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Covid-19 as a Risk Factor for Cardiovascular Disease

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Annotation: It is generally recognized that non-communicable diseases, including arterial hypertension (AH), are a major public health problem in all countries, since about 70% of the causes of death in the world are associated with non-communicable diseases. However, the sudden emergence of an infectious disease - a new coronavirus infection - has changed the established understanding of diseases that pose the greatest threat to health. The coronavirus pandemic has affected all areas of people's lives, including health, economics, education and psychological aspects. It is predicted that the coronavirus pandemic will cause a new pandemic of non-communicable diseases, mostly cardiovascular (CVD). This prognosis seems very likely, given the decrease in physical activity, tense emotional environment, increased consumption of alcohol and smoking, increased stress levels during the pandemic, which are risk factors for CVD, including increased blood pressure (BP). In the context of the coronavirus pandemic, first of all, attention should be paid to patients with hypertension, given the high prevalence of this disease, as well as the fact that the components of the renin-angiotensin-aldosterone system (RAAS) are interested in the penetration of a new virus into the body. The consensus considered current data on the management of patients with hypertension in a pandemic, available as of August 2020.

Prevalence of hypertension in the population Elevated blood pressure remains the main cause of death worldwide and accounts for 10.4 million deaths per year [2]. AH is a leading risk factor for the development of CVD (myocardial infarction, stroke, coronary heart disease, chronic heart failure), cerebrovascular (ischemic, hemorrhagic stroke, transient ischemic attack) and renal diseases [3]. The prevalence of hypertension among the adult population in the general population is 30–45% [4]. According to experts, in 2010, 1.39 billion people in the world had AH [5]. In the Russian population among men aged 25–65 years, the prevalence of AH reaches 47%, among women - 40% [6]. The prevalence of hypertension increases with age, overweight and obesity. Since there is an increase in the number of such individuals in the population, it is predicted that the prevalence of hypertension will increase worldwide.

According to experts, by 2025 the number of patients with hypertension will increase by 15–20% and reach about 1.5 billion people [7]. COVID-19 pandemic, background In early December 2019, cases of severe primary viral pneumonia with fatal outcomes appeared in the Hubei province of the People's Republic of China. The first case of such pneumonia was officially registered in Wuhan on December 8, 2019 [8]. On December 30, 2019, the Wuhan City Health Committee issued an urgent notice of the occurrence of pneumonia of unknown etiology. On January 7, 2020, information was received on the identification of the etiological agent of the disease, which turned out to be a representative of the coronavirus family, and it was assigned the temporary designation 2019-nCoV (novel coronavirus 2019) [9] . On January 30, 2020, the World Health Organization declared the outbreak in Hubei Province an international public health emergency.

The main target cells for SARSCoV-2 are alveolar cells of the 2nd type, which leads to the frequent occurrence of atypical pneumonia with the development of acute respiratory distress syndrome (ARDS). The SARS-CoV-2 virus is assigned to the 2nd level of pathogenicity, as well as some other representatives of this family (SARS- CoV , MERS- CoV), in relation to which there are frequent cases of lethal outcomes [11]. RAAS and ACE-2 RAAS include humoral factors and enzymes with proteolytic activity, through which intracellular cascades of reactions are triggered, which play a leading role in the regulation of blood pressure.

The first proteolytic enzyme involved in these processes is renin, synthesized by the kidneys, with the participation of which liver angiotensinogen is cleaved to inactive angiotensin I (AT I). The transition of AT I to angiotensin II (AT II) is carried out by an angiotensin-converting enzyme (ACE) associated with the cell membrane. AT II is the main effector peptide of the RAAS, which, by binding to specific receptors in organs and tissues, mediates various hemodynamic effects of the RAAS. First of all, it is vasoconstriction, pro-inflammatory and proliferative effects, as well as activation of other pressor hormones - catecholamines , aldosterone, vasopressin.

There are 4 types of specific receptors for AT II: angiotensin receptors 1, 2, 3, 4 types (AT1, AT2, AT3, AT4 receptors), of which two are the most studied - AT1 and AT2 receptors, which differ significantly as according to the signal reactions regulated through them, and according to the physiological responses of target cells [15]. Binding of the AT1 receptor to agonists, including AT II, leads to stimulation of vasoconstriction, proliferation, and inflammation. In contrast to the AT1 receptor, stimulation of AT2 receptors increases the activity of various NO synthase isoforms, thereby activating NO-dependent pathways, causing vasodilation, suppression of endothelial and vascular smooth muscle cell proliferation, and anti-inflammatory effects.

There is a 2nd type of ACE - ACE-2. Exopeptidase ACE-2, despite the great similarity in amino acid composition with ACE, has radically opposite functional effects - antiproliferative , anti-inflammatory and promotes vasodilation. This is due to the fact that ACE-2, acting on AT II, breaks it down to angiotensin 1-7 (AT1-7), and AT I - to inactive AT1-9, which is metabolized to AT1-7 by means of A.C.E. Ultimately, AT1-7 binds, like AT II, to specific cell receptors (MAS receptors) and exerts vasodilating and antiproliferative effects. Thus, the MAS receptor is a functional AT1 receptor antagonist, while AT1–7 is an AT II antagonist and has protective effects on the cardiovascular system (CVS). But for its formation, a sufficient concentration of ACE-2 is required.

There are 2 forms of ACE-2 - membrane-bound and soluble [11]. The membrane-bound form of ACE-2 is functionally active and includes an N-terminal ectodomain , a transmembrane domain, and a cytoplasmic domain. The soluble form of ACE-2 is formed by deamination of the extracellular part of the ACE-2 molecule. The process of deamination occurs with the participation of the ADAM17 protease, which is a transmembrane protein [17, 18]. The presence of two forms of ACE-2 plays an important role in the penetration of the SARS-CoV-2 virus into target cells. The mechanism of penetration of the SARS-CoV-2 virus into cells As already noted, the SARS-CoV-2 virus has a pronounced similarity, both functional and structural, with the virus - the causative agent of acute respiratory syndrome - SARS- CoV .

It was found that the penetration of the virus into the host cell occurs through the use of the membrane-bound form of ACE-2. Subsequently, a proteolytic enzyme, which is necessary for such penetration, was identified, which is the transmembrane serine protease TMPRSS2, which is highly expressed in human lung epithelial cells [19]. It is important that virus replication in cells with increased expression of the TMPRSS2 protease is not accompanied by an increase in the ability of the virus to infect, which indicates that the TMPRSS2 protease is involved in the process of virus penetration through the cell membrane, and not in the control of its further replication [13].

A high level of expression of ACE-2 and ADAM17 was found in the heart, lungs, kidneys, intestines, brain, and testicles; it was in insignificant other tissues. It is known that cleavage of ACE-2 by the ADAM17 protease leads to the appearance of a soluble form of ACE-2. It was found that the soluble form of ACE-2 specifically binds to the SARS- CoV virus, thereby preventing its interaction with the transmembrane form of ACE-2 and preventing infection of the target cell [15].

Thus, TMPRSS2-induced cleavage of ACE-2 promotes cell infection with the virus, while ADAM17-induced cleavage of ACE-2, on the contrary, inhibits this process [14].

It has now been proven that the receptor of the SARSCoV-2 virus, through which it enters the target cell, is the transmembrane form of ACE-2. In addition, the TMPRSS2 protease has been shown to play an extremely important role in the ACE-2-mediated entry of the SARS-CoV-2 virus into the target cell [16]. The target of the TMPRSS2 protease is the Spike protein in the structure of the virus, which, after cleavage, acquires the ability to effectively interact with the transmembrane form of ACE-2 and form the ACE-2–S (SARS-CoV-2) complex, which ensures the internalization of the virus into the cell by endocytosis [12] . This theory is confirmed by the results of in vitro experiments, in which a cell culture with an expressed TMPRSS2 protease had a high ability to become infected with SARS-CoV-2, while in another cell culture, where the TMPRSS2 protease was absent, the virus did not penetrate into the cells and there was no infection. happened [24]. No direct evidence has been obtained regarding the role of the ADAM17 protease in SARS-CoV-2 infection.

There is a hypothesis, by analogy with SARS- CoV that the ADAM17 protease can interact with the soluble form of ACE-2, preventing interaction with the transmembrane form of ACE-2, and thereby influencing its participation in the penetration of the virus into the cell. However, unambiguous conclusions can be drawn only after appropriate studies have been carried out. Expression of ACE-2 in the body The main group of patients who most often have a severe course of coronavirus infection caused by SARS-CoV-2 are the elderly, patients with hypertension, coronary heart disease, diabetes mellitus, chronic lung diseases, and obesity. Many of these diseases are caused or associated with impaired RAAS function and are accompanied by compensatory or drug-induced changes in ACE-2 expression [5, 8]. Since the membrane -bound form of ACE-2 is an essential condition for the penetration of SARS-CoV-2 into the target cell, an increase in the expression and amount of this form of the enzyme in the membrane can contribute to infection with the SARS-CoV-2 virus and aggravate the course of COVID-19. In this regard, it is logical to assume that in this category of people, who are more susceptible to severe COVID-19, the concentration of ACE-2 in the cells should be the highest. Previous animal studies have shown an age-related decrease in ACE-2 levels in the lungs. However, a recent prospective observational study that analyzed data from patients of all ages, including neonates, children, young people, and the elderly over 65 years of age, who were mechanically ventilated for ARDS, demonstrated that ACE-2 activity in discharged bronchoalveolar lavage was not significantly associated with age [17]. However, another study found no evidence that genetic variations in the gene encoding ACE-2 located on the X chromosome can affect susceptibility to COVID-19 [19]. Analysis of transcriptome sets of unaffected lung tissue did not reveal significant differences in ACE-2 expression between racial (Asian and Caucasian), age (age over 60 years and less) groups, and gender [19]. The prevalence of hypertension among patients with COVID-19 the first reports from China showed a high prevalence of hypertension among patients with COVID-19 - about 30–50% [13, 11]. Then a hypothesis appeared in the global medical community about a higher susceptibility of patients with hypertension to infection with SARS-CoV-2. However, a detailed analysis of data on the incidence of hypertension among patients with COVID-19 in different European sources showed that the percentage of patients with hypertension among people with coronavirus infection will be close to the percentage of prevalence of hypertension in the general population of this region. Thus, in studies reporting a high prevalence of hypertension among patients with COVID-19, hypertension was detected in 30.4% (58/191) of middle-aged Chinese patients 56 years and in 46% (509/1043) of middle-aged Italian patients. 63 years old. A national study in China showed that 44.6% of the population aged 55–64 years had hypertension, and 45.2% of the Italian population aged 60–69 years also had hypertension according to the Italian national registry [12]. The highest rates of hypertension in hospitalized patients with COVID-19 are presented in a number of American reports, which included 5700 patients, among which AH was in 3026 (56.6%) patients [33]. At the same time, this indicator turned out to be lower than in the general US population, where the prevalence of hypertension in this age group ranges from 63 to 77% [14]. At the time of this writing, no reliable data have emerged demonstrating an increased risk of SARS-CoV-2 infection in persons with hypertension. The impact of hypertension on the severity and mortality of patients with COVID-19 The penetration of the SARS-CoV-2 virus

into the cells of the lungs and other organs through the binding of the Spike protein of the virus to the transmembrane form of ACE-2 has become a real revelation for many medical professionals, especially cardiologists, who are well represent the involvement of the RAAS in the pathogenetic processes of most CVDs. The question arose whether the mechanism of penetration of SARS-CoV-2 into target cells could affect the severity of the disease and mortality, especially in the context of the presence of concomitant hypertension in patients. As data on COVID-19 accumulated to assess whether hypertension is an independent risk factor for an adverse course of coronavirus infection, patients with mild and severe disease were analyzed. In a retrospective study of 548 patients in the Chinese city of Wuhan, where the first outbreak of COVID-19 occurred, the prevalence of hypertension was significantly higher in patients with severe disease than in non-severe cases, at 38.7 and 22.2% ($p < 0.001$) respectively. In an age-adjusted logistic model, high levels of lactate dehydrogenase and D- dimer revealed an independent association of hypertension with the severity of COVID-19 [35]. In another Chinese study of 487 patients with COVID-19, 49 patients had severe disease and 438 had mild disease, with the prevalence of hypertension in patients with severe disease being statistically significantly higher at 53.1% versus 16.7% with mild course ($p< 0.0001$). Subsequent multivariate analysis showed that male gender, age over 50, and hypertension were - independent factors in the severity of COVID-19 [13]. Such data can be explained by the high prevalence of AH among elderly patients, their greater vulnerability to SARS-CoV-2 infection and the more severe course of any infectious diseases [17].

On the other hand, retrospective studies have appeared in which, in AH patients, no relationship was noted with the progression of COVID-19, which was determined by the need for invasive mechanical ventilation, and in multivariate analysis, AH did not show itself as an independent factor in the severity of COVID-19 [38]. The US Centers for Disease Control and Prevention has not included AH in the list of risk factors for the severity of COVID-19 [39]. Currently, there is no clear epidemiological evidence to support that hypertension per se is an independent risk factor for severe disease in patients with COVID-19.

Although different in nature, the world has been living with another pandemic for several decades now – the obesity pandemic. Every year, the number of overweight and obese people around the world is steadily increasing. It is known that AH and obesity are pathogenetically closely related, and just as obesity can lead to the development of AH, AH can contribute to the development of metabolic disorders. According to the ESSE-RF epidemiological study, overweight and obesity occur in more than 1/2 of patients with AH [40].

In the context of the pandemic, obesity has been recognized as a new risk factor for the severity of COVID-19 [41]. American researchers have revealed a high prevalence of comorbid obesity among patients with COVID-19 - about 36%, which was not reported in the studies of Chinese colleagues, due to the different prevalence of obesity in the USA and China in general in the population. In addition, 43% of ventilated patients also had obesity, which is considered as a risk factor for respiratory failure and the need for invasive mechanical ventilation [42]. Retrospective analysis has shown that obesity may be a factor in determining the severity of COVID-19 disease, regardless of age and the presence of hypertension [43, 44]. Obesity may worsen the clinical course of COVID-19 by reducing expiratory reserve volume, obstructing diaphragmatic excursion, and restricting ventilation [45]. It is known that visceral obesity activates pro- inflammatory reactions, oxidative stress and can cause an increase in blood pressure, disorders of carbohydrate and lipid metabolism, which in turn can potentiate and increase the risk of complications in COVID-19.

Obesity is a state of chronic inflammation. Adipocytes secrete pro- inflammatory agents such as cytokines, transforming growth factor b, adipokines , monocyte chemoattractant protein-1, and hemostatic proteins [46]. The main inflammatory cytokines secreted by adipose tissue are tumor necrosis factor a, interleukin (IL)-6 and IL-1. In obese individuals, there is an increased level of tumor necrosis factor a, which plays a role in the inflammation process. IL-1 can activate transcription factors that enhance inflammatory signaling and overexpression of vascular endothelial growth factor. Elevated IL-6 in obesity plays an important role in inflammation-related carcinogenesis through the Janus kinase signaling transducer . Many cytokines released by

dysfunctional hypertrophic adipocytes in visceral adipose tissue increase the recruitment of macrophages, which produce even more pro- inflammatory molecules [47]. The cumulative effect of chronic inflammation and hypercytokinemia in obesity appears to be able to induce a hyperinflammatory response through macrophage activity syndrome , especially in patients with severe COVID-19. Inflammation subsequently leads to hypoxia and ischemia, which activates the processes of oxidative stress. As a result, protein synthesis by hypertrophic and hypoxic adipocytes - changes towards increased production of cytokines and other inflammatory proteins. The vicious circle between increased cytokine release and a state of increased metabolic inflammation may likely contribute to the "cytokine storm" in patients infected with SARS-CoV-2, which leads to the development of ARDS and increased mortality from COVID- 19.

Viral diseases occur with various symptoms , including changes in the cardiovascular system, namely, destabilization of the blood pressure level. These phenomena can be observed both in healthy individuals and in patients with hypertension. The latter are most susceptible to changes in the blood pressure profile during acute respiratory diseases. The reaction of the CCC, as a rule, is most pronounced against the background of febrile conditions. Fluctuations in blood pressure against the background of an increase in body temperature can be both in the direction of increasing blood pressure, and its significant decrease to a level to which the patient is not adapted. At the peak of fever, an increase in blood pressure is a consequence of a spasm of peripheral vessels, and during a period of critical temperature drop due to vasodilation, increased diuresis, blood pressure decreases and can lead to hypotension up to collapse. Pronounced uncontrolled fluctuations in blood pressure are associated with a high risk of developing cardiovascular complications (CVS) in patients with hypertension, primarily stroke and acute coronary syndrome [48]. It is currently known that the course of COVID-19 may be accompanied by hyperthermia from subfebrile to hyperpyretic figures. Therefore, it is very important to control blood pressure in patients with COVID-19, not only in the acute phase of the disease, but also after normalization of temperature. It is also important to follow the generally accepted recommendations for managing patients with hypertension during viral diseases: to minimize the use of local agents with a vasoconstrictive effect, to exclude alcohol, caffeinated drinks, smoking, to refuse hot baths, rubbing and body wraps.

One of the pathogenetic mechanisms of worsening of the course of hypertension in COVID-19 may be due to the involvement of the central nervous system. A significant level of ACE-2 expression was found not only in the lungs, but also in some parts of the brain. A high content of SARS-CoV-2 viral particles was found in the brainstem and cranial nerves extending from it [49]. As a result of viral damage, apoptosis of these cells was noted , which led to disruption of the functioning of the brain centers responsible for the regulation of blood pressure and respiration. In addition, a decrease in the level of ACE-2 in the brainstem can cause a violation of the tone of the sympathetic nervous system and lead to destabilization of blood pressure in patients with hypertension [50].

According to the data of foreign and Russian epidemiological studies, a high proportion of people with AH is revealed who are not aware of their condition and do not receive appropriate treatment [51]. It can be assumed that the disease of such patients with COVID-19 is associated with a higher risk of developing CVD in the presence of untreated hypertension.

Given these facts and the presence of moderate to severe forms of the course of COVID-19, it is important not to miss the symptoms of CVD caused by BP destabilization, which can be masked by the general malaise of a patient with COVID-19.

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