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Assessment of Endothelial Dysfunction in Patients with Covid-19 Based on Chronic Heart Failure and its Significance in the Effectiveness of the Treatment

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Abstract. This article discusses the importance of endothelial dysfunction in patients with COVID-19 due to chronic heart failure and the effectiveness of its treatment.

Key words: medicine, heart failure, COVID-19, patient, endothelial dysfunction, treatment methods.

The new coronavirus infection COVID-19 is one of the most serious challenges facing basic and clinical medicine in the last few decades. This is due not only to the wide spread of the infection, but also to a fairly high mortality rate, especially in older age groups, with frequent complications and consequences of the disease.

The main route of entry of the SARS-CoV-2 virus into the body is the angiotensin-converting enzyme 2 receptor (ACE2, ACE2) [1]. Unlike the SARS-CoV-1 virus, the SARS-CoV-2 virus has a higher affinity for the ACE2 receptor [2], as well as a higher replication activity [3], which makes it more contagious compared to the SARS-CoV-1 virus. .

Initially, COVID-19 was considered as a disease affecting the respiratory system. However, the accumulated clinical material indicates that other organs and systems can be possible targets for the SARS-CoV-2 virus. This is due to the fact that ACE2 receptors are expressed not only in alveolar type II epithelial cells, but also in other cell types in various organs and tissues [4], including endotheliocytes [5] and pericytes [6]. The expression of ACE2 receptors has also been shown in different structures and regions of the brain [7]. These circumstances explain the possibility of involvement of different organs and systems with the development of multiple organ damage and various neurological complications. According to M. Heneka et al. [8], in the acute period of COVID-19, more than 1/3 of patients develop neurological symptoms, of which 25% can be attributed to direct CNS damage. Most often, all these complications arise due to the penetration of the virus into the systemic circulation, its dissemination and damage to the endothelium of the vascular bed.

Main functions of the vascular endothelium.

Normally, the endothelium of the vascular bed is an active endocrine and paracrine organ, which plays a leading role in the regulation of vascular tone, primarily in the microvasculature, and in maintaining vascular homeostasis [9]. The endothelium is directly involved in many physiological processes due to the constant interaction with the uniform and plasma components of the blood and other circulating cells. Endothelial cells secrete factors into the lumen of the vessel that ensure the dynamic balance of hemostasis, maintain and change local blood flow at the level of microcirculation, and also have a trophic effect on the adjacent subendothelium and the layer of smooth muscle cells, and affect angiogenesis.

The assessment of the state and function of the endothelium is carried out using laboratory and instrumental examination methods, in which it is important to take into account not only absolute deviations beyond the reference values, but also the possibility of a total contribution of several indicators that are within the upper/lower quartiles of normal values in development of endothelial dysfunction [10].

Causes and mechanisms of endothelial dysfunction in COVID-19

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Endothelial dysfunction is accompanied by an imbalance of hemostasis with a shift to the procoagulant side, a decrease in the release of vasodilators and an increase in the release of vasoconstrictor factors and a tendency to spastic reactions in the microvasculature, increased migration of leukocytes through the endothelium with the development of a local inflammatory process. Prolonged exposure to factors leading to endothelial dysfunction contributes to the acquisition of a pro-inflammatory and prothrombotic phenotype by endothelial cells [11], depletion of the pool of progenitor endothelial cells [12, 13], which ultimately limits the possibility of restoring its normal phenotype and function.

A variety of reasons can lead to the development of endothelial dysfunction. Endothelial dysfunction can be a reflection and background condition in a number of chronic non-communicable diseases, such as arterial hypertension, generalized atherosclerotic lesions of the vascular bed, diabetes mellitus, obesity/high body mass index (BMI), and chronic obstructive pulmonary disease [9]. Endothelial function is impaired by smoking, which is associated with the direct effect of nicotine and tobacco smoke components on endotheliocytes. Severe infectious, including viral, diseases can also cause endothelial dysfunction. In these cases, endothelial dysfunction can be caused either directly by a viral attack or indirectly through excessive activation of the endothelium due to a maladaptive immune response [10].

