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Acute myocardial injury in new coronavirus infection: contribution of mast cells

Budnevsky A.V.¹, Avdeev S.N.², Ovsyannikov E.S.¹, Tokmachev R.E.¹, Feigelman S.N.¹, Shishkina V.V.¹, Perveeva I.M.³, Chernik T.A.¹, Arkhipova E.D.¹, Budnevskaya S.A.¹

¹ N.N. Burdenko Voronezh State Medical University
 10 Studencheskaya St., 394036 Voronezh, Russian Federation

² I.M. Sechenov First Moscow State Medical University
 8-2 Trubetskaya St., 119048 Moscow, Russian Federation

³ Voronezh Regional Clinical Hospital No. 1
 151 Moskovsky Ave., 394066 Voronezh, Russian Federation

ABSTRACT

The new coronavirus infection, COVID-19, led to a global pandemic in 2019–2023. The infection affects not only the lung tissue, but also other organs and systems, including the heart. This causes the frequent development of myocarditis, arrhythmia, and acute coronary syndrome in these patients, as well as worsening of coronary heart disease and chronic heart failure. One of the important mechanisms of heart damage in COVID-19 is the excessive activation of mast cells, which produce cytokines and chemokines with pro-inflammatory activity, thus causing a so-called “cytokine storm” – a special severe form of systemic inflammatory response that can be fatal.

The aim of the literature review was to analyze and summarize published data on cardiovascular complications in COVID-19, including the effect of mast cell proteases on myocardial damage.

Keywords: COVID-19, mast cells, cytokine storm, heart

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Острое повреждение миокарда при новой коронавирусной инфекции: вклад тучных клеток

Будневский А.В.¹, Авдеев С.Н.², Овсянников Е.С.¹, Токмачев Р.Е.¹, Фейгельман С.Н.¹, Шишкина В.В.¹, Первеева И.М.³, Черник Т.А.¹, Архипова Е.Д.¹, Будневская С.А.¹

¹ Воронежский государственный медицинский университет (ВГМУ) им. Н.Н. Бурденко
 Россия, 394036, г. Воронеж, ул. Студенческая, 10

✉ Feigelman Sofia N., s.feigelman@gmail.com

²Первый Московский государственный медицинский университет им. И.М. Сеченова (Сеченовский Университет) Россия, 119048, г. Москва, ул. Трубецкая, 8-2

³Воронежская областная клиническая больница № 1 (ВОКБ № 1) Россия, 394066, г. Воронеж, Московский проспект, 151

РЕЗЮМЕ

Новая коронавирусная инфекция COVID-19, вызвавшая масштабную пандемию в 2019–2023 гг., поражает не только легочную ткань, но и другие органы и системы, в том числе сердце, что обуславливает частое развитие у данных пациентов миокардита, аритмий, острого коронарного синдрома, а также ухудшение течения ишемической болезни сердца и хронической сердечной недостаточности. Одним из важных механизмов повреждения сердца при COVID-19 является избыточная активация тучных клеток, которые вырабатывают цитокины и хемокины, обладающие провоспалительной активностью, вызывая, таким образом, «цитокиновый шторм» – особую тяжелую форму системной воспалительной реакции, которая может заканчиваться летальным исходом.

Цель литературного обзора заключалась в проведении анализа и обобщении опубликованных данных о сердечно-сосудистых осложнениях при COVID-19, включая влияние протеаз тучных клеток на поражение миокарда.

Ключевые слова: COVID-19, тучные клетки, протеазы, цитокиновый шторм, сердце

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

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LITERATURE REVIEW METHODS

A systematic literature review was conducted including original articles on myocardial damage associated with the novel coronavirus infection, COVID-19, as well as the role of mast cell proteases in the development of cardiovascular complications among patients with this disease. PubMed and eLIBRARY were used as electronic search engines. The primary search was performed using the keywords “COVID-19”, “mast cells”, and “heart”. Based on these criteria, we found and reviewed 436 articles published between 1996 and 2024.

When reviewing the summaries of the selected articles, we excluded 134 publications from the PubMed electronic database and 32 publications from eLIBRARY as they were not relevant to the topic of our systematic literature review. After a detailed analysis of full-text publications, we excluded 207 articles. For example, we excluded 12 studies that

examined the effect of mast cells on coronary heart disease, chronic heart failure, and acute coronary syndrome in patients without COVID-19. In two clinical trials, the sample size was too small (less than 30 individuals), and in three publications, full access to the results was blocked. Finally, we included 41 studies in our review.

BRIEF EPIDEMIOLOGY OF COVID-19

During the period of sanitary and epidemiological monitoring in the 21st century, there were three significant episodes of mass coronavirus infection. A common feature of these epidemics was that humans were primarily infected from animals, forming a natural source of anthroponozoonotic infection [1].

The severe acute respiratory syndrome (SARS) epidemic was first reported in 2002 in China. Cases were recorded in 37 other countries, and in 2003, the causative agent SARS-CoV was identified [2]. During this time, 8,096 cases of the disease were confirmed,

of which 774 were fatal. Since 2004, no new cases of SARS-CoV have been reported [3].

The second epidemic caused by a coronavirus occurred in 2012 in Saudi Arabia. It was caused by the Middle East respiratory syndrome-related coronavirus (MERS-CoV) [4]. According to the World Health Organization (WHO), the epidemic had a high mortality rate of 36% among those infected. Due to the spread of the virus from infected dromedaries to humans, high-risk groups included shepherds and workers at slaughterhouses [1]. In addition, people with chronic lung diseases, chronic kidney diseases, obesity, diabetes, and immunodeficiency conditions were also at an increased risk of infection [5, 6]. The epidemic spread to 27 countries, mostly in the Arabian Peninsula and surrounding areas, and cases of MERS-CoV continue to be identified at present [6].

