Research Article

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COVID-19 and Cardiovascular System. Part 1. Pathophysiology, Pathomorphology, Complications, Long-Term Prognosis

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AIM OF STUDY Like other respiratory viruses, COVID-19 has extrapulmonary manifestations. The effect of the virus leads to the cardiovascular system (CVS) damage in particular, which pathophysiological mechanisms are not fully understood. In this article we analyze modern ideas about COVID-19, consider possible links of pathogenesis, make an attempt to systematize pathophysiological mechanisms of cardiovascular impairment and its complications, analyze the relation with cardiovascular comorbidity, describe pathomorphological features and discuss possible long-term prognosis. The information in this article can contribute to understanding the two-way interaction of cardiovascular diseases and the effects of COVID-19 in order to develop effective preventive measures and make the right decision in choosing therapeutic tactics for a patient.

Keywords: COVID-19, SARS-CoV-2, cardiovascular system, cardiovascular diseases, angiotensin converting enzyme 2 (ACE2), pathophysiology, pathomorphology, comorbidity, complications, long-term prognosis

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AH - arterial hypertension
ATII - Angiotensin II
ACE2 - angiotensin converting enzyme 2
IHD - Ischemic heart disease
MI - myocardial infarction
CA - coronary artery
CMP - cardiomyopathy
PH - pulmonary hypertension
HRD - heart rhythm disturbance

ACS - acute coronary syndrome
ATI - acute tubular injury
RV - right ventricle
PCR - polymerase chain reaction
RAAS - renin-angiotensin-aldosterone system
DM - diabetes mellitus
HF - heart failure
SNiEF - HF with intact ejection fraction
CVD - cardiovascular disease
CVC - cardiovascular complications
CVEv - cardiovascular events
CVS - cardiovascular system
ST - sinus tachycardia
RF - risk factors
CED - chronic endothelial dysfunction
ECG - electrocardiography
EchoCG – echocardiography
NST - nuclei of the solitary tract
ST - ST rise
CoV - the genome of the coronavirus
E - shell protein
HCoV - Human Coronavirus
IL – interleukin
M - membrane protein
MERS - Middle East Respiratory Syndrome
N - nucleocapsid protein
PAI - plasminogen activator inhibitor
S - thorn protein
TNF - tumor necrosis factor
tPA - tissue plasminogen activator

INTRODUCTION

The relationship between acute respiratory tract infections and cardiovascular disease (CVD) is admitted fact; acute respiratory viral infection, influenza, respiratory syncytial infection, bacterial pneumonia - are the triggers of CVD, and the initial pathology of the cardiovascular system (CVS) increases the likelihood of the development and progression of the infectious process [1]. The demonstration of this fact is reflected in the current COVID-19 pandemic: a significant proportion of coronavirus-affected patients are reported to have CVD [2]. In this regard, the need for a fundamental study of the pathophysiological changes occurring in the CVS as a result of the potential effects of coronavirus is being formed, which, however, presents a number of difficulties. Nevertheless, without understanding these processes, it is impossible to predict the development of certain cardiovascular events (CVEv), and, as a consequence, to choose the right treatment tactics. In this context, the evidence obtained, as well as the analysis of previous coronavirus pandemics, are informative. For cardiologists, this issue is especially acute, since the defeat of the CVS is the second cause of mortality in COVID-19 and the consequences of the cardiac involvement and blood vessels in the long term are unknown.

BIOLOGICAL FEATURES OF SARS-COV-2

For the first time, the human coronavirus (HCoV) was identified in cultured tissues of the trachea of the embryo in 1965, and until 2002 it was believed that the virus is not highly pathogenic. The view changed after a massive SARS outbreak, called atypical pneumonia, reported in China in 2002. 10 years later, an outbreak of Middle East Respiratory Syndrome (MERS) was reported in Saudi Arabia. As of May 2020, the Coronaviridae family includes 43 types of RNA viruses. The spread of coronaviruses in nature is extensive, they are combined into two subfamilies that infect mammals, including humans, birds and amphibians. On the basis of phylogenetic analysis, the subfamilies were divided into 4 groups: □, □, □and □of which only □and □ infect the human organism [3]. The above outbreaks were caused by different strains of the virus (SARS-CoV and MERS-CoV, respectively), but both of these viruses, as well as the

SARS-CoV-2 strain, which is the causative agent of the current pandemic, belong to the □-coronavirus group. SARS-CoV and MERS-CoV were originally identified in bats, which are now believed to be a natural reservoir for pathogens. Viruses that are genetically similar to the SARS-CoV and MERS-CoV of bats have been isolated from the number of organisms around the world. In particular, SARS-CoV-2, isolated from humans, has a high genetic sequence similarity to the SARS-like coronavirus (CoV) of Chinese horseshoe bats. In this regard, the original name of the current Wuhan virus - 2019-nCoV has been changed to SARS-CoV-2, which reflects the existing taxon.

The CoV genome is represented as a single-stranded RNA with positive polarity, about 30,000 nucleotides long, with 10 open reading frames encoding from 24 to 27 genes. Approximately two thirds of the 5 'end of the genome encode the pp1a and pp1ab polyproteins, which are further cleaved into 16 non-structural proteins, including the enzyme RNA-dependent RNA polymerase (RdRP). The structural proteins of the virus are encoded by one third of the 3 'end of the genome [1].

