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Role of Mast Cell Proteases in Cardiac Damage in New Coronavirus Infection

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ABSTRACT

INTRODUCTION: Coronavirus Disease 2019 (COVID-19) is the cause of the global pandemic of 2019–2023. Despite the fact that COVID-19 primarily affects the lung tissue, cardiovascular complications are not uncommon both at the height of the disease, and in the post-COVID period. The presence of previous cardiovascular diseases and advanced age of the patient are proven risk factors of adverse outcomes in COVID-19.

AIM: Based on the analysis of the current literature sources, to determine the role of mast cell proteases in the pathogenesis of cardiovascular complications of COVID-19.

Excessive production of pro-inflammatory cytokines and chemokines by mast cells in the new coronavirus infection conditions the initiation of a severe systemic inflammatory response that affects not only the lung tissue, but also the myocardium. One most significant mechanism of the development of cardiovascular complications in patients with COVID-19 is endothelial dysfunction of the microcirculatory system with the formation of ischemic areas with subsequent local apoptosis of cardiac myocytes.

CONCLUSION: Cardiovascular complications of COVID-19 develop primarily due to the damaging effect of proinflammatory cytokines, the production of which is stimulated by proteases of activated mast cells. Because of small amount of published data, additional investigation is required.

Keywords: COVID-19; mast cells; proteases; myocardial damage; cytokine storm.

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Роль протеаз тучных клеток в поражении сердца при новой коронавирусной инфекции

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АННОТАЦИЯ

Введение. Коронавирусная инфекция 2019 года (англ.: *CoronaVirus Disease-19*, COVID-19) стала причиной глобальной пандемии 2019–2023 годов. Несмотря на то что при COVID-19 поражается в первую очередь легочная ткань, сердечно-сосудистые осложнения также развиваются достаточно часто как во время разгара заболевания, так и в «постковидном» периоде. Наличие предшествующих сердечно-сосудистых заболеваний и пожилой возраст пациента — доказанные факторы риска неблагоприятных исходов при COVID-19.

Цель. На основании анализа актуальных литературных источников определить механизмы действия протеаз тучных клеток в патогенезе сердечно-сосудистых осложнений COVID-19.

Избыточная выработка провоспалительных цитокинов и хемокинов тучными клетками при новой коронавирусной инфекции COVID-19 обусловливает возникновение тяжелой системной воспалительной реакции, из-за чего поражается не только легочная ткань, но и миокард. Одним из наиболее значимых механизмов развития сердечно-сосудистых осложнений у больных COVID-19 является эндотелиальная дисфункция микроциркуляторного русла с формированием участков ишемии и последующим локальным апоптозом кардиомиоцитов.

Заключение. Осложнения COVID-19 со стороны сердечно-сосудистой системы развиваются в первую очередь за счет повреждающего действия провоспалительных цитокинов, выработку которых стимулируют протеазы активированных тучных клеток. В связи с малым количеством опубликованных данных требуется проведение дополнительных исследований.

Ключевые слова: COVID-19; тучные клетки; протеазы; повреждение миокарда; цитокиновый шторм.

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INTRODUCTION

Mast cells (MCs) are multifunctional effector cells of the innate immunity originating from the pluripotent MC-committed $CD34^+$ stem cells of the bone marrow, which then migrate to the peripheral blood and most of extramedullary organs for further differentiation and specialization in the target tissues under the influence of growth factors and cytokines [1]. MCs play an essential role in immune-inflammatory reactions functioning as important regulators of immune response. Their main function is to produce and secrete a variety of biologically active substances that affect the activity of various immune cells. These mediators can have both *proinflammatory* and *anti-inflammatory* effects, which makes MCs important components of the *initiation of the inflammatory response*, as well as of its control [2].

Secreted MC mediators can be classified into three main classes:

The *first class* is mediators that are already preformed and stored in the cytoplasmic granules (e.g., histamine, serotonin, some proteases). They can be rapidly released in response to various stimuli, as in allergic reaction or tissue injury;

The *second class* is lipid mediators, which are formed from membrane lipids (e.g., prostaglandins, leukotrienes) and synthesized in the process of cell activation. These mediators play an important role in regulation of vascular permeability, attraction of immune cells to the site of inflammation, and increase pain;

The *third class* is newly synthesized mediators (e.g., interleukins) that are formed in response to activation of MC receptors by various stimuli, such as allergens, foreign microorganisms or injuries [1, 2].

Coronavirus disease 2019 (COVID-19) is characterized by excessive activation of mast cells, which produce a large amount of proinflammatory cytokines, which, in addition to damaging the lung parenchyma, can also affect other organs and systems, including the heart. In a retrospective study conducted in China, 19.7% of 416 patients with COVID-19 were found to have signs of myocardial injury, and the mortality rate of patients with myocardial injury was 51.2%, while in patients without myocardial injury it was 4.5% [3].

The **aim** of this study to determine the mechanisms of action of mast cell proteases in the pathogenesis of cardiovascular complications of coronavirus disease 2019 based on an analysis of the current literature sources.

A systematic literature search was conducted, which included original studies and literature reviews in Russian and English on myocardial damage in COVID-19, including the role of MC proteases in the development of cardiovascular complications. The PubMed electronic search engine and the eLIBRARY.ru scientific electronic library were used.

The primary search for articles was carried out using the keywords 'COVID-19', 'mast cells' and 'heart'. Based on these criteria, 224 articles for the period from 2013 to 2024 were identified and selected for study. The analysis also included two articles published before 2019 (the year the new coronavirus infection was identified), which were not directly related to this disease, but allowed us to identify some patterns in the pathogenesis of heart damage in COVID-19.

When studying the abstracts of the selected articles, 73 publications of the PubMed electronic search system and 23 publications of the scientific electronic library eLibrary.ru that were not related to the topic of this systematic literature review were excluded.

After a detailed analysis of the full text of the publications, another 89 articles were excluded. For example, 7 articles studied the effect of MCs on the development of coronary heart disease, chronic heart failure, and acute coronary syndrome in patients without COVID-19. Two clinical studies had too small a sample size (<30), and four publications did not provide full access to the results obtained.

As a result, 39 studies were included in the analysis.

Role of Mast Cells in Immune-Inflammatory Reactions Including COVID-19

The mechanism of formation of an excessive systemic response to SARS-CoV-2 viral infection is presented in Figure 1.

MCs contain a high amount of intragranular proteases, which may make up to 35% of the total cell protein. Their absolute majority belong to the family of *endopeptidases*, which are associated with chymotrypsin-related serine proteases [1]. MC proteases playing the most significant role in the pathogenesis of COVID-19 are tryptase, chymase, carboxypeptidase A3, caspase 3 [2].

Tryptase (Enzyme Classification (EC) 3.4.21.59) is a neutral serine protease with trypsin-like specificity with a molecular weight of 134 kDa and a tetrameric structure consisting of non-covalently bound subunits that hydrolyzes peptide bonds at the carboxyl terminus of basic residues such as arginine or lysine. Tryptase is stored in a fully active form in mast cell granules. Five different tryptase isoforms have been described in humans: α (released from MCs into the bloodstream); β (concentrated in MC secretory granules and released only after degranulation); γ, δ, and ε-tryptase. The major protease present in human mast cells is β-tryptase [4].

In acute and chronic *in vivo* reactions to allergens, human skin MCs secrete tryptases with histamine, which are used as diagnostic markers of mastocytosis and systemic anaphylaxis. In addition, tryptases are powerful activators of fibroblast migration and proliferation, as well as collagen synthesis, stimulating tissue regeneration in wound healing and fibrosis, inducing proliferation of smooth muscles of the airways, promoting smooth muscle cell hyperplasia in bronchial asthma [5].

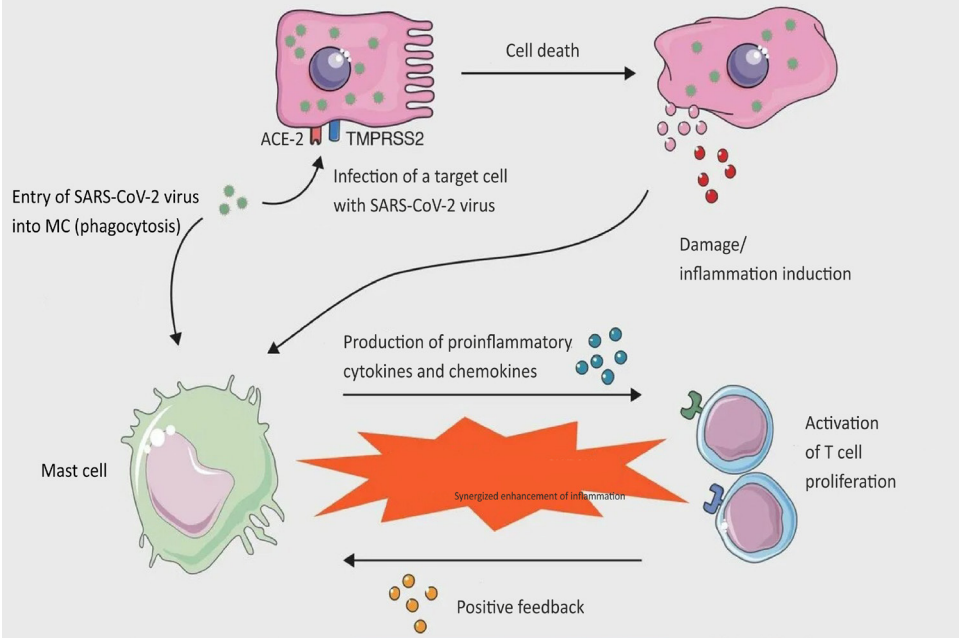

Fig. 1. Mechanism of formation of excessive systemic inflammatory response to SARS-CoV-2 viral infection: ACE-2 — type 2 angiotensin-converting enzyme, SARS-CoV-2 — Severe Acute Respiratory Syndrome-Related CoronaVirus 2, TMPRSS2 — Transmembrane Protease, Serine 2, MC — mast cell.

Excessive production of tryptase by MCs in COVID-19 contributes to the production of high amounts of proinflammatory cytokines that play an important role in the development of a 'cytokine storm', which causes damage not only to lung tissue, but also to the heart due to pronounced vasoconstriction of the coronary vessels and myocardial ischemia, as well as inflammatory infiltration of cardiomyocytes [6].

Chymase (EC 3.4.21.39) is a chymotrypsin-like serine MC protease, which cleaves the C-terminal side of aromatic amino acids (phenylalanine, tyrosine, tryptophan) of proteins. Chymase can cleave the inactive peptide angiotensin 1 to its bioactive peptide angiotensin 2, as well as the precursors of matrix metalloproteinase-9 (MMP-9) and transforming growth factor beta (TGF-β) to their active forms [7].

Chymase is also involved in mechanisms of the development of inflammation and allergy, angiogenesis and oncogenesis, remodeling of extracellular matrix of the connective tissue and alteration of histoarchitecture of organs. In patients with COVID-19, chymase participates in the production of angiotensin 2 and recruitment of leukocytes, and, consequently, supports inflammatory process in the endothelium. The development of SARS-CoV-2-associated endothelial dysfunction of capillaries contributes to the myocardial ischemia and the subsequent local apoptosis of cardiomyocytes, which aggravates the existing heart failure [2].

Carboxypeptidase A3 (CPA3) (EC 3.4.17.1) is zinc-binding metallocarboxypeptidase of the M14 family, similar to carboxypeptidase of pancreas, which cleaves C-terminal amino acid residues of proteins and peptides. CPA3 is involved in the pathogenesis of cancer, inflammatory diseases of the gastrointestinal tract, respiratory and cardiovascular systems, disorders of musculoskeletal system, and also in the immunogenesis. In particular, CPA3 can also be considered for assessing the severity of COVID-19, as well as a diagnostic marker and pharmacological target in the treatment of a number of pathological conditions [2]. In addition, a positive correlation was found between increased CPA3 and pulmonary fibrosis. This phenomenon is poorly studied, but it is suggested that CPA3 may be involved in the regulation of endothelin-1 levels, as well as in the formation and degradation of angiotensin 2 [8].

Caspase (EC: 3.4.22) are a family of cysteine proteases that cleave peptide bonds formed with the participation of aspartic acid. There are distinguished initiator and effector caspases. The former include caspases 8, 9, 10, 12, which, being activated, affect effector caspases 3, 6, 7, 14. In the cell, caspases are present as inactive monomeric precursors and for activation require cleavage of the proenzyme and subsequent dimerization. The mechanisms of assembling various caspases differ depending on the type of adapter protein, with which procaspase interact. Caspases are able to activate each other, forming a caspase cascade. The

caspase cascade can be initiated in two different ways. In the first case, a cell receives an external signal from the plasma membrane, and caspases 8 and 10 act as initiator caspases. In the second case, the signal is DNA damage, and caspase 9 acts as the initiator caspase. However, no matter which pathway the cascade is triggered by, its effector caspase is caspase 3 [9].

Caspases play a key role in cell apoptosis, participating in chromatin condensation and DNA fragmentation, in COVID-19 as well. For example, in studies by S. Karabulut Uzuncakmak et al. (2022), caspase 3 expressions directly correlated with the severity of COVID-19, with apoptosis occurring not only in lung parenchyma, but also in cardiomyocytes, which suggests high expression of these proteases in them [9]. Caspases contribute to a progressive decline of cardiac contractile function in heart failure, promoting degradation of myofibrillar proteins. Selective inhibition of the proteolytic functions of caspase 3 may be a promising approach to the treatment of heart failure [10].

S. Gebremeskel et al. (2021) identified elevated levels of chymase, β-tryptase, and CPA3 in the serum of COVID-19 patients, indicating systemic activation of MCs [11].

One of the most significant mediators of MCs is histamine, which is histidine amino acid decarboxylation product. Histamine accounts for about 10% of the dry matter of MCs. Histamine realizes its effect by binding to four receptors, H1, H2, H3, and H4, on target cells in various tissues. The main effects of histamine are contraction of smooth muscle cells, vasodilation, increase in vascular permeability and mucus secretion, tachycardia, changes in blood pressure and arrhythmia, as well as stimulation of hydrochloric acid secretion in the stomach and stimulation of nociceptive nerve fibers. In addition, histamine is known to be involved in neurotransmission, immunomodulation, hematopoiesis, wound healing, regulation of biorhythms, etc. [12].

MCs and histamine they produce are involved in the development of cardiovascular diseases, including heart failure, in COVID-19 as well. In the heart, histamine, through H1-receptors improves the conduction of the AV node, and through H2-receptors stimulates ino- and chronotropic activity. Excessive histamine in the heart due to degranulation of mast cells in response to infection with SARS-CoV-2 virus, promotes reduction of pericytes and endothelial cells of capillaries, which leads to ischemia and local apoptosis of cardiomyocytes [13].

MC proteases induce the production of large amounts of proinflammatory cytokines that have a damaging effect on the myocardium, induce endothelial dysfunction and apoptosis of cardiomyocytes [14]. Histamine, one of the most significant mediators of MCs, apart from vasodilating effect, can also produce a proarrhythmogenic effect on the heart.

Cardiovascular Manifestations of COVID-19

Cardiovascular manifestations of COVID-19 are quite common. For example, acute heart failure and worsening of the course of chronic heart failure were noted in 20–30% of hospitalized patients and were associated with high mortality, especially in patients with severe comorbidities. It is assumed that the development of acute coronary syndrome in a large number of patients with COVID-19 may be provoked by a rupture of an atherosclerotic plaque, spasm or microthrombosis of coronary vessels caused by a systemic inflammatory response and a 'cytokine storm'. In general, the mechanisms underlying cardiovascular manifestations include increased myocardial stress, hypoxemia, hypervolemia, myocardial injury, arrhythmias, myocarditis, stress-induced cardiomyopathy, acute damage to kidney and, as noted above, a systemic inflammatory response with the release of excess cytokines and chemokines [15].

One important mechanism of cardiovascular complications in COVID-19 is binding of SARS-CoV-2 to the angiotensin-converting enzyme type 2 receptor (ACE-2) to penetrate the cell. This enzyme has high expression not only in alveolar cells but also in cardiac pericytes, especially in patients with heart failure, which determines high contagiousness and mortality in these patients. Infection of cardiac pericytes with SARS-CoV-2 causes micro- and macrovascular endothelial dysfunction. In addition, an excessive immune response can potentially destabilize atherosclerotic plaques, which may explain the more frequent development of acute coronary syndrome in COVID-19 patients, and activated T cells and macrophages can penetrate the infected myocardium, leading to the development of fulminant myocarditis and severe cardiac injury. In addition, ACE-2 has anti-inflammatory, antioxidant and antifibrotic activity, and in SARS-CoV-2 infection, the level of this enzyme significantly decreases [16].

Patients with COVID-19 frequently present with arrhythmias, both new-onset and aggravation of existing ones. K. Liu et al. (2020) noted that heart palpitations were one of symptoms in 7.3% of patients with COVID-19 [17]. The main types of rhythm and conduction disorders in patients with COVID-19 included atrial fibrillation, antrioventricular block, ventricular tachycardia and ventricular fibrillation. One study of 700 patients with COVID-19 reports 9 cases of cardiac arrest, 25 cases of atrial fibrillation, 9 cases of clinically significant bradyarrhythmia and 10 cases of unstable ventricular tachycardia in them [18]. Among 241 patients with COVID-19, the prevalence of arrhythmia was 8.7%, with atrial tachyarrhythmia being most common (76.2%). A high risk of developing arrhythmia was observed in patients with heart failure, and 3.3% of COVID-19 patients experienced cardiac arrest followed by death during hospitalization [19]. Potential mechanisms of the development of arrhythmia in patients with COVID-19 are not completely understood, but putative variants include

metabolic dysfunction, myocarditis and activation of the sympathetic nervous system. Neuroimmune interactions play a critical role in the pathogenesis of arrhythmias, and MCs are important mediators between the immune and nervous systems. In the study by M. Mohajeri et al. (2019), almost 29% of patients with systemic mastocytosis, characterized by activation of MCs and release of mediators, and at least 20% of patients with MC activation syndrome, showed a marked temporary increase in the level of MC-produced mediators (e.g., tryptases) in blood serum, manifested by arrhythmias and heart arrest [20]. It has also been established that the immune system is also involved in the pathogenesis of arrhythmias through the production of autoantibodies and proinflammatory cytokines, such as tumor necrosis factor α, IL-1, and IL-6, which can be arrhythmogenic. IL-6 is the most important inflammatory effector molecule of MCs, and MCs are among the important sources of IL-6 [21]. Thus, possible risk factors for the development of arrhythmias in COVID-19 may include hypoxia, myocarditis, abnormal immune response, myocardial ischemia, electrolyte imbalance, metabolic dysfunction, sympathetic nervous system activation, arterial hypotension, and drug side effects. It is worth noting that some drugs for the treatment of COVID-19 can prolong the QT interval and have an arrhythmogenic effect [22].

In an international online study by H.E. Davis et al. (2021) involving 3762 patients, cardiac symptoms including chest pain (~53%), palpitations (~68%), and syncope (~13%) were observed in ~86% of patients within 7 months after COVID–19 infection [23]. The mechanisms causing irreversible cardiac damage in post-COVID syndrome are still not fully understood. One of the putative mechanisms is a chronic inflammatory process caused by persistent viral foci in the heart after acute infection. In the presence of obesity in a patient, inflammation can be significantly enhanced by the production of adipokines by adipose tissue, which aggravates endothelial dysfunction by uncoupling endothelial nitric oxide synthase and the production of reactive oxygen species. As a result, latent tissue damage occurs in the myocardium with subsequent development of fibrosis, which leads to a decrease in ventricular compliance, impaired perfusion and increased myocardial rigidity, decreased contractility and the occurrence of arrhythmias. The second mechanism of delayed cardiovascular complications is an autoimmune response to cardiac antigens due to molecular mimicry [24].

The most common manifestations of the cardiovascular damage in COVID-19 include a direct myocardial damage, arrhythmias and thromboembolic complications.

Laboratory Parameters of Cardiovascular Damage and their Prognostic Value in COVID-19

MC proteases, especially tryptase, chymase, carboxypeptidase A3 and caspases produced in response to COVID-19 viral infection, have a significant direct and indirect effect on the myocardium. Cardiovascular complications of COVID-19 are the second most common after complications from the respiratory system, increasing the risk of death. Therefore, using mainly laboratory diagnostic methods, the attending physician must early suspect their formation to timely prescribe adequate treatment.

Cardiac biomarkers, electrocardiography and transthoracic echocardiography play a key role in risk stratification and early detection of cardiovascular complications in COVID-19 patients [25]. Recent data suggest that cardiac biomarkers, including natriuretic peptide and troponins, can reflect the extent of cardiovascular damage, and are also closely associated with a poor prognosis and a high probability of death [26].

Z. Qiang et al. (2021) ranked cardiovascular markers in COVID-19 patients according to the calculated odds ratio (OR). The highest OR coefficient (11.83) was observed for troponin T, indicating the association of this biomarker with COVID-19 severity. It is followed by N-terminal prohormone of brain natriuretic peptide (NT-proBNP) (OR 7.57), troponin I (OR 6.32), lactate dehydrogenase (LDH; OR 4.79), D-dimer (OR 4.10), creatine kinase (OR 3.43) and creatine phosphokinase-MB (CPK-MB; OR 3.35). All laboratory parameters studied were statistically significantly associated with severe COVID-19, the need for intensive care, and mortality (p <0.01). The presence of concomitant cardiovascular and respiratory diseases, diabetes mellitus, and obesity may also adversely affect the prognosis [27].

Elevated troponin T level in the cardiac muscle was associated with a more severe acute respiratory distress syndrome and myocardial necrosis. Troponin T level was found to be significantly higher in patients with acute respiratory distress syndrome that ended in death than in patients who survived (0.008) [28]. Similarly, in many patients with confirmed COVID-19, elevated level of cardiac troponins was noted in blood serum, with statistically significant differences between patients who died and those who recovered. Mortality rate was 1.3%, 11.1%, 36.2%, and 91.3% in patients with COVID-19 with high-sensitivity troponin I levels below 0.006 ng/ml, 0.006–0.04 ng/ml, 0.04–0.78 ng/ml, and above 0.78 ng/ml respectively. Patients with cardiac involvement had a more than thirty-fold increase in high-sensitivity troponin I levels compared to patients without cardiac manifestations of COVID-19 (0.19 ng/ml vs. < 0.006 ng/ml) [3].

Increase in troponin level in the acute period of COVID-19 is suggested to be the result of direct injury of myocardial cells by SARS-CoV-2 or a consequence of a 'cytokine storm' caused by inflammatory reactions leading to myocarditis. C. Chen et al. (2020) revealed

a sharp rise of IL-6 level in COVID-19 patients with myocarditis, which plays a key role in the 'cytokine storm' inducing hyperinflammation and leading to production of plasminogen-1 activator inhibitor that launches a cascade of coagulation reactions [29]. Moreover, inhibition of IL-6 signaling in treatment with tocilizumab reliably reduced the production of plasminogen-1 activator inhibitor and eliminated the clinical manifestations of COVID-19. Thus, a potential mechanism of myocardial injury may be the IL-6-induced 'cytokine storm', which leads to the development of fulminant myocarditis [30]. However, it should be noted that the 'cytokine storm', in addition to worsening the clinical course of COVID, leads to the activation of MCs, which release cytokines that maintains and enhances the immune response.

In some cases, elevated troponin level in COVID-19 was associated with changes in the electrocardiogram and led to admission to intensive care unit [31]. However, despite the proven prognostic value of troponins, routine determination of their level still remains a matter of debate due to the presence of other factors that influence the disease outcome.

In the study by Z. Qiang et al. (2021), brain natriuretic peptide, a widely used biomarker of heart failure, was ranked the second biomarker most strongly associated with the severity of COVID-19. In COVID-19 patients with cardiac involvement, NT-proBNP level was more than 10-fold higher than in patients without signs of heart damage (1,689 pg/ml vs. 139 pg/ml) [3]. NT-proBNP level was found to significantly increase during hospitalization in patients who died, with no such dynamic changes observed in survived patients [15]. Some studies demonstrate that systemic inflammatory and procoagulant activity may persist long after hospitalization for COVID-19 with lung involvement, the clinical manifestations of which are significantly associated with an increased risk of cardiovascular disease within 10 years after recovery [32].

Q. Wu et al. (2017) found that lipid metabolism remains abnormal in SARS survivors for 12 years after clinical recovery, especially free fatty acid levels, which is likely due to intake of glucocorticoids [33]. Cholesterol and lipoproteins play an important role in infection with COVID-19. Cholesterol enhances the entry of SARS-CoV-2 into target cells using alipoprotein E transport protein [34]. At the peak of the disease, the level of total cholesterol and low-density lipoprotein cholesterol decreased proportionally to the severity of COVID-19. Widely used lipid-lowering drugs such as 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) may play a protective role in terms of the severity of COVID-19 disease, since cell wall cholesterol can promote viral entry into cells through ACE-2 receptors and also has pleiotropic effects — proinflammatory and prothrombotic [35]. O. Saeed et al. (2020) found that in-hospital mortality from COVID-19 was reduced by 12% (p <0.01) in patients with COVID-19 who took statins [36].

LDH, D-dimer and creatine kinase are less specific biomarkers of cardiovascular diseases than NT-proBNP, troponins T and I. LDH and creatine kinase can be used as indicators of the existence and severity of tissue damage, whereas D-dimer is an important biomarker of enhanced thrombosis, especially in deep vein thrombosis, pulmonary embolism, disseminated intravascular coagulation, etc. [37]. In a meta-analysis by B.M. Henry et al. (2020), elevated LDH levels were associated with a six-fold increase in the likelihood of severe COVID-19 [38]. CPK-MB is mainly found in the outer plasma layer of myocardial cells and is the most specific creatine kinase isoenzyme for the diagnosis of myocardial injury. A. Zinellu et al. (2021) conducted a meta-analysis of 55 studies including 11,791 COVID-19 patients, in which the relationship between CPK-MB levels and disease severity was assessed. The results of the studies demonstrate a significant increase in CPK-MB in patients with severe COVID-19, including fatal cases, compared to patients with mild and moderate COVID-19 [39].

Thus, most significant cardiovascular markers are troponins T and I, NT-proBNP, LDH, D-dimer, creatine kinase and CPK-MB.

CONCLUSION

Hyperactivation of mast cells by SARS-CoV-2 viral particles causes excessive production of proinflammatory cytokines and chemokines, to the extent of a 'cytokine storm', which can considerably impair the prognosis of COVID-19. These immune-inflammatory reactions occur not only in the lungs, but also in the heart, causing local ischemia of cardiac myocytes with subsequent apoptosis of damaged cells, which may lead to the development or worsening of heart failure.

Mediators released by mast cells, play a significant role in the pathogenesis of cardiac failure, the development of ischemia and occurrence of arrhythmias. Unfortunately, most of the pathophysiological and pathanatomical aspects of the new coronavirus infection remain incompletely understood, however, their understanding will help create a new therapeutic targets and approaches to the treatment of this disease.

ADDITIONAL INFORMATION

Author contributions. A.V. Budnevskiy — scientific guidance; S.N. Avdeev — concept of the study; E.S. Ovsyannikov, R.E. Tokmachev — editing; S.N. Feygelman, V.V. Shishkina, I.M. Perveeva — literature review; T.A. Chernik, E.D. Arkhipova — writing the text. All authors approved the manuscript the publication version), and also agreed to be responsible for all aspects of the work, ensuring proper consideration and resolution of issues related to the accuracy and integrity of any part of it.

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