The third wave of the coronavirus infection in December 2019 was identified as the most widespread, soon receiving the status of a pandemic. On January 13, the first case of the infection was recorded outside of China, and on January 30, person-to-person spread of the virus was confirmed [7]. A coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified as the etiological factor of COVID-19 [8]. Bats, minks, and some members of the felidae family are thought to be the natural reservoirs of SARS-CoV-2, as well as a number of other potential intermediate hosts, including pangolins, ferrets, and snakes [9]. Humans are susceptible to this virus due to its affinity for the human angiotensin-converting enzyme 2 (ACE2) receptor [10]. At the same time, the contagiousness, virulence, replication rate, and other characteristics of different genetic variants of the SARS-CoV-2 virus vary [11]. A sick person or an asymptomatic carrier can transmit SARS-CoV-2. Airborne transmission is the most significant way of spreading the virus, followed by transmission through airborne dust particles and household contact. Fecal-oral transmission is considered less likely [12].

In the Russian Federation during the pandemic caused by the novel coronavirus infection, five significant increases in morbidity and mortality, known as waves, were recorded. The average incidence rate for all recorded waves was 248 cases per 10,000 people, with an overall average mortality rate of 2.4%. The highest incidence occurred in the fifth wave, and the highest mortality was in the fourth one [13]. When studying global patterns of morbidity fluctuations during the pandemic, it was found that waves subside after an average of 48 days, regardless

of the initial conditions [14]. Due to the improved epidemic situation, the World Health Organization declared an end to COVID-19 as a public health emergency on May 5, 2023. As of now, COVID-19 can be considered a seasonal disease [12].

Etiology and Pathogenesis of Coronavirus Infections, Including Novel Coronavirus Infection (COVID-19)

Phylogenetic analysis of the SARS-CoV-2 virus genome allowed it to be assigned to the genus *Betacoronavirus*, the family *Coronaviridae*. This RNA-containing enveloped pleomorphic virus has round particles ranging from 60 to 140 nm in diameter. The SARS-CoV-2 genome is 50% identical to that of SARS-CoV and 75% identical to that of MERS-CoV [15].

SARS-CoV and SARS-CoV-2 viruses, as well as pathogens of mild respiratory infections – alphacoronaviruses HCoV-NL63 and HCoV-229E and betacoronaviruses HCoV-OC43 and HCoV-HKU1, use the ACE2 receptor to enter cells, which was first identified in 2003 [16, 17]. ACE2 is an 805-amino-acid carboxypeptidase that cleaves one amino acid from the C-terminus of its substrates. Being a part of the renin-angiotensin-aldosterone system, ACE2 converts angiotensin I and angiotensin II into angiotensin-(1–9) and angiotensin-(1–7), respectively [18].

The coronavirus virion consists of nucleocapsid (N), membrane (M), envelope (E), and spike (S) proteins. The penetration of viral particles into the cell is mediated by S-glycoprotein, which embedding into the membrane of the virion in several copies of the homotrimer gives it a crown-shaped appearance. Glycoproteins of many viruses, including HIV-1, Ebola, and avian influenza viruses, are cleaved into two subunits in infected cells — extracellular and transmembrane (this cleavage occurs prior to the virus release from the producing cell). Similarly, the S-protein of some coronaviruses is cleaved into S1 and S2 subunits during their biosynthesis in infected cells, but the S-protein of other coronaviruses is cleaved only when the next target cell is reached. SARS-CoV-2, like MERS-CoV, belongs to the first category: its S-protein is cleaved by protein convertases in virus production cells [17].

Thus, the S-protein of a mature virion consists of two non-covalently bound subunits: the S1 subunit binds to ACE2, and the S2 subunit attaches the S-protein to the membrane [19]. The interaction of receptors with viral glycoproteins in the presence of

specific triggers causes significant conformational changes in both subunits, which bring the viral and cell membranes closer together, eventually creating a fusion pore through which the viral genome enters the cytoplasm of the cell. For SARS-CoV-2, one of these triggers is the cleavage of an additional region within the S2 subunit, called the “S2’ region”, which is exposed after interaction with ACE2. The cleavage of the S2’ region by transmembrane protease, serine 2 (TMPRSS2) on the cell surface or by cathepsin L in the endosomal vesicle after ACE2-mediated endocytosis releases the merging peptide, initiating the formation of a pore that ensures the penetration of the viral genome into the cell [20–22].

Analysis of animal models and human transcriptome databases demonstrates that the expression of ACE2 in the lower parts of the lungs is represented only by type II alveolar cells, however, it is much higher in the epithelium of the bronchi and nose, especially in ciliated cells. The difference in ACE2 levels across the respiratory tract may explain the variable infection gradient of SARS-CoV-2, while the ciliated cells of the nasal cavity are the main target for virus replication in the early stages of the disease [23].

Despite the fact that the airborne transmission of SARS-CoV-2 infection is the dominant route, the highest level of ACE2 expression is observed in the intestine, testicles, kidneys, myocardium, and thyroid gland [24]. Cardiac infection with SARS-CoV-2 was often detected at autopsy, and the presence of ACE2 in colon and kidney cells has been proposed as an explanation for gastrointestinal and renal complications caused by SARS-CoV-2 [25, 26]. The expression of ACE2 in the gastrointestinal tract is consistent with the fact that many coronaviruses are transmitted not only using the airborne route but also by the fecal-oral route [26]. Inflammatory cytokines released during the “cytokine storm” in severe COVID-19, such as IL-1 β and type I and III interferons, can increase the expression of ACE2, potentially creating a positive feedback loop for viral replication [27].

Concomitant diseases, including arterial hypertension, hyperlipidemia, diabetes mellitus, chronic lung diseases, old age, and smoking, are risk factors for COVID-19 infection, and some of them may affect ACE2 expression. Widespread epidemiological data suggest that smoking increases the risk of severe disease, but it is not fully known whether smoking causes an increase in ACE2 expression and whether it is associated with worsening of the infection [12]. Many biochemical studies have demonstrated that

the expression of ACE2 is increased in lung tissue samples from smokers and patients with chronic obstructive pulmonary disease, as well as in the lungs of mice exposed to cigarette smoke [28, 29].