The structure of SARS-CoV-2 is a nucleo-capsid surrounded by a protein membrane and a lipo-containing outer shell, from which the clavate spine processes extend. Outwardly, these formations resemble a crown, for which the family got its name [3]. These processes are represented by one of the 4 structural proteins of the coronavirus - the spike protein (S), which ensures the attachment of the virus to the receptor of the host cell, as well as further fusion with the cell membrane. Other structural proteins are nucleocapsid protein (N), membrane protein (M), and envelope protein (E).

In a living organism, the coronavirus has the highest affinity for the integral plasma membrane protein of the angiotensin-converting enzyme 2 (ACE2) [4]. It is widespread in the body and can be found on the surface of the membrane of endothelial cells, specialized epithelial cells, including the epithelium of the nervous system, nerve endings, and also in the cells of the reproductive system. ACE2 is of the greatest importance in the regulation of CVS, but its physiological functions are not limited to this: it takes part in the processes of metabolism of various biologically active peptides and in the hematopoiesis [5].

Penetration into the cell occurs by binding of the SARS-CoV-2 protein S to the zinc ACE2 peptidase. After S binding, the protein is cleaved in two regions (S protein priming) by the transmembrane serine protease TMPRSS2, which, in turn, promotes the fusion of the viral membrane with the host cell and the direct penetration of the virus into the cytoplasm by endocytosis [4].

Protein S SARS-CoV-2 has a number of features compared to that of SARS-CoV. First, the SARS-CoV-2 S protein has a high affinity for the cells of a living organism, which has been proven by cryogenic electron microscopy. Second, the SARS-CoV-2 S protein has an insert of 4 amino acid residues at the interface between the S1 and S2 subunits, which are formed under the action of TMPRSS2. This introduces a new additional cleavage site by the serine protease . This cleavage site has not been observed in SARS-CoV or other SARS-like coronaviruses, and its function is unknown. Similar cleavage sites have been described for highly pathogenic avian influenza viruses and Newcastle disease virus. Presumably, this feature expands cellular and tissue tropism and contributes to the multiorgan lesion of SARS-CoV-2 [1, 2]. It should be noted that ACE2 is localized in the walls of the epithelium of arteries and veins, epithelial cells of the respiratory tract, the immune system, and the epithelium of the small intestine. However, the serine protease TMPRSS2 is highly expressed in the cells of the respiratory tract [1]. Hence, it can be assumed that, since the main clinical manifestations of infection are respiratory symptoms, the tropism of SARS-CoV-2 to various tissues and the extent of their damage are due not only to the level of expression of ACE2, but also by the expression of TMPRSS2, with the help of which the S protein is cleaved.

Further, the processes of transcription, replication and translation typical for viruses take place, which ultimately leads to the formation of new viral particles and their exit from the cell. Moreover, each link in the life cycle of the virus can be considered as a potential therapeutic target for leveling the various effects of coronavirus infection on the organism.

PATHOLOGICAL PHYSIOLOGY OF COVID-19 IN THE CONTEXT OF THE CARDIOVASCULAR SYSTEM

Until now, it has not been possible to link together the sequence of events occurring in the body under the influence of a new coronavirus infection, including for CVS. The spectrum of the course of COVID-19 varies from asymptomatic virus-carriage to severe acute respiratory syndrome (SARS) [2]. The problem is compounded by the lack of reliable data on the role of an additional furin cleavage site. SARS-CoV-2 bears many similarities with the SARS-CoV genome and other SARS-like pathogens. Therefore, the analysis of previous pandemics and the slowly growing base of the latest information allow us to make assumptions

about the pathological physiology of COVID-19 in humans. At the moment, the literature presents several pathophysiological mechanisms of the impact of COVID-19 on CVS. Additionally, the effects of drug therapy taken by patients are highlighted both for the treatment of the coronavirus infection itself and for concomitant diseases.

SYSTEMIC INFLAMMATORY RESPONSE

Inhibition of ACE2 can be one of the factors of lung damage, as well as the cause of systemic inflammation with the release of cytokines, which contributes to the development of acute respiratory distress syndrome and multiple organ dysfunction [6]. Decreased ACE2 level leads to the level increase in blood of angiotensin II, mediating pulmonary vasoconstriction. Liu et al. (2020) [7] showed that elevated angiotensin II (ATII) level in the serum were significantly associated with high viral load and more severe lung injury in COVID-19. Due to the immune response, high levels of chemokines are synthesized to attract inflammatory effector cells. This inappropriate immune response with the secretion of inflammatory chemokines results in lung infiltration and hyperactivation of monocytes and macrophages producing proinflammatory cytokines (IL-6, IL-8 and IL-□ as well as TNF□) and chemokines (such as CCL2, IFN□-induced protein-10 and CCL3). The increased local production of cytokines and chemokines attracts more inflammatory neutrophils and monocytes to the lung tissue, causing edema and reducing gas exchange in the alveoli [8]. There is evidence of cases of illness of patients with COVID-19, in which deposits of activated proteins of the complement system in the tissues of the lungs and other organs were detected. Experimental evidence suggests that the interaction of the coronavirus N: MASP-2 protein leads to uncontrolled activation of the lectin complement pathway. High levels of circulating complement proteins such as C3, C3a, C4, and C5a have been associated with an increased risk of CVEv. It is assumed that in acute CVEv the complement system promotes both thrombosis and ischemic reperfusion injury after restoration of blood flow in the ischemic tissue [9].

OXYGEN IMBALANCE

Lung lesions described at autopsy lead to the development of hypoxemia. When arterial oxygen saturation (PaO2) falls below 40 mmHg, shortness of breath occurs. It should be noted that the normal response to hypoxemia is an increase in tidal volume and respiratory rate. However, over the course of the COVID-19 pandemic, there have been increasing reports of patients not showing this compensatory response despite critically low oxygen saturation levels. In the English-language literature, this phenomenon is called “happy hypoxemia” [10]. There are several hypotheses explaining the mechanism of the development of this phenomenon. Thus, according to one of these hypotheses, SARS-CoV-2 alters the expression of mitochondrial proteins responsible for peripheral chemoreception in glomus caroticus [11]. In addition, the central mechanism can also be involved in disrupting the work of this reflex. Thus, damage to the nucleus of the solitary tract (NST) as a result of viral invasion leads to impairment of the effective perception of afferent stimuli from the glomus caroticus. On the other hand, elevated blood levels of proinflammatory cytokines, such as, for example, IL-1□ lead to impaired efferent signal transmission from the central respiratory centers [12]. Under the influence of an increased level of IL-1□ the sensitivity of both central and peripheral receptors decreases. In this case, the central effect of IL-1□ occurs not directly, but indirectly, through the synthesis of eicosanoids, including prostaglandins. Inhibition of cyclooxygenase with drugs such as Diclofenac, Ibuprofen or Dexamethasone restores the original sensitivity of the chemoreceptors [13].

According to another theory, damage to the NST can lead to the so-called neurogenic pulmonary edema, loss of inhibitory effects in the rostral ventrolateral nucleus of the spinal cord, and loss of switching to the vagus nerve nuclei. In turn, this leads to increased sympathetic influences, causing excessive vasoconstriction, leading to pulmonary edema due to an increase in hydrostatic pressure. The hypertensive state can subsequently lead to a decrease in vascular tone and hypotension [14].

Theoretically, such damage to the peripheral and central regions, which are responsible for the regulation of respiration, can lead to a disruption in the work of the Savitsky – Euler – Liljestrand reflex. The physiological meaning of this reflex is to optimize blood circulation due to a constrictor reaction of pulmonary vessels with an increase in precapillary resistance (narrowing of pulmonary arterioles) in response to a decrease in the partial pressure of oxygen in the alveolar air.

Indirect evidence of impaired Savitsky – Euler – Liljestrand reflex can be detected by transthoracic echocardiography (EchoCG) and autopsy, signs of right ventricular (RV) overload and pulmonary hypertension (PH) [15, 16]. It should be noted that, according to some authors, PH is associated with a “worse prognosis” [17].

It should be added that hypoxia itself is responsible for the development of procoagulant states by stimulating the secretion of von Willebrand factor, which, acting on the GP Ib-V-IX platelet receptors, leads to their activation. Moreover, hypoxia increases blood levels of proinflammatory cytokines such as IL-1□, IL-2, IL-6, IL-12, IL-18, TNF-□, TNF-□, etc. [18].

The direct effect of coronavirus on the elements of the CVS is understood not only as a direct effect on the cells that form this system. Many links in the pathogenesis of COVID-19 are realized due to the peculiarities of the penetration of the virus into the target cell, namely the target molecule - ACE2. According to modern concepts, it is possible to distinguish several ways of the effect of the virus on the components of the CVS: dysregulation in the ACE / ACE2 system; damage to the endothelium and disorder of the system of regulation of the aggregate state of blood.

DISREGULATION IN THE ACE / ACE2 SYSTEM

The SARS-CoV-2 virus uses the intracellular protein ACE2 to enter the cell [1]. ACE2 is part of the angiotensin-aldosterone system, which is responsible for a number of physiological functions. In particular, under the action of ACE2, ATII decomposes to angiotensin-1.7 [19]. As it multiplies in the cells of the body, SARS-CoV-2 blocks more and more ACE2, therefore, the amount of circulating ATII in the blood increases [7, 20]. The biological effect of ATII is vasoconstriction, development of fibrosis, activation of a number of inflammatory cytokines, and disruption in the hemostasis system [21, 22]. In addition, the action of ATII is associated with the activation of the sympathetic nervous system [23]; it is also capable of modulating both the presynaptic ganglia of the sympathetic system and the adrenal medulla, which leads to increased release of norepinephrine and adrenaline from it [24]. By activating the sympathetic nervous system, ATII increases cardiac output and also increases blood pressure [25], thus increasing myocardial oxygen demand, which contributes to ischemic myocardial damage.

