a decrease in the VMRI. When examining the main arteries of the head and neck, the VMRI should be determined to assess the state of cerebral hemodynamics and develop treatment measures. Despite the disastrous consequences of hypertension and post-Covid disease, impaired cerebral blood flow, the state of the vascular bed and associated changes in brain tissue in patients with hypertension in clinical manifestations, the impact on quality of life, prognosis for vascular complications have not been sufficiently studied.

With regard to the diagnosis of early signs of brain damage and post-Covid in hypertension, as well as monitoring the effectiveness of medical rehabilitation, it is advisable to introduce the use of functional breathing tests with the determination of cerebrovascular reserve according to the vasomotor reactivity index in a sonographic study.

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