THE ROLE OF MAST CELLS IN THE PATHOGENESIS OF COVID-19

Mast cells (MCs) are cells of innate immunity of myeloid origin, which also participate in the reactions of acquired immunity. They are present everywhere in the body, but are mainly concentrated in the lungs, respiratory tract, heart, gastrointestinal tract, skin, nasal cavity, and meninges. MCs differ in their ultrastructure, morphology, mediator content, receptor expression, and response to stimuli, and they play an important role in the first line of defense against viruses and bacteria entering the body. Recent data indicate that after entering the body, coronaviruses activate cells of the innate immune system – monocytes/macrophages, neutrophils, T-cells, natural killers (NK-cells), MCs, and epithelial and endothelial cells. Activation of MCs in response to a viral infection performs a protective function, directly countering infection and influencing the immune system [30–32].

The immune response to COVID-19 can be divided into physiological and pathological – excessively active, contributing to damage to the lungs, heart, and other organs, which can significantly aggravate the course of the disease. Initially, SARS-CoV-2 infection causes a local immune response, including the attraction of MCs, macrophages, and monocytes to the infection site, their production of interferons and cytokines, as well as activation of the adaptive immune response of T and B cells.

In most cases, this process eliminates the infection, but in some cases, immune system dysfunction occurs, which leads to severe damage to internal organs. When the immune response is disrupted, immune cells hyperactivate with excessive infiltration of monocytes, macrophages, and T-cells in the lungs, which causes excessive production of pro-inflammatory cytokines, the so-called “cytokine storm” or “cytokine release syndrome,” which can eventually lead to acute respiratory distress syndrome, pulmonary edema, and other multiple injuries to internal organs, including the heart [33–35].

A “cytokine storm” is a potentially dangerous exaggerated inflammatory response that involves the activation of macrophages, leukocytes, MCs, and endothelial cells as a result of an autocrine and paracrine effect associated with the release of

large amounts of pro-inflammatory cytokines and chemokines (for example, IL-6, IL-8, IL-1 β , tumor necrosis factor α (TNF α), CCL2 (chemokine (C-C motif) ligand), CCL5, IL-17, IL-18, IL-33, CXCL-10 (C-X-C motif chemokine ligand), IFN γ , IL-12, and granulocyte-macrophage colony-stimulating factor) [36]. Lymphopenia caused by a “cytokine storm” prevents the immune system from producing antiviral antibodies, which are necessary for the destruction of viruses [37]. Elevated IL-6 levels correlate with the need for mechanical ventilation and mortality, and leukotrienes and reactive oxygen species released by neutrophils cause lung damage by destroying endothelial cells and pneumocytes [38].

Damage to the cardiovascular system as a result of the “cytokine storm” is probably caused by endothelial dysfunction, instability or rupture of atherosclerotic plaques, apoptosis of cardiomyocytes, and myocarditis. The mechanisms of endothelial dysfunction in patients with COVID-19 are not limited to increased concentrations of pro-inflammatory cytokines and include direct infection with viral particles of endothelial cells, angiotensin II hyperactivity, complement activation, and other variants of immune regulation disorders, such as the formation neutrophil extracellular traps (NETs) [39].

SARS-CoV-2 viruses have been detected in endothelial cells of various tissues, which may contribute to an imbalance between ACE2 and angiotensin II. It was found that complement activation was directly correlated with microthrombosis in a small number of COVID-19 patients, and NET formation was associated with acute respiratory distress syndrome caused by COVID-19. The complement system recognizes viral pathogens, thereby activating the innate immune response to viral infections, while NET cells stimulate the secretion of IL-1 β by macrophages and are involved in the development of atherosclerosis, causing endothelial damage and dysfunction.

Moreover, endothelial cells undergoing apoptosis have been shown to activate the complement system, which can further enhance cytokine secretion, contributing to microthrombosis. Thus, direct infection of endothelial cells with SARS-CoV-2 virus particles, subsequent angiotensin II hyperactivity, and the pro-inflammatory effects of complement activation and NET formation cause both direct and indirect disruptions to the cardiovascular system, exacerbating the “cytokine storm” [33].

An increase in the level of cytoplasmic Ca²⁺ within

endothelial cells is a critical factor in disrupting interendothelial connections and, consequently, increasing vascular permeability. The reason for the increased influx of Ca²⁺ is the activation of channels with a temporary receptor potential, which is induced by TNF α , causing destabilization of microtubules [33]. J.H. Tinsley et al. demonstrated the role of cytokines (TNF α , IL-1 β , and IL-6) in increasing vascular permeability through the signaling pathways of protein kinase C and myosin light chain kinase (MLCK) in cultured endothelial cells of rat heart microvessels. The results obtained have been reproduced *in vivo* in a model of heart failure in rodents with ischemia/reperfusion [40].

Thus, the influx of Ca²⁺ into endothelial cells caused by the “cytokine storm” may be one of the mechanisms underlying the disruption of interendothelial connections and increased vascular permeability. In addition, cytokine-induced stimulation of protein kinase C and MLCK leads to direct damage to heart tissue and can exacerbate existing cardiovascular diseases, which is quite common in patients with severe COVID-19 [33].

The Relationship between the Number of Mast Cells and Laboratory Blood Values in COVID-19 Patients

Positive correlations were found between the content of tryptase-positive MCs and the level of band neutrophils in the complete blood count in COVID-19 patients, which can be explained both by the local effect of MCs on the chemotaxis of neutrophils in the focus of inflammation and by the systemic effect of MCs on the number of neutrophils in peripheral blood [41].

The positive correlation between the content of tryptase-positive MCs and the level of eosinophils in the blood of COVID-19 patients is due to the effect of tryptase on the activation status of eosinophils due to the release of eosinophil peroxidase and beta-hexosaminidase. In addition, MCs are involved in the pathogenesis of other diseases accompanied by blood eosinophilia: eosinophilic esophagitis, bronchial asthma, chronic rhinosinusitis, etc. [41].

The positive correlation between the content of tryptase-positive MCs and the level of blood basophils in COVID-19 patients may hypothetically be due to activating signals common to MCs and basophils: through Fc epsilon RI receptors, fragments of complement C3a, C4a, and C5a; mediators of activated neutrophils, and some neurotransmitters [41].

Negative correlations were found between the absolute content of single carboxypeptidase A3 (CPA3)-positive MCs in the autopsy material of lungs of patients with COVID-19 and the content of monocytes in the blood. It is known that monocytes, macrophages, and MCs infected with SARS-CoV-2 produce pro-inflammatory cytokines and chemokines that contribute to the development of local tissue inflammation and a systemic reaction in the form of a “cytokine storm.” Low expression of ACE2 by monocytes/macrophages in patients with COVID-19 may also contribute to the development of pathological reactions due to the pro-inflammatory properties of angiotensin II and dysfunction of the renin-angiotensin system [41].

No statistically significant correlations were found between the number of MCs and total leukocyte count [41].

Positive correlations were found between the content of CPA3-positive MCs and the level of hemoglobin in the blood. Increased levels of glycolysis intermediates were observed in the red blood cells of patients with COVID-19, which is accompanied by oxidation and fragmentation of membrane proteins. Laboratory tests in patients with COVID-19 demonstrate a decrease in hemoglobin concentration and a pathologically increased concentration of ferritin. The level of ESR negatively correlated with the content of tryptase-positive and chymase-positive MCs [41].

No statistically significant correlations were found between the number of MCs and the level of CRP [41].

FEATURES OF DAMAGE TO THE CARDIOVASCULAR SYSTEM IN COVID-19

Although macrophages are the predominant cells of the innate immune system in the heart, MCs also play an important role in the development of a large number of cardiometabolic diseases. Mast cells are present in the endocardium, myocardium, and epicardium, in the left and right ventricles and atria, as well as around coronary and microcirculatory vessels, in atherosclerotic plaques, and near sensory neurons [42]. For example, in the left ventricle of the human heart, the density of MCs is usually about 5.3 MCs/mm³, and the number of macrophages is about 10 times greater. The density of MCs in heart tissues in patients with dilated cardiomyopathy and ischemic cardiomyopathy is approximately 18 MCs/mm³ [43].

Cardiovascular complications, which often develop in COVID-19, include arrhythmias, worsening of coronary heart disease (CHD), heart failure, cardiogenic shock, myocarditis, or myopericarditis, which can occur both during the acute phase of COVID-19 and in the post-COVID period [44, 45]. Patients with pre-existing heart diseases and risk factors are more susceptible to cardiovascular complications of COVID-19, more severe course of the disease, and death [46, 47]. Nevertheless, these conditions can occur even in patients without concomitant diseases [47]. Regardless of the clinical pattern, acute myocardial injury, defined as an increase in serum troponin levels above the 99th percentile of the upper limit of normal, was associated with a more severe course of COVID-19 and an increased risk of death [48, 49].

The high prevalence of co-occurring acute myocardial injury and clinically pronounced heart failure in patients with severe COVID-19 strongly supports the diagnosis of acute myocarditis, which was initially confirmed by two series of autopsies of patients with COVID-19 at the beginning of the pandemic [50, 51]. However, as subsequent series of autopsies were published, it became clear that these studies represent only isolated cases. Of 277 autopsies of COVID-19 deaths reported in 22 articles in the first year of the pandemic, less than 8% showed histological signs of myocarditis [52]. Moreover, only a small part of the described cases would meet the Dallas or Marburg criteria of the World Health Organization, which makes acute lymphocytic myocarditis in COVID-19 patients a rare disease (<1.4%) [53, 54]. In contrast to these signs of myocarditis, other acute histopathological changes in the heart including macro- and microvascular thrombosis, damage to endothelial cells, focal necrosis, injury to cardiomyocytes distributed across the heart muscle, and infiltrates of immune cells without damage to adjacent cardiomyocytes are much more common in COVID-19 [55, 56].

Thus, an increase in the number of macrophage infiltrates was observed in the interstitial myocardium of deceased COVID-19 patients, which, according to the Dallas criteria, does not correspond to the diagnosis of myocarditis [53, 57]. Nevertheless, the density of interstitial CD68+ macrophages in the myocardium was significantly higher in those who died from COVID-19 with myocarditis than in those who died from COVID-19 without myocarditis. In rare cases of lymphocytic myocarditis caused by

COVID-19, the density of CD3+ T-cells and CD4+ T helper cells in the myocardium, but not CD8+ cytotoxic T-cells, was also increased compared with those who died from COVID-19 without myocarditis [58, 59]. It is assumed that infiltrating macrophages in the myocardium of patients with COVID-19 probably originate from circulating monocytes [60].

It is worth noting that myocarditis occurs 10–15 days after the onset of COVID-19 symptoms. The degree of myocardial damage is mainly due to the activity of viral replication, immune, and other mechanisms. Acquired T-cell immunity plays a key role in the development of this disease. Most scientists believe that delayed myocardial inflammation may be associated with at least two pathogenetic mechanisms. Firstly, the “cytokine storm” contributes to the occurrence of subclinical autoimmune myocarditis. Secondly, myocardial damage and/or molecular mimicry can cause autoimmune reaction [61].

During the first wave of the pandemic, a single-center study using both hematoxylin and eosin staining and immunohistochemical staining assessed hearts of 69 COVID-19 patients regarding six acute histopathological changes, which were observed in 97% of the deceased. Microthrombi were found in 70% of the deceased, which makes them the most frequently detected acute histopathology of the heart. Damage to microvascular endothelial cells was observed in 36%, scattered necrosis of individual cardiomyocytes in 36%, focal myocardial necrosis without any adjacent inflammatory infiltrate in 20%, focal inflammatory infiltrates without concomitant damage to cardiomyocytes in 17%, and focal myocarditis in only 4.6% of the deceased. SARS-CoV-2 virus particles were detected in the cardiomyocytes of 62% of the deceased [62].

The effects of COVID-19 on the heart can largely be characterized as apoptosis of cells (pericytes, endothelial cells, and cardiomyocytes), severe disorders of the innate immune response, and coagulopathy in the form of hypercoagulation. Coronary microvascular pericytes are the most likely primary target for SARS-CoV-2 infection, although some experimental data confirm the primary infection of cardiomyocytes. Infection of pericytes leads to their dysfunction and death, which further leads to a loss of functional support for endothelial cells. It is believed that the death of endothelial cells and cardiomyocytes is largely due to the inflammatory reaction caused by SARS-CoV-2, which also activates fibroblasts, which play an important role in immune-

mediated thrombosis in COVID-19. Dysregulation of the kallikrein-kinin system, the complement system, and the coagulation cascade all contribute to the occurrence of cardiovascular complications in COVID-19. Many details of the described pathological mechanisms, including the sequence of events, are not fully understood [55].

According to O. Dmytrenko et al., SARS-CoV-2 affects the cardiovascular system through direct infection of myocardial cells and systemic inflammation. Infection of cardiomyocytes through ACE2 leads to disruption of the sarcomere structure, decreased contractility, and release of cytokines and chemokines, which can lead to the death of infected cells. Replication contributes to the further spread of the virus. Moreover, severe injury in COVID-19 causes a systemic inflammatory reaction that promotes the attraction of immune cells and increases prothrombotic activity [63].

CONCLUSION

In patients with COVID-19, researchers tend to pay more attention to the study of damage to the cardiovascular system, the most common manifestations of which include arrhythmias, myocardial damage, and thromboembolic complications. The main clinical symptoms include exercise intolerance, chest pain, and fatigue. Recent studies conducted by several groups of scientists have demonstrated the presence of SARS-CoV-2 RNA and proteins in the myocardium of patients with COVID-19. Cardiomyocytes and pericytes of the heart were found to be the most susceptible to infection, which promotes the release of immune mediators, changes in basic cell functions, and ultimately the death of infected cells. The noted virus-mediated effect on MC activation is in the form of increased degranulation, while increased release of mediators also contributes its pathogenetic effects to the mechanism of development of myocardial damage. However, most of the literature data are still contradictory.

It should be noted that different studies have analyzed different pathologies, often focusing on specific heart damage (for example, myocardial necrosis, endothelial damage, or inflammatory infiltration). In some studies, only conventional hematoxylin and eosin staining was used, while others used immunohistochemical staining. In addition, there were no standardized methods and criteria. Moreover, studies conducted using autopsy material cover several waves of the COVID-19 pandemic, and

different strains of SARS-CoV-2 can affect the heart in different ways.

Thus, it can be assumed that even systematic reviews are limited by biased data selection and presentation [57]. Further research is needed to better understand the mechanisms of heart damage in COVID-19.

REFERENCES

1. Lvov D.K., Alkhovskiy S.V. Source of the COVID-19 Pandemic: Ecology and Genetics of Coronaviruses (Betacoronavirus: Coronaviridae) SARS-CoV, SARS-CoV-2 (Subgenus Sarbecovirus), and MERS-CoV (Subgenus Merbecovirus). *Problems of Virology*. 2020;65(2):62–70. (In Russ.).
2. Machhi J., Herskovitz J., Senan A.M., Dutta D., Nath B., Oleynikov M.D. et al. The natural history, pathobiology, and clinical manifestations of SARS-CoV-2 infections. *J. Neuroimmune Pharmacol.* 2020;15(3):359–386. DOI: 10.1007/s11481-020-09944-5.
3. Zarubin E.A., Kogan E.A. Pathogenesis and Morphological Changes in the Lung in COVID-19. *Arkhiv Patologii*. 2021;83(6):54–59. (In Russ.).
4. Zaki A.M., van Boheemen S., Bestebroer T.M., Osterhaus A.D., Fouchier R.A. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. *N. Engl. J. Med.* 2012;367(19):1814–1820. DOI: 10.1056/NEJMoa1211721.
5. Rahman A, Sarkar A. Middle East respiratory syndrome coronavirus (MERS-CoV) infection: Analyses of risk factors and literature review of knowledge, attitude and practices. *Zoonoses Public Health*. 2022;69(6):635–642. DOI: 10.1111/zph.12952.
6. Apostolopoulos V., Chavda V., Alshahrani N.Z., Mehta R., Satapathy P., Rodriguez-Morales A.J. et al. MERS outbreak in Riyadh: A current concern in Saudi Arabia. *Infez. Med.* 2024;32(2):264–266. DOI: 10.53854/liim-3202-15.
7. Tian H., Liu Y., Li Y., Wu C.H., Chen B., Kraemer M.U.G. et al. An investigation of transmission control measures during the first 50 days of the COVID-19 epidemic in China. *Science*. 2020;368(6491):638–642. DOI: 10.1126/science.abb6105.
8. Yu W.B., Tang G.D., Zhang L., Corlett R.T. Decoding the evolution and transmissions of the novel pneumonia coronavirus (SARS-CoV-2/HCoV-19) using whole genomic data. *Zool Res.* 2020;41(3):247–257. DOI: 10.24272/j.issn.2095-8137.2020.022.
9. Magateshvaren Saras M.A., Patro L.P.P., Uttamrao P.P., Rathinavelan T. Geographical distribution of SARS-CoV-2 amino acids mutations and the concomitant evolution of seven distinct clades in non-human hosts. *Zoonoses Public Health*. 2022;69(7):816–825. DOI: 10.1111/zph.12971.
10. Andersen K.G., Rambaut A., Lipkin W.I., Holmes E.C., Garry R.F. The proximal origin of SARS-CoV-2. *Nat. Med.* 2020;26(4):450–452. DOI: 10.1038/s41591-020-0820-9.
11. Bolze A., Luo S., White S., Cirulli E.T., Wyman D., Dei Rossi A. et al. SARS-CoV-2 variant Delta rapidly displaced variant Alpha in the United States and led to higher viral loads. *Cell Rep. Med.* 2022;3(3):100564. DOI: 10.1016/j.xcrm.
12. Ministry of Health of the Russian Federation. Interim Guidelines: Prevention, Diagnosis and Treatment of Novel Coronavirus Infection (COVID 19). 14th ed. (December 27, 2021). (In Russ.). URL: https://static-0.minzdrav.gov.ru/system/attachments/attaches/000/064/610/original/%D0%92%D0%9C%D0%A0_COVID-19_V18.pdf
13. Karpova L.S., Komissarov A.B., Stolyarov K.A., Popovtseva N.M., Stolyarova T.P., Pelikh M.Yu. et al. Features of the COVID-19 Epidemic Process in Each of the Five Waves of Morbidity in Russia. *Epidemiology and Vaccinal Prevention*. 2023;22(2):23–36. (In Russ.). DOI: 10.31631/2073-3046-2023-22-2-23-36.
14. Bali Swain R., Lin X., Wallentin F.Y. COVID-19 pandemic waves: Identification and interpretation of global data. *Heliyon*. 2024;10(3):e25090. DOI: 10.1016/j.heliyon.2024.e25090.
15. Zhu N., Zhang D., Wang W., Li X., Yang B., Song J. et al. China novel coronavirus investigating and research team. a novel coronavirus from patients with pneumonia in China, 2019. *N. Engl. J. Med.* 2020;382(8):727–733. DOI: 10.1056/NEJMoa2001017.
16. Wang Q., Zhang Y., Wu L., Niu S., Song C., Zhang Z. et al. Structural and functional basis of SARS-CoV-2 entry by using human ACE2. *Cell*. 2020;181(4):894–904.e9. DOI: 10.1016/j.cell.2020.03.045.
17. Hofmann H., Pyrc K., van der Hoek L., Geier M., Berkhout B., Pöhlmann S. Human coronavirus NL63 employs the severe acute respiratory syndrome coronavirus receptor for cellular entry. *Proc. Natl. Acad. Sci. USA*. 2005;102(22):7988–7993. DOI: 10.1073/pnas.0409465102.
18. Donoghue M., Hsieh F., Baronas E., Godbout K., Gosselin M., Stagliano N. et al. A novel angiotensin-converting enzyme-related carboxypeptidase (ACE2) converts angiotensin I to angiotensin 1-9. *Circ. Res.* 2000;87(5):e1–9. DOI: 10.1161/01.res.87.5.e1.
19. Shang J., Wan Y., Luo C., Ye G., Geng Q., Auerbach A. et al. Cell entry mechanisms of SARS-CoV-2. *Proc. Natl. Acad. Sci. USA*. 2020;117(21):11727–11734. DOI: 10.1073/pnas.2003138117.
20. Baklaushev V.P., Kulemzin S.V., Gorchakov A.A., Yusubalieva G.M., Lesnyak V.N., Sotnikova A.G. COVID-19. Etiology, Pathogenesis, Diagnosis and Management. *Clinical Practice*. 2020;1:7–20. (In Russ.). DOI: 10.17816/clinpract26339.
21. Huang I.C., Bosch B.J., Li F., Li W., Lee K.H., Ghiran S. et al. SARS coronavirus, but not human coronavirus NL63, utilizes cathepsin L to infect ACE2-expressing cells. *J. Biol. Chem.* 2006;281(6):3198–3203. DOI: 10.1074/jbc.M508381200.
22. Bayati A., Kumar R., Francis V., McPherson P.S. SARS-CoV-2 infects cells after viral entry via clathrin-mediated endocytosis. *J. Biol. Chem.* 2021;296:100306. DOI: 10.1016/j.jbc.2021.100306.
23. Hou Y.J., Okuda K., Edwards C.E., Martinez D.R., Asakura T., Dinno K.H. 3rd et al. SARS-CoV-2 reverse genetics reveals a variable infection gradient in the respiratory tract. *Cell*. 2020;182(2):429–446.e14. DOI: 10.1016/j.cell.2020.05.042.
24. Wang Y., Wang Y., Luo W., Huang L., Xiao J., Li F. et al. A comprehensive investigation of the mRNA and protein level of ACE2, the putative receptor of SARS-CoV-2, in human tis-

- sues and blood cells. *Int. J. Med. Sci.* 2020;17(11):1522–1531. DOI: 10.7150/ijms.46695.
25. Lindner D., Fitzek A., Bräuninger H., Aleshcheva G., Edler C., Meissner K. et al. Association of cardiac infection with SARS-CoV-2 in confirmed COVID-19 autopsy cases. *JAMA Cardiol.* 2020;5(11):1281–1285. DOI: 10.1001/jamacardio.2020.3551.
 26. Jackson C.B., Farzan M., Chen B., Choe H. Mechanisms of SARS-CoV-2 entry into cells. *Nat. Rev. Mol. Cell Biol.* 2022;23(1):3–20. DOI: 10.1038/s41580-021-00418-x.
 27. Zhuang M.W., Cheng Y., Zhang J., Jiang X.M., Wang L., Deng J. et al. Increasing host cellular receptor-angiotensin-converting enzyme 2 expression by coronavirus may facilitate 2019-nCoV (or SARS-CoV-2) infection. *J. Med. Virol.* 2020;92(11):2693–2701. DOI: 10.1002/jmv.26139.
 28. Jacobs M., Van Eeckhoutte H.P., Wijnant S.R.A., Janssens W., Joos G.F., Brusselle G.G. et al. Increased expression of ACE2, the SARS-CoV-2 entry receptor, in alveolar and bronchial epithelium of smokers and COPD subjects. *Eur. Respir. J.* 2020;56(2):2002378. DOI: 10.1183/13993003.02378-2020.
 29. Leung J.M., Yang C.X., Tam A., Shaipanich T., Hackett T.L., Singhera G.K. et al. ACE-2 expression in the small airway epithelia of smokers and COPD patients: implications for COVID-19. *Eur. Respir. J.* 2020;55(5):2000688. DOI: 10.1183/13993003.00688-2020.
 30. Kolesnikova N.V. Mast cells in allergic and infectious inflammation. *Russian Medical Inquiry.* 2022;6(2):79–84 (In Russ.). DOI: 10.32364/2587-6821-2022-6-2-79-84.
 31. Budnevsky A.V., Avdeev S.N., Ovsyannikov E.S., Shishkina V.V., Esaulenko D.I., Filin A.A. et al. The Role of Mast cells and their proteases in lung damage associated with COVID-19. *Pulmonologiya.* 2023;33(1):17–26. (In Russ.). DOI: 10.18093/0869-0189-2023-33-1-17-26.
 32. Budnevskiy A.V., Avdeev S.N., Ovsyannikov E.S., Alekseeva N.G., Shishkina V.V., Savushkina I.A. et al. Certain Aspects of Mast Cell Carboxypeptidase A3 Involvement in the Pathogenesis of COVID-19. *Tuberculosis and Lung Diseases.* 2024;102(1):26–33. (In Russ.). DOI: 10.58838/2075-1230-2024-102-1-26-33.
 33. Ellison-Hughes G.M., Colley L., O'Brien K.A., Roberts K.A., Agbaedeng T.A., Ross M.D. The role of MSC therapy in attenuating the damaging effects of the cytokine storm induced by COVID-19 on the heart and cardiovascular system. *Front. Cardiovasc. Med.* 2020;7:602183. DOI: 10.3389/fcvm.2020.602183.
 34. Budnevsky A.V., Avdeev S.N., Ovsyannikov E.S., Savushkina I.A., Choporov O.N., Shishkina V.V. et al. On the Role of Mast Cells and Their Proteases in the Severe COVID-19. *The Russian Archives of Internal Medicine.* 2024;14(3):181–189. (In Russ.). DOI: 10.20514/2226-6704-2024-14-3-181-189.
 35. Budnevsky A.V., Avdeev S.N., Kosanovic D., Shishkina V.V., Filin A.A., Esaulenko D.I. et al. Role of mast cells in the pathogenesis of severe lung damage in COVID-19 patients. *Respiratory Research.* 2022;23(1):1–10. DOI: 10.1186/s12931-022-02284-3.
 36. Azkur A.K., Akdis M., Azkur D., Sokolowska M., van de Veen W., Brüggemann M.C. et al. Immune response to SARS-CoV-2 and mechanisms of immunopathological changes in COVID-19. *Allergy.* 2020;75(7):1564–1581. DOI: 10.1111/all.14364.
 37. Manjili R.H., Zarei M., Habibi M., Manjili M.H. COVID-19 as an acute inflammatory disease. *J. Immunol.* 2020;205(1):12–19. DOI: 10.4049/jimmunol.2000413.
 38. Vardhana S.A., Wolchok J.D. The many faces of the anti-COVID immune response. *J. Exp. Med.* 2020;217(6):e20200678. DOI: 10.1084/jem.20200678.
 39. Ravindran M., Khan M.A., Palaniyar N. Neutrophil extracellular trap formation: physiology, pathology, and pharmacology. *Biomolecules.* 2019;9(8):365. DOI: 10.3390/biom9080365.
 40. Tinsley J.H., Hunter F.A., Childs E.W. PKC and MLCK-dependent, cytokine-induced rat coronary endothelial dysfunction. *J. Surg. Res.* 2009;152(1):76–83. DOI: 10.1016/j.jss.2008.02.022.
 41. Budnevsky A.V., Avdeev S.N., Kosanovic D., Ovsyannikov E.S., Savushkina I.A., Alekseeva N.G. et al. Involvement of mast cells in the pathology of COVID-19: clinical and laboratory parallels. *Cells.* 2024;13(8):711. DOI: 10.3390/cells13080711.
 42. Poto R., Marone G., Galli S.J., Varricchi G. Mast cells: a novel therapeutic avenue for cardiovascular diseases? *Cardiovasc. Res.* 2024;120(7):681–698. DOI: 10.1093/cvr/cvae066.
 43. Patella V., Marino I., Arbustini E., Lamparter-Schummert B., Verga L., Adt M. et al. Stem cell factor in mast cells and increased mast cell density in idiopathic and ischemic cardiomyopathy. *Circulation.* 1998;97(10):971–978. DOI: 10.1161/01.cir.97.10.971.
 44. Daugherty S.E., Guo Y., Heath K., Dasmariñas M.C., Jubilo K.G., Samranvedhya J. et al. Risk of clinical sequelae after the acute phase of SARS-CoV-2 infection: retrospective cohort study. *BMJ.* 2021;373:n1098. DOI: 10.1136/bmj.n1098.
 45. Xie Y., Xu E., Bowe B., Al-Aly Z. Long-term cardiovascular outcomes of COVID-19. *Nat. Med.* 2022;28(3):583–590. DOI: 10.1038/s41591-022-01689-3.
 46. Tomasoni D., Inciardi R.M., Lombardi C.M., Tedino C., Agostoni P., Ameri P. et al. Impact of heart failure on the clinical course and outcomes of patients hospitalized for COVID-19. Results of the Cardio-COVID-Italy multicentre study. *Eur. J. Heart Fail.* 2020;22(12):2238–2247. DOI: 10.1002/ejhf.2052.
 47. Zhou F., Yu T., Du R., Fan G., Liu Y., Liu Z. et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet.* 2020;395(10229):1054–1062. DOI: 10.1016/S0140-6736(20)30566-3.
 48. Guo T., Fan Y., Chen M., Wu X., Zhang L., He T. et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA Cardiol.* 2020;5(7):811–818. DOI: 10.1001/jamacardio.2020.1017.
 49. Shi S., Qin M., Shen B., Cai Y., Liu T., Yang F. et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA Cardiol.* 2020;5(7):802–810. DOI: 10.1001/jamacardio.2020.0950.
 50. Falasca L., Nardacci R., Colombo D., Lalle E., Di Caro A., Nicastri E. et al. Postmortem findings in Italian patients with COVID-19: a descriptive full autopsy study of cases with and

- without comorbidities. *J. Infect. Dis.* 2020;222(11):1807–1815. DOI: 10.1093/infdis/jiaa578.
51. Schurink B., Roos E., Radonic T., Barbe E., Bouman C.S.C., de Boer H.H. et al. Viral presence and immunopathology in patients with lethal COVID-19: a prospective autopsy cohort study. *Lancet Microbe.* 2020;1(7):e290–e299. DOI: 10.1016/S2666-5247(20)30144-0.
 52. Halushka M.K., Vander Heide R.S. Myocarditis is rare in COVID-19 autopsies: cardiovascular findings across 277 post-mortem examinations. *Cardiovasc. Pathol.* 2021;50:107300. DOI: 10.1016/j.carpath.2020.107300.
 53. Aretz H.T., Billingham M.E., Edwards W.D., Factor S.M., Fallon J.T., Fenoglio J.J. Jr. et al. Myocarditis. A histopathologic definition and classification. *Am. J. Cardiovasc. Pathol.* 1987;1(1):3–14.
 54. Richardson P., McKenna W., Bristow M., Maisch B., Mautner B., O'Connell J. et al. Report of the 1995 World Health Organization/International Society and Federation of Cardiology Task Force on the Definition and Classification of Cardiomyopathies. *Circulation.* 1996;93:841–842. DOI: 10.1161/01.cir.93.5.841.
 55. Tsai E.J., Čiháková D., Tucker N.R. Cell-specific mechanisms in the heart of COVID-19 patients. *Circ. Res.* 2023;132(10):1290–1301. DOI: 10.1161/CIRCRESA-HA.123.321876.
 56. Pellegrini D., Kawakami R., Guagliumi G. et al. Microthrombi as a Major Cause of Cardiac Injury in COVID-19: A Pathologic Study. *Circulation.* 2021;143(10):1031–1042. DOI: 10.1161/CIRCULATIONAHA.120.051828.
 57. Sewanan L.R., Clerkin K.J., Tucker N.R., Tsai E.J. How does COVID-19 affect the heart? *Curr. Cardiol. Rep.* 2023;25(3):171–184. DOI: 10.1007/s11886-023-01841-6.
 58. Basso C., Leone O., Rizzo S., De Gaspari M., van der Wal A.C., Aubry M.C. et al. Pathological features of COVID-19-associated myocardial injury: a multicentre cardiovascular pathology study. *Eur. Heart J.* 2020;41(39):3827–3835. DOI: 10.1093/eurheartj/ehaa664.
 59. Bearse M., Hung Y.P., Krauson A.J., Bonanno L., Boyraz B., Harris C.K. et al. Factors associated with myocardial SARS-CoV-2 infection, myocarditis, and cardiac inflammation in patients with COVID-19. *Mod. Pathol.* 2021;34(7):1345–1357. DOI: 10.1038/s41379-021-00790-1.
 60. Chen S.T., Park M.D., Del Valle D.M., Buckup M., Tabachnikova A., Simons N.W. et al. A shift in lung macrophage composition is associated with COVID-19 severity and recovery. *Sci. Transl. Med.* 2022;14(662):eabn5168. DOI: 10.1126/scitranslmed.abn5168.
 61. Shao H.H., Yin R.X. Pathogenic mechanisms of cardiovascular damage in COVID-19. *Mol. Med.* 2024;30(1):92. DOI: 10.1186/s10020-024-00855-2.
 62. Brenner M.I., Hulke M.L., Fukuma N., Golob S., Zilinyi R.S., Zhou Z. et al. Clinico-histopathologic and single-nuclei RNA-sequencing insights into cardiac injury and microthrombi in critical COVID-19. *JCI Insight.* 2022;7(2):e154633. DOI: 10.1172/jci.insight.154633.
 63. Dmytrenko O., Lavine K.J. Cardiovascular tropism and sequelae of SARS-CoV-2 infection. *Viruses.* 2022;14(6):1137. DOI: 10.3390/v14061137.

Author Contribution

Budnevsky A.V. – conception and design, final approval of the manuscript for publication. Avdeev S.N. – conception and design. Ovsyannikov E.S., Tokmachev R.E., Shishkina V.V., Pervееva I.M. – justification of the manuscript or critical revision for important intellectual content. Feigelman S.N., Chernik T.A., Budnevskaya S.A., Arkhipova E.D. – data analysis and interpretation.

Author Information

Budnevsky Andrey V. – Dr. Sci. (Med.), Professor, Distinguished Inventor of the Russian Federation, Head of Faculty Therapy Department, Vice-Rector for Research, N.N. Burdenko VSMU, Voronezh, Russia, budnev@list.ru, <https://orcid.org/0000-0002-1171-2746>

Avdeev Sergey N. – Academician of the Russian Academy of Sciences, Dr. Sc. (Medicine), Professor, Head of Pulmonology Department, I.M. Sechenov First Moscow State Medical University, Moscow, Russia, serg_avdeev@list.ru, <https://orcid.org/0000-0002-5999-2150>

Ovsyannikov Evgeniy S. – Dr. Sci. (Med.), Associate Professor, Professor, Faculty Therapy Department, N.N. Burdenko VSMU, Voronezh, Russia, ovses@yandex.ru, <https://orcid.org/0000-0002-8545-6255>

Tokmachev Roman E. – Cand. Sci. (Med.), Director of the Research Institute of Experimental Biology and Medicine, Associate Professor, Faculty Therapy Department, N.N. Burdenko VSMU, Voronezh, r-tokmachev@mail.ru, <https://orcid.org/0000-0001-6379-4635>

Feigelman Sofia N. – