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Changes of the endothelial properties in patients with coronary artery disease after COVID-19

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Abstract

COVID-19, like other respiratory viruses, has extra pulmonary manifestations. Like other organs cardiovascular system suffers from the virus. In particular, exposure to the virus leads to damage to the cardiovascular system (CVS), the pathophysiological mechanisms of which are not completely clear; a full understanding of the mechanisms of interaction between COVID-19 and CVS has not been formed. The article analyzes current ideas about COVID-19, considers possible links in pathogenesis, attempts to systematize the pathophysiological mechanisms of CVS damage and their complications, analyzes the relationship with cardiovascular comorbidity, and describes the features of pathomorphology and a hypothetical long-term prognosis. The presented information 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 a therapeutic tactic for a patient within a systematic approach.

Keywords: Cardiovascular system; Pathogenesis of COVID-19 damage; Angiotensin-converting enzyme-2; Renin-angiotensin system; Endothelial dysfunction; Microcirculation; Hemostasis system

1. Introduction

Despite the progress achieved in the treatment of cardiovascular diseases (CVD), cardiovascular diseases remain the main cause of death in many countries of the world. The majority of patients over 65 years of age in the world are patients with cardiovascular diseases, and 38 million people worldwide suffer from these diseases [1]. In 2017 alone, 17.8 million people died from CVD. This is 1/3 of all deaths in the world [2]. According to the latest annual report of the American Heart Association (American Heart Association), in 2016, 48% of elderly people have CVD [3]. Early detection and treatment of cardiovascular diseases not only prevent early death from cardiovascular diseases, but also increase the risk of heart failure. According to research results, one person dies of cardiovascular disease in every 36 seconds in the United States [4]. In the United States alone, 659,000 people die from cardiovascular disease each year, that is, 1 in 4 deaths are caused by cardiovascular disease [5, 6]. In the United States alone, 2016–2017 cardiovascular disease costs alone, including hospital, healthcare provider, and drug costs, totaled $363 billion [7].

Cardiovascular diseases, including ischemic heart disease (IHD), are pathological conditions that develop as a result of the influence of several genomic, genetic, environmental and lifestyle factors [8]. Year by year, the increase of CKD, cardiovascular diseases leading to this pathological process, i.e., hypertension and atherosclerosis, are among the most urgent issues of modern medicine. Because the poor prognosis and high mortality rates pose a serious threat to human life and lead to increased economic costs for society and patients.

CHD is one of the main causes of death and disability in the world, and according to the definition of the American Heart Association and the American College of Cardiology, the coronary arteries of the heart cannot pump enough blood to

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meet the needs of the heart, in other words, the heart the balance between the demand for oxygen and its supply is disturbed. According to the definition of the European association of cardiologists, CHD is a pathological process caused by atherosclerosis, thrombosis or several other factors, in which the coronary arteries of the heart cannot supply blood according to the needs of the heart [5, 18, 19]. CHD is the most common type of cardiovascular disease, causing 360,900 deaths worldwide in 2019 alone [9]. UIC is a pathological process that is often preventable and leads to bad consequences if not treated in time.

Ischemic heart disease can be chronic or acute. Chronic ischemic heart disease is a relatively stable process. Nevertheless, acute periods, i.e. acute coronary syndrome or myocardial infarction, are observed in chronic ischemic heart disease. Chronic ischemic heart disease (stable angina) is often classified according to the Canadian classification, which is evaluated by the severity of symptoms, their impact on the patient's physical activity and daily activities [10]. Acute coronary syndrome is characterized by a sudden worsening or rapid reappearance of anginal pain and symptoms in the heart. Acute coronary syndrome often develops suddenly [11, 20]. In the development of acute coronary syndrome, the formation of atherothrombosis or rupture of atherosclerotic plaques is often the main reason. Blood cells - platelets play an important role in this. Under the influence of various factors, as a result of destabilization and rupture of platelets, an obstacle to blood flow appears on the wall of coronary vessels. In this case, the increased aggregation of platelets increases the process, causes the formation of a thrombus, and blocks the blood flow with the resulting thrombus. As a result, acute ischemia is observed in myocardial tissue and causes acute corner syndrome. If appropriate treatment measures are not taken in time, acute coronary syndrome, can endanger the patient's life and lead to the formation of arrhythmias or acute heart failure, ending in death. From this point of view, the use of antiplatelet drugs in the treatment of ischemic heart disease is the most important strategy. Antiplatelet drugs are divided into several groups. Although aspirin is an integral part of standard treatment in patients with ischemic heart disease, it is used along with aspirin as antiplatelet therapy after acute coronary syndrome and coronary artery stenting.

Despite the fact that the attention of a huge number of researchers around the world is focused on the development of effective clinical protocols and recommendations for managing patients with a new coronavirus infection, the presence of a large number of severe forms of the disease and deaths suggests that doctors have not yet formed a complete picture pathogenesis of this disease, allowing for its effective treatment and prevention of the development of critical complications. In a number of studies in patients with severe forms of the course of COVID-19, a statistically significant relationship was found between the detection of micro thrombi in the pulmonary vessels, disorders of the coagulation balance, and damage to the vascular endothelium [5]. However, when describing the pathogenesis of COVID-19, as well as the factors involved in the development of complications of a new coronavirus infection, insufficient attention is paid to endothelial dysfunction. The pathogenesis of intravascular coagulation disorders in coronavirus infection is represented by three interconnected processes that form a vicious pathological circle [6]:

- Cytopathic damaging effect of the virus on vascular endothelial cells that carry ACE2 and CD147 molecules, with which the virus gets the opportunity to interact with the destruction of the air-blood barrier and developing viremia;
- "cytokine storm", which has a damaging effect on the vascular endothelium and provides an inflammatory response with recruitment of leukocytes, macrophages, lymphoid elements to the site of damage and activation of blood coagulation ("inflammatory-coagulation (thrombotic) tornado");
- The development of systemic vasculitis with lesions of small and medium-sized vessels, the role of virus-induced autoimmune reactions is also not excluded.

It should be borne in mind that in older people, who are most sensitive to coronavirus infection, in many cases, endothelial function is impaired even without additional viral influences. Damage to the endothelium can be due to many reasons, among which an important role is assigned to exogenous ones - injuries, chronic intoxication with psychoactive substances and heavy metal compounds [7, 8, 9, 10], which in turn increase the risk of COVID-19 morbidity and further affect the severity of the infection [11, 12, 13]. In the work of E.E. Ermolaeva et al. It has been shown that the vascular endothelium is one of the main targets of organophosphorus compounds during chronic exposure to even subsymptomatic concentrations [14]. Intoxication in interaction with stress factors can initiate the activation of lipid peroxidation, the products of which can damage endotheliocyte membranes, causing the development of atherosclerotic processes [15]. In addition to exogenous factors, concomitant oncological diseases, arterial hypertension, neurological pathology, diabetes mellitus, obesity, chronic obstructive pulmonary disease, etc., can have a significant impact on the severity of the course of COVID-19, and endothelial dysfunction is also considered in the complex basis of the development and progression of which [16 , 17, 18, 19].

The combined effect of exogenous and endogenous factors should largely determine the course and outcome of COVID-19. Therefore, a holistic view of endothelial dysfunction as a significant link in the pathogenesis of COVID-19 will prevent

the risk of pathology that complicates the course of a new coronavirus infection, including through the development of pathogenetically substantiated directions of pharmacotherapy.

2. Endothelial damage

"Under normal physiological conditions, the vascular endothelium prevents aggregation, blood coagulation and vasospasm by 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 blood plasma (thrombin). And, finally, the endothelium adsorbs anticoagulants from blood plasma, preventing adhesion and aggregation of platelets on its surface (heparin, proteins C and S)" [20]. Viral invasion into cells depends both on the expression of ACE2 and on the availability of TMPRSS-2 or other proteases required for viral spike cleavage. 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 [17]. Developed endothelial dysfunction causes disturbances in blood coagulation [28]. It is important to note that endothelial injury specifically activates the complement lectin pathway, as demonstrated in human in vitro and animal studies [29]. Histopathological studies have confirmed direct viral infection of endothelial cells, endotheliitis (inflammation of the wall of blood vessels), and micro- and macrovascular thrombosis in both venous and arterial circulation [18]. Based on these data, it can be concluded that SARS-CoV-2 contributes to 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 endothelitis may explain the systemic impairment of microcirculatory function in various vascular beds and their clinical consequences in patients with COVID-19 [20].

3. Cardiovascular complications of COVID-19

The hypothesis that acute respiratory infections, such as the influenza virus, are triggers for acute cardiovascular injury and death was proposed in the 1930s. Then, for 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 such reasons as organic heart pathology, hemorrhagic stroke, and diabetes mellitus (DM) [1, 6]. SARS-CoV-2 is no exception, which, based on of putative pathophysiological mechanisms his actions lead to the development of events such as myocarditis, pericarditis, acute coronary syndrome (ACS), decompensated heart failure (HF), takotsubo syndrome, sudden cardiac death, cardiomyopathies (CMP), arrhythmias, cardiogenic shock and venous, arterial thromboembolic complications. In one study, 7% of patients in a cohort of 150 had irreversible myocardial damage and developed HF; these conditions were accompanied by elevated levels of troponin in the blood [38]. Although the exact mechanisms of cardiovascular complications (CVD) in COVID-19 are still to be elucidated and systematized, the literature describes the predominant influence of the following processes:

1) direct cardiotoxicity; 2) systemic inflammation; 3) discrepancy between myocardial oxygen demand and 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 thrombosis; 8) imbalance of electrolytes. 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 perspective, monitoring of cardiac markers such as troponin, N-terminal natriuretic peptide B, and creatine kinase may help identify patients at risk for CVD at an earlier stage. This factor can be useful for preventive purposes and provide timely pathogenetic treatment [18].

4. Myocardial infarction

Due to 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 ST elevation MI (↑ST) in patients with COVID-19 is the rupture of an unstable atherosclerotic plaque [14–16]. 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 hemostasis system in the form of hypercoagulability and microthrombi, microemboli can also provoke and/or aggravate the development of MI, including type 2 MI [17]. Of interest is the treatment of patients with COVID-19 and advanced ST-segment elevation MI. The American College of Cardiology recommends that thrombolysis be performed only in low-risk patients with inferior wall MI without RV involvement, and those with lateral wall MI without significant hemodynamic compromise. The preferred method of treatment is percutaneous coronary intervention, which is performed in most cases [18].

5. Thromboembolic complications

Patients with COVID-19 are at increased risk of developing thrombotic events. This is due to systemic inflammation, multiple disorders of the hemostasis system and multiple organ involvement and directly depends on the severity of the disease. A number of studies have found significant increases in blood levels of D-dimer in patients with COVID-19 pneumonia. D-dimer levels greater than 1 μg/mL have been found to be associated with an increased risk of patient death during hospitalization. It is assumed that anticoagulation with low molecular weight heparin is associated with an increase in the survival of patients with a 6-fold increase in serum D-dimer, as well as in severe COVID-19 [19, 21].

6. 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. Cardiovascular status should be assessed in patients with suspected or confirmed COVID-19 who have underlying CV disease 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; magnetic resonance imaging of the heart should be considered. COVID-19 patients with myocardial injury are likely to remain at risk for 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 state whether a full recovery of the cardiovascular system after COVID-19 is possible, and when the functional recovery of its elements will occur after the disease. Long-term studies and observation of patients will allow the development of preventive measures and tactics for the treatment of damage to the cardiovascular system in COVID-19.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest.

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