DAMAGE TO ENDOTHELIUM

"Under normal physiological conditions, the vascular endothelium prevents blood aggregation, coagulation and vasospasm, synthesizing a group of active substances: nitric oxide, prostacyclin, antithrombin III, etc.In addition, the endothelium, forming thrombomodulin, blocks active coagulants secreted by the liver and located in the blood plasma (thrombin). And finally, the endothelium adsorbs anticoagulants from blood plasma, preventing the adhesion and aggregation of platelets on its surface (heparin, proteins C and S) "[26]. Viral invasion of cells depends on both the expression of ACE2 and the availability of TMPRSS-2 or other proteases required for cleavage of the viral spike. Previously, it was shown that TMPRSS-2 is expressed in human endothelial cells, but its expression can vary in the microvascular and macrovascular beds and in different organs [27]. The developed endothelial dysfunction causes blood coagulation disorders [28]. It is important to note that, as demonstrated in in vitro human studies and animal studies, endothelial damage specifically activates the lectin complement pathway [29]. Histopathological studies confirmed direct viral infection of endothelial cells, endotheliitis (inflammation of the blood vessel wall), and micro- and macrovascular thrombosis in both venous and arterial blood flow [27]. Based on these data, it can be concluded that SARS-CoV-2 promotes the induction of endotheliitis in various organs, which is both a direct consequence of viral damage and a secondary inflammatory response of the body to infection. COVID-19-associated endotheliitis may explain the systemic impairment of microcirculatory function in various vascular beds and their clinical consequences in patients with COVID-19 [30].

PATHOLOGY OF THE HEMOSTASIS SYSTEM IN COVID-19

Information on coagulopathy in COVID-19 is still evolving. Thrombotic coagulation disorders are more common in severe COVID-19 than bleeding, therefore standard anticoagulant therapy is strongly recommended [31]. Prothrombotic conditions in patients with COVID-19 are manifested by arterial and deep vein thrombosis, pulmonary embolism, strokes, and intracardiac and microvascular thrombi. Several pathogenetic mechanisms are involved in these processes, including endothelial dysfunction characterized by an increased level of von Willebrand factor, systemic inflammation due to activation of the Toll-like receptor, and a procoagulant state due to activation of the tissue factor pathway. In a subgroup of patients with severe COVID-19, high proinflammatory cytokines levels in plasma were observed [32]. The activation of the complement system itself may be responsible for the development of procoagulant states [33]. In addition, during vascular and tissue damage, the initiation of the complement cascade is triggered in the immediate spatiotemporal proximity of platelet activation and thrombosis [34]. It was found that platelets in COVID-19 patients aggregated faster. The increase in platelet activation and

aggregation may in part be attributed by the increased activation of the mitogen-activated protein kinase (MAPK) pathway and thromboxane generation. These results indicate that SARS-CoV-2 infection is associated with platelet hyperreactivity [35].

An important role should be given to the fibrinolytic system associated not only with blood coagulation (which is directly or indirectly stimulated by thrombin), but also with the renin-angioten-aldosterone system (RAAS). After the binding of the virus, ACE2 is consumed competitively, and ATII remains in excess, thus freely acting as a potent stimulant of the plasminogen activator inhibitor (PAI 1, the main inhibitor of fibrinolysis). At the same time, an increased level of bradykinin as a result of activation of the above-mentioned factor XII stimulates the main natural fibrinolytic agent, tissue plasminogen activator (tPA) [36]. Thus, fibrinolysis can undergo a simultaneous increase in activation and / or inhibition (PAI I), causing a prothrombotic or pro-hemorrhagic state, depending on the areas and phases of the biological process. The phase or areas of locally increased activity of tPA may explain intraalveolar bleeding, while phases or areas with increased inhibitory activity of PAI I may contribute to the preservation or deterioration of microthrombosis and evolution towards pulmonary fibrosis. Moreover, the complete inhibition of fibrinolysis in the blood was recently demonstrated against the background of a severe form of COVID-19 [37].

The hypothesis that acute respiratory infections, such as the influenza virus, are triggers of CVS acute injury and death, was proposed in the 1930s. Then was the first time a relationship was noted between the seasonal activity of the influenza virus and higher mortality from both bronchopulmonary pathology, pulmonary tuberculosis, and for reasons such as organic heart disease, hemorrhagic stroke, and diabetes mellitus (DM) [1, 6]. SARS-CoV-2 is no exception, which, based on the alleged pathophysiological mechanisms of its action, leads to the development of events such as myocarditis, pericarditis, acute coronary syndrome (ACS), decompensated heart failure (HF), takotsubo syndrome, sudden cardiac death, cardiomyopathy (CMP), arrhythmias, cardiogenic shock and venous, arterial thromboembolic complications. According to the results of one of the studies, from 7% of patients in a cohort of 150 people were revealed irreversible myocardial damage and developed HF; these conditions were accompanied by an increased level of troponin in the blood [38]. Although the exact mechanisms of development of cardiovascular complications (CVC) in COVID-19 are still to be elucidated and systematized, the predominant influence of the following processes is described in the literature:

1) direct cardiotoxicity;
2) systemic inflammation;
3) inadequacy of myocardial oxygen demand with its delivery;
4) plaque rupture and coronary thrombosis;
5) side effects of therapy during hospitalization;
6) sepsis, leading to the development of disseminated intravascular coagulation syndrome;
7) increased systemic thrombus formation;
8) electrolyte imbalance.

According to statistics, the main cause of myocardial damage is direct viral damage to cardiomyocytes and the effects of systemic inflammation [39]. From a clinical point of view, monitoring markers of heart disease such as troponin, N-terminal natriuretic peptide B, and creatine kinase may help identify patients at risk of CVC at an earlier stage. This factor can be useful for preventive purposes and provide timely pathogenetic treatment [38].