In COVID-19, endothelial injury and dysfunction most often result from a combination of a number of causes (Fig. 3). One of them may be the direct penetration of the SARS-CoV-2 virus into endothelial cells. Thus, Z. Varga [14] revealed the presence of fragments of the SARS-CoV-2 virus and apoptotic bodies in the endothelium of the vessels of the microvasculature of the lungs, myocardium, kidneys, liver, and small intestine during histological examination. The features of the SARS-CoV-2 virus compared to the influenza virus H1N1 09 (swine flu 2009) are a much more active inflammatory response and a more pronounced damage to endothelial cells, determined on the basis of analysis of the expression of interleukin-6, tumor necrosis factor-α, intracellular adhesion molecules-1 and caspase-1 [15]. Other causes of endothelial dysfunction in patients with COVID-19 may be cytokine storm and immune-mediated damage to endotheliocytes. Cytokines and protein pro-inflammatory mediators are key factors that contribute to endothelial dysfunction [16]. Thus, proteomic analysis of 185 markers reflecting inflammation and dysfunction of the endothelium in the systemic circulation showed that the presence of a cytokine storm was combined with diffuse damage to the vascular endothelium [17]. According to A. Petrey et al. [18], an increase in the content of pro-inflammatory cytokines in patients with COVID-19 directly correlates with an increase in the levels of markers that reflect systemic vascular damage by the type of vasculitis and markers of vascular bed remodeling. In addition, there is a relationship between the clinical severity of the disease, including the development of somatic complications, and the likelihood of the development and severity of a cytokine storm and endothelial dysfunction. With COVID-19, there is a shift in hemostasis to the procoagulant side, which is reflected in an increase in the level of fibrinogen, fibrin breakdown products, D-dimer, and von Willebrand factor, and this increase correlates with the severity of the disease and the risk of thrombosis and is a reflection of endothelial dysfunction [19].

Contribute to the aggravation of endothelial dysfunction in COVID-19 arterial hypertension, impaired glucose tolerance and diabetes mellitus, increased BMI and obesity, impaired lipid spectrum, etc. (see Fig. 3). The combination of COVID-19 with these risk factors can significantly worsen the prognosis due to an increased risk of macro- and microvascular complications [20].

Mechanisms of development and clinical spectrum of cognitive impairment in COVID-19.

According to R. Chen et al. [7], in the human brain, the expression of ACE2 receptors is noted in the choroid plexuses and various cortical and subcortical regions of the cerebral hemispheres. It is also important to note that, according to the data obtained in this study, ACE2 receptors were expressed not only by endothelial cells, but also by pericytes, neurons, and astrocytes. This makes the brain potentially vulnerable to COVID-19.

According to available data, the main causes of brain damage in COVID-19 are respiratory failure and hypoxia, SVR syndrome and cytokine storm, hemostasis disorders, and direct damage to the endothelium of the microvasculature. The possibility of direct damage to the brain, including through the mechanism of molecular mimicry, is also discussed [21, 22].

Morphological studies that showed the presence of the SARS-CoV-2 virus in the endothelium of cerebral capillaries and the substance of the brain confirmed the assumption that the hematogenous route of

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spread is the main route of penetration of the virus into the CNS [23]. Autopsy of patients who died from COVID-19 revealed extensive damage to microvessels with multiple thromboses due to hypercoagulability [4]. In another study, post-mortem magnetic resonance microscopy, histological and immunohistochemical analysis showed the presence of multifocal brain damage involving the microvasculature, neurons and astrocytes and microglia activation [5]. Generalized vascular disease may underlie the development of cerebrovascular complications in patients with COVID-19. According to A. Merkler et al. [6], ischemic stroke in patients with COVID-19 was diagnosed 8 times more often than in patients with influenza (1.6%, 95% CI=1.1–2.3% and 0.2%, 95% CI= 0.0-0.6%, respectively).

Tropism of the SARS-CoV-2 virus to the endothelium of the vascular bed increases the risk of neurological disorders, not only due to the possible involvement of various parts of the brain with the development of ischemic and / or hemorrhagic complications, but potentially also due to chronic post-infectious complications, including prolonged dysfunction of the blood-brain barrier (BBB) and activation of pro-inflammatory cytokines in the brain [7].

A number of studies consider the possibility of SARS-CoV-2 damage to various organs and systems, including the brain, by the mechanism of molecular mimicry. G. Lasso et al. [21] found that human coronaviruses can use the mechanism of molecular mimicry towards more than 150 host proteins. In most cases, mimicry affected the features of the immune response, including complement activation, which is one of the key components in the regulation of inflammation. In a study by H. Yapici-Eser et al. [22], based on mathematical modeling, the possibility of molecular mimicry of a number of proteins of the SARS-CoV-2 virus with respect to human proteins involved in synaptic transmission, regulating the activity of a number of ion channels, including those affecting the permeability of the BBB, neuron activation, and synthesis of trophic factors.

To date, there are not many works evaluating the state of cognitive functions in patients with COVID-19, which is probably largely due to the severity of the disease and high contagiousness, which creates limitations for neuropsychological examination. A number of studies have reported impaired attention [8, 9] and executive functions, apathy [3]. According to O. Del Brutto et al. [1], cognitive decline was noted in patients with mild symptomatic COVID-19. This study is unique in that it prospectively assessed changes in cognitive function before and after the onset of the COVID-19 pandemic in individuals infected or not infected with SARS-CoV-2. In a multivariate analysis, the likelihood of developing cognitive decline was significantly higher in the SARS-CoV-2 virus seropositive group compared to seronegative individuals [1]. A comparison of 93 asymptomatic COVID-19 patients with 102 comparison patients showed that asymptomatic COVID-19 patients had a lower Montreal Cognitive Assessment score. Differences were especially pronounced in assessing visual perception, naming objects, and fluency [2].

Brain damage in COVID-19 may have a long-term impact on cognitive processes [3]. When studying the frequency, nature, and severity of cognitive impairment 3–4 months after discharge from the hospital, clinically significant cognitive impairment, depending on the applied threshold, was detected in 59–65% of the examined patients, with verbal learning and executive functions suffering the most [4]. The largest study was conducted by A. Hampshire et al. [5], which studied cognitive functions in 84,000 people, of whom >12,000 had COVID-19. Compared to healthy participants, the COVID-19 survivor group had significantly worse results on cognitive tests. The main violations concerned executive functions. Approximately 65% of patients who recovered from severe COVID-19 performed much worse on cognitive tasks. Cognitive decline in the worst cases was equivalent to 10 years of aging. It is assumed that patients with COVID-19 have an increased risk of developing cognitive decline due to delayed consequences of the acute period of the disease: respiratory failure, systemic inflammation, impaired hemostasis, etc. [8, 6]. It is not excluded that other pathogenetic mechanisms may determine the persistence of cognitive disorders after the acute period. So, J. Helms et al. [7] noted hypoperfusion in the frontotemporal areas of the cerebral hemispheres in patients with COVID-19. In a review article by V. Montalvan et al. [8] showed the possibility of developing structural changes in the thalamic and temporal regions. In a multicenter observational study [9], MRI showed no structural changes in the brain, but 18F-FDG PET revealed hypometabolism in a vast area that included the frontal cortex, anterior cingulate gyrus, insula, and caudate nucleus. When re-examined after 6 months, most patients had an improvement in their general condition, but cognitive and emotional disorders of varying severity remained. There were impairments in executive functions and attention, as well as

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anxiety and depressive symptoms, combined with changes in glucose metabolism in the prefrontal, insular, and subcortical regions [9]. All these data indicate that the development of cognitive impairments against the background of COVID-19 has a complex, multifactorial mechanism and is not always directly related to the severity of the disease itself.

Directions for correction of endothelial dysfunction

Correction of endothelial dysfunction should be carried out taking into account the leading pathogenetic factors of its development and in most cases is achieved by the combined administration of antihypertensive, anticoagulant, antiplatelet, hypolipidemic and some other drugs. In addition, in patients with COVID-19, especially with the development of severe SVR with a cytokine storm, glucocorticoids, monoclonal antibodies, and other drugs with a systemic anti-inflammatory effect can have an indirect beneficial effect on endothelial function [4].

A special group of drugs are neuroprotectors that can correct neurological, including cognitive impairment and have a positive effect on the endothelium of the vascular wall. One of these drugs is Actovegin.

Actovegin is a deproteinized hemoderivative that does not contain antigens and proteins, obtained from calf blood through two stages of ultrafiltration, resulting in a complex of more than 200 bioactive components with a molecular weight of <5000 Da, which allows them to penetrate the BBB [4]. The action of Actovegin is multifaceted and includes the following main effects: metabolic, antioxidant, anti-apoptotic, neuroprotective and microvascular (Fig. 4), which may be significant in the correction of neurological disorders in patients with COVID-19. Preclinical data have shown that the drug improves metabolic processes in the brain, increasing the uptake of glucose and oxygen, including in conditions of ischemia. Actovegin reduces the release of interleukin-1β and the production of reactive oxygen species in peripheral blood cells, thus providing anti-inflammatory and antioxidant effects [2]. In an in vitro study, M. Elmlinger et al. [3] showed possible neuroregenerative effects of the drug. The components that make up Actovegin counteract inflammation and apoptosis by reducing the activation of caspase-3, which determines its anti-apoptotic effect [4]. Actovegin improves oxygen and glucose consumption and energy production in the brain, for example, in the hippocampus, thereby affecting spatial learning and memory [4].

One of the main targets of Actovegin is the endothelium, the improvement of which function entails a wide range of different clinical effects [5]. In clinical conditions, when studying with the help of laser flowmetry, an increase in the rate of capillary blood flow and the number of functioning capillaries, a decrease in arterio-venular shunting against the background of the administration of Actovegin was shown [6]. This effect could be associated with the effect of Actovegin on the activation of nitric oxide production by the endothelium, as well as with the direct myotropic effect of the drug on the precapillary bed [6]. Appointment of Actovegin to patients with hypertension and coronary artery disease with mild and moderate impairment of cognitive functions made it possible to achieve a significant improvement in cognitive functions, and when analyzing blood flow in the microvasculature, an increase in the number of functioning capillaries and a decrease in their functional desolation was noted [7]. In another study [8], the use of Actovegin led to the formation of smaller and less durable erythrocyte aggregates, lengthening the time of formation of coin columns and improving their deformability, i.e. to improve hemorheological parameters. The results obtained indicate a positive effect of Actovegin on microcirculation. In general, during treatment with Actovegin, in 81% of cases, a decrease in subjective symptoms and an improvement in somatic status were noted, as well as a positive trend in neuropsychological status, most significantly expressed in the study of attention and memory. After a course of Actovegin, according to fMRI data, an increase in the zones of functional activity in the brain was revealed [8]. Appointment of Actovegin to patients with chronic cerebral ischemia and COVID-19 contributed to the reduction of asthenic and emotional manifestations, normalization of sleep, and improvement of cognitive functions. The drug had the greatest effect on the normalization and improvement of visual-constructive/executive skills, orientation, memory and attention [9].

Thus, the currently available research results indicate the involvement of the vascular endothelium in COVID-19, which allows us to regard this condition as endothelitis [14] and to say that endothelial dysfunction in COVID-19 is one of the important mechanisms underlying damage to various organs and systems. The development of endothelial dysfunction in COVID-19 is primarily associated with acute

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respiratory distress syndrome and hypoxia, systemic inflammatory response and cytokine storm and can lead to macro- and microvascular complications. Cognitive impairment in COVID-19 is a common complication that is not always directly related to the severity of the underlying disease.

The development of endothelial dysfunction in COVID-19 determines the importance of its timely correction using various etiotropic and pathogenetic drugs. One of these drugs is Actovegin, which has proven effective in reducing endothelial dysfunction, improving microcirculation and cognitive sphere.

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