MYOCARDITIS

Myocarditis is one of the leading causes of death in COVID-19 in cardiac patients. Initially, patients complain of chest pain, shortness of breath, later dysrhythmia is revealed. Cases of fulminant myocarditis with rapid evolution and developed ventricular dysfunction associated with diffuse myocardial edema have been described. In these patients, nonspecific changes in the ST segment on the electrocardiogram (ECG) and an increase in the level of troponin in the blood were observed [38]. The most probable mechanism for the development of myocarditis and its acute damage is a direct cytopathogenic effect on a cell with tropism for the myocardium, and the subsequent virus-induced inflammatory process. The invasion of the virus into the target-cell provokes the activation of nonspecific antiviral defense mechanisms implemented by macrophages and natural killer cells. Activated macrophages and other cells of the immune system, through the production of chemokines, attract T- and B-lymphocytes to the inflammatory tissue. The latter implement the mechanisms of cell-mediated cytolysis, due to which the production of antibodies against the virus occurs - the mechanism of apoptosis of cardiomyocytes is

triggered [1]. An early Chinese study were found high troponin levels with myocardial damage in 7–17% of patients with COVID-19, of which 22–31% were admitted to the intensive care unit [40]. Myocarditis was indicated by autopsy data of some patients, where infiltration with mononuclear antibodies and traces of the genome of the virus itself in the myocardium were found [41, 42]. The long-term effects of myocarditis associated with SARS-CoV-2-are unknown. It is assumed that subclinical myocarditis may be a risk factor for sudden cardiac death with physical activity of moderate and high intensity [43].

MYOCARDIAL INFARCTION

Due to the extensive inflammation and hypercoagulability, patients with SARS-CoV-2 are at risk of developing acute myocardial infarction (MI). Due to severe systemic inflammation, the main mechanism for the development of ACS and MI with ST-elevation (ST) in patients with COVID-19 is the rupture of an unstable atherosclerotic plaque [44–46]. However, this is not the only mechanism for the development of ACS. Against the background of systemic inflammation, increased oxygen consumption with reduced oxygen delivery, endothelial dysfunction, disturbances in the hemostatic system in the form of hypercoagulation processes and microthrombi, microemboli can also provoke and / or aggravate the development of MI, including type 2 MI [47]. Of interest is the treatment of patients with COVID-19 who have developed IM with ST-segment elevation . According to the recommendations of the American College of Cardiology, thrombolysis is performed only in low-risk patients with MI localization on the inferior wall without involvement of the RV, as well as localization on the lateral wall without pronounced hemodynamic impairment. The preferred treatment is percutaneous coronary intervention, which is performed in most cases [48].

HEART FAILURE (HF)

Symptoms of acute HF may be the first sign of manifestation of coronavirus infection, which occurs in 23% of patients. In a number of studies have established a high percentage of patients with acute HF and CMP as the first manifestations of COVID-19 [46, 49]. At the same time, the root cause of the development of HF is not clear enough. In some cases, these are the consequences of the CMP developed in the patient, in other cases it is an exacerbation of previously undetected HF. It should be noted that the difficulty in understanding is exacerbated by the fact that half of the patients in the above studies had no previous CVD [50].

HEART RATE DISORDERS

Patients with advanced cardiac arrhythmias (HRD) make up a significant percentage of all COVID-19 cases. The most common are atrial flutter and sinus tachycardia (ST) [41]. In the context of the general symptoms of respiratory viral infection, ST can be considered as a normal variant. The occurrence and severity of other HRD are determined by the severity of the underlying disease, the extent of myocardial damage, the degree of inflammation, as well as the effects of some drugs that prolong the QT interval (lopinavir, ritonavir, azithromycin) [44, 51]. Results from one of the aforementioned studies indicate that malignant arrhythmias such as ventricular tachycardia with transition to ventricular fibrillation are often detected in groups of patients with elevated troponin levels [38].

The pathophysiological mechanisms in this case are represented by hypoxia, an inflammatory element and metabolic disorders. In an Italian study, inflammatory cytokines, including IL-6, were shown to have a direct effect on hERG-K1 channels. This phenomenon leads to an increase in the action potential of the ventricles, which, together with accompanying factors, provokes the risk of life-threatening arrhythmias [52]. The ventricular nature is characteristic of arrhythmias accompanied by elevated serum troponin levels [45]. In this case, it is necessary to carry out differential diagnosis with acute myocarditis and ACS [52].

THROMBOEMBOLIC COMPLICATIONS

Patients with COVID-19 are at an high risk group of developing thrombotic events. This is due to systemic inflammation, multiple disorders of the hemostatic system and multiple organ involvement and directly depends on the severity of the disease. Several studies have found significant increases in blood levels of D-dimer in patients with COVID-19 pneumonia. It has been found that D-dimer levels above 1 μg / ml are associated with an increased risk of death in patients during hospitalization. It is assumed that anticoagulation with low molecular weight heparin is associated with an increase in the survival rate of patients with a 6-fold increase in serum D-dimer, as well as in severe COVID-19 [49, 53].

ROLE OF COMORBIDITY

Comorbidity is a predisposing factor for the development of adverse outcomes with SARS-CoV-2 infection. It includes diseases affecting several body systems: respiratory (sleep apnea syndrome, chronic obstructive pulmonary disease), cardiovascular (arterial hypertension (AH), coronary artery disease (CAD), HF, HRD), excretory (chronic diseases kidney), as well as endocrine (obesity, DM). These diseases, both alone and in combination, increase the risk of adverse outcomes. The deceased previously had a higher prevalence of AH (48%), DM (31%) and CVD (24%). The mortality rate increased with age, amounting to 1.3% among patients from 50 to 59 years old, 3.6% - from 60 to 69 years old, 8% - from 70 to 79 years old, and 14.8% - among people over 80 years old. Elderly patients with AH and DM, as well as people with CVD (IHD, CMP and cerebrovascular diseases) are susceptible to the development of severe form of COVID-19 and CVC. About 80% of patients with comorbidity have a severe course of COVID-19 [6]. It is assumed that in COVID-19, endothelial dysfunction, as one of the links in the pathophysiology of viral infection, makes a great contribution to the development of decompensation of comorbid conditions. This is due to chronic endothelial dysfunction (CED) and close interaction of organs that maintain homeo- and hemo-stasis. CED occurs in chronic diseases (IHD, DM, AH, obesity, oncology, etc.). In COVID-19 with comorbidity, CED and/or direct viral infection of endothelial cells lead to a dysfunctional endothelial reaction, which is one of the mechanisms of pneumonia development , acute respiratory syndrome, microcirculation disorders of the myocardium (damage) and other organs (kidneys, brain, liver and etc.). Lymphopenia and hypoalbuminemia in patients with severe COVID-19 can partly be explained by disruption of the integrity of the endothelial barrier in vascular or lymphatic capillaries [54].

The RAAS affects both the excretory (renin and aldosterone are synthesized in the kidneys) and the respiratory (ACE is synthesized in the lungs, and also ACE2 is present) systems and CVS. In this regard, it was proposed to introduce such supnosological concepts as "cardiorenal continuum", "cardiorenal metabolic syndrome" and "cardiorenal syndrome" [55]. Cardiorenal relationships under physiological norm were presented by A. Guyton (1990) in the form of a hemodynamic model, “in which the kidneys control the volume of extracellular fluid by regulating the processes of sodium excretion and reabsorption, while the heart controls systemic hemodynamics. The central link of this model is the RAAS, endothelium-dependent factors and their antagonists - natriuretic peptides and the kallikreinkinin system. When one of the organs is damaged due to the activation of the RAAS and the sympathetic nervous system, the development of endothelial dysfunction and chronic systemic inflammation, a vicious circle is formed - a pathophysiological condition in which the combination of cardiac and renal dysfunctions leads to an accelerated decrease in the functional capacity of each of the organs, remodeling of the myocardium, vascular wall and renal tissue, increased morbidity and mortality ”[56]. This hypothesis has an important prognostic value, since it is known that for SARS-CoV-2, the target protein is ACE2, one of the links of the RAAS.

In the context of concomitant CVD, AH is considered separately. Some experts have suggested that this prevalence of this disease among patients with COVID-19, including in severe form, is explained by the high prevalence of AH in the general population [57]. The full contribution of this disease is not completely clear, and the question remains whether AH is a risk factor for an unfavorable outcome of COVID-19. There was a hypothesis about the effect of treatment with RAAS blockers on the worsening prognosis in COVID-19 due to an increase in ACE2 expression [58], but it was refuted [59]. The data available at the moment do not allow to unambiguously determine the role of the RAAS and its blockers in the development of complications and the severity of the outcomes of coronavirus infection. At the same time, for groups of patients with AH, chronic HF, IHD who have undergone MI, for people with DM, drugs of RAAS blockers are crucial for the prognosis and are vital [60]. Patients should not be canceled antihypertensive therapy with drugs from the ACE inhibitors / sartans groups, since their abrupt withdrawal can lead to destabilization of blood pressure against the background of an infectious process, which will negatively affect the outcome of the disease [61]. However, the question of using these drugs as a starting therapy during a pandemic for people with newly diagnosed AH who have not been treated before remains open.

PATHOMORPHOLOGY OF COVID-19

On autopsy of patients with SARS-CoV-2, pathological changes are determined in almost all organs and tissues. This is due to the fact that ACE2 is expressed in many organs and tissues [67].

BRAIN

Infection with the SARS-CoV-2 virus can cause brain damage, both directly and indirectly. So, COVID-19 leads to a "cytokine storm" that can damage the blood-brain barrier and disrupt the normal functioning of the central nervous system, simultaneously creating conditions for the penetration of the virus from the systemic circulation. COVID-19 is associated with a prothrombotic condition that can lead to occlusion of the vessels supplying the brain.

Finally, ACE2, a functional receptor for SARS-CoV-2, can promote direct virus invasion into neurons and cerebrovascular endothelial cells, which leads to their apoptosis and necrosis [63]. So, according to B. Schurink et al. (2020) [64], histological examination of the tissues of the brain and cerebellum revealed hypoxic changes in the brain, manifested in the form of hypereosinophilia or nuclear and cytoplasmic condensation of neurons, detected by staining tissues with hematoxylin and eosin. A massive inflammatory response was observed in all patients affecting both white and gray matter, regardless of the course of the disease. The most pronounced inflammatory response was observed in the medulla oblongata and olfactory bulb. Paniz Mondolfi et al. [65] reported the results of histological examination and electron microscopy of a man who was hospitalized with symptoms of fever, confused consciousness and two episodes of falling at home. Polymerase chain reaction (PCR) analysis for COVID-19 was positive. At autopsy, viral particles were seen in the frontal lobe of the brain, as well as in the endothelial cells of the cerebral vessels. A PCR test of brain tissue also confirmed the presence of SARS-CoV-2. Von Weyhern et al. [66] identified damage to the brain stem (interstitial encephalitis). In particular, the motor nuclei of the vagus nerve, the nucleus of the trigeminal nerve, the NST, the nucleus of the dorsal suture and fasciculis longitudinalis medialis were involved in the pathological process.

LUNGS

Histological examination of lung tissue shows diffuse alveolar damage with hyaline membranes, fibrinous alveolar exudate, hyperplasia of type II alveolocytes, fibrin and platelet thrombi of pulmonary vessels of small and medium caliber. In some cases, in patients with intravital focal pneumonia, the presence of CD3−, CD4−, and CD8 + T cells was determined by immunohistochemistry [67]. In a number of cases, early changes were found with a sharp increase in the content of IL1-β and IL-6 mRNA, neutrophilic capillaritis, and capillary microthrombosis [68]. Magro et al. [69] reported damage to the alveolar septum capillaries, accompanied by extensive deposition of complement C4d and C5b-9 in 2 patients. The authors described thrombogenic vasculopathy, thus hypothesizing the activation of the virus-associated complement pathway. Ronny et al. [70] identified two different patterns of immunopathological response at fatal COVID-19. One sample demonstrates high local expression of interferon-stimulated genes (ISGhigh) and cytokines, high viral load, and limited lung damage. Another specimen shows severely damaged lungs, low ISG (ISGlow), low viral loads, and profuse infiltration of activated CD8 + T cells and macrophages. ISGhigh patients die much earlier after hospitalization than ISGlow patients.

HEART AND VESSELS

In the myocardium of the deceased, various hypoxic, metabolic and ischemic injuries, less often microangiopathy, petechial and confluent hemorrhages, were revealed. With thrombosis of the coronary arteries (CA), small-focal, less often - transmural MI developed. Lindner et al. [71] performed autopsies on 39 patients who died from COVID-19 (mean age 85). Cardiac tissue contained SARS-CoV-2 in 24 deaths (61.5%). In 16 cases (41.0%), a high viral load was detected based on the results of quantitative reverse transcription PCR; along with this, each deceased with a similar high viremia had the expression of proinflammatory genes. Basso et al. [16] reported that lymphocytic myocarditis occurred in 3 cases (14%) out of 21. In 2 of them, CD4 + T-lymphocytes predominated, and in one - CD8 + T-lymphocytes. Increased infiltration of interstitial macrophages was observed in 18 cases (86%). In 4 cases, mild pericarditis occurred. Acute damage to pancreatic RV cardiomyocytes, most likely due to stress / overload, occurred in 4 cases. There was a slight upward trend in serum troponin levels in patients with myocarditis compared to troponin levels in patients without myocarditis. There were no destabilized plaques in the CA, or CA aneurysms . The question remains whether the observed damage and inflammation of the myocardium are associated with direct viral damage or a systemic immune response secondary to infection [73]. Oudit et al. [74], based on the experience of the past epidemic caused by SARS-CoV, suggested that the interaction between SARS-CoV and ACE2 in the heart may contribute to SARS-mediated inflammation and myocardial damage. They reported that SARS-CoV viral RNA was detected in dissected human heart samples, suggesting direct virus invasion of cardiomyocytes. They also indicated a downregulation of

ACE2 and a decrease in the content of ACE2 protein in heart samples. Autopsies of patients with COVID-19 invariably reveal endotheliitis and the accompanying macro- and microvascular thrombosis in arteries, veins, arterioles, capillaries and venules in all major organs. Endothelial cells respond to inflammatory conditions for producing microvesicles and inflammatory mediators, including cytokines, thrombin, and complement proteins. In turn, microvesicles violate the integrity of blood vessels, gap junctions, promote binding of neutrophils, release neutrophilic extracellular traps, and also contribute to inflammation at the tissue level. The widespread vasculitis described in COVID-19 patients is likely to result in thrombosis, hemodynamic instability, and autonomic dysregulation [43].

KIDNEY

Autopsy data on kidney damage are conflicting. H. Su et al. analyzed kidneys in a series of autopsies from 26 COVID-19 patients. 9 patients out of 26 had clinical signs of kidney damage in vivo, including increased serum creatinine levels and / or new-onset proteinuria. Light microscopy showed diffuse damage to the proximal tubules with loss of brush border, degeneration of vacuoles, and even obvious necrosis. In some cases, hemosiderin granules and pigment casts were found. In addition, erythrocyte aggregates were found obturating the lumen of capillaries without platelets or fibrinous clots. There were no signs of vasculitis, interstitial inflammation, or hemorrhage. Electron microscopic examination showed accumulations of coronavirus-like particles with characteristic spines in the tubular epithelium and podocytes [75]. D. Santoriello et al. [76] examined the renal histopathology of 42 patients who died from COVID-19. The most significant findings included mild acute tubular injury (ATI), as well as the absence of classic viral nephropathy, diffuse thrombotic microangiopathy, or acute glomerulonephritis. In situ hybridization failed to identify a definitive positive for SARS-CoV-2. Detection of only a mild ATI in the presence of a severe increase in creatinine levels suggests a pathogenesis associated with tubular damage, hemodynamic factors (such as aggressive "infusion" of fluid) and the ability to restore kidney function after resolution of the infection.

LONG TERM FORECAST

The results of current research have provided insight into the CVEv that occurs in COVID-19 patients in the short term. In terms of the prognosis of long-term complications from the heart and blood vessels, an analysis of previous SARS-CoV pandemics is probably informative. Although SARS, MERS and COVID-19 are caused by viruses from the same family, there are key differences between them. For this reason, studying the other two diseases does not provide a reliable way to predict the long-term consequences of COVID-19. If COVID-19 does cause long-term effects, are the underlying mechanisms immunological, or are they caused by new or recurrent inflammation, ongoing infection, or side effects of immunomodulatory treatment? Long-term follow-up of patients will allow the development of strategies for prevention and treatment [77].

It is assumed that in patients with previous COVID-19, myocardial damage may be the initiator of subsequent fibrosis. If the degree and spread of fibrosis causes electrophysiologic abnormalities that predispose to atrial fibrillation and ventricular arrhythmias, early detection and intervention can improve long-term outcomes. Patients with subclinical disease may have a high risk of cardiac arrhythmias. Patients with asymptomatic but overt heart disease will benefit from standard therapy. Thus, the identification of survivors of COVID-19 infection with subclinical myocardial disease and / or arrhythmia provides a rationale for considering drugs with demonstrated cardioprotective properties, such as mineralocorticoid antagonists, β-blockers and statins. R.D. Mitrani et al. [78] suggest that increased surveillance and treatment of COVID-19 survivors with significant electrophysiological abnormalities can significantly reduce the burden of subsequent complications and mortality. The study of the results of magnetic resonance imaging of the heart of 100 recovered patients (after 2 months) showed that 78 of them were diagnosed with structural changes in the heart, in 76 - the content of biomarkers indicating heart damage was increased, and in 60 patients there were signs of inflammation. The fact that 78% of those who recovered had evidence of ongoing heart damage means that the heart is affected in most patients, even if COVID-19 disease does not manifest with classic heart symptoms such as angina and chest pain. COVID-19 may be a trigger for the progression of preexisting asymptomatic HF to overt HF with preserved left ventricular ejection fraction (HFEF). Survival after suffering COVID-19 may represent a new independent risk factor (RF) for the development of SNiEF , similar to the fact that CMP associated with AIDS virus can manifest itself primarily as subclinical diastolic dysfunction. Many COVID-19 survivors, especially those who have recovered from severe illness with severe hypoxic respiratory failure and thromboembolic complications, will be at risk for chronic right ventricular HF, PH, and diastolic

dysfunction. These unfavorable structural and functional changes in the heart can occur as a result of myocardial damage during an acute infection, and as a result of chronic lung disease [72]. The increased incidence of HF as a major consequence of COVID-19 is of concern, which has significant potential consequences for the elderly population with comorbidity, as well as for young, previously healthy patients, including athletes [79].

In world practice, specialists have already developed a certain set of tactics for managing and monitoring patients at risk, as well as those with already developed cardiac complications in COVID-19. The importance of determining the level of troponin and natriuretic peptide as important prognostic factors is noted. However, all of these algorithms are aimed at the short term. Only future research will make it clear whether there is a "post-COVID-19 cardiac syndrome" and how to manage such patients. Some sources suggest a tactic for screening examination CVS in patients during the recovery period. Certain criteria for the volume and type of this survey should be highlighted, otherwise this issue should be resolved individually. It is proposed to conduct a standard ECG and EchoCG 2–6 months after recovery, however, in this case, studies may be of little information. Therefore, the option of tissue Doppler imaging, speckle-tracking echocardiography and magnetic resonance imaging with gadolinium can be considered [78].

CONCLUSION

Damage to the cardiovascular system in COVID-19 is multifactorial, it occurs both as a result of the direct effect of the virus on the elements of this system, and indirectly. The cardiovascular system in patients with comorbidity, regardless of age, is more susceptible to myocardial damage and the development of complications with a high risk of death. It is necessary to assess the state of the cardiovascular system in patients with suspected or confirmed COVID-19 who initially have cardiovascular diseases and / or risk factors; cardiovascular symptoms / signs; changes in the level of biomarkers (D-dimer, troponin, NT-proBNP, etc.). Electrocardiography and transthoracic echocardiography should be the first choice for assessing cardiac function; cardiac magnetic resonance imaging should be considered. COVID-19 patients with myocardial injury are likely to remain at risk of cardiovascular events in the long term. However, the mechanisms for the development of long-term effects on the cardiovascular system have not been studied. At the moment, it is impossible to unequivocally assert whether it is possible to completely restore the cardiovascular system after COVID-19, and when the functional recovery of its elements after a previous illness will occur. Long-term research and patient follow-up will allow developing preventive measures and treatment tactics for cardiovascular damage in COVID-19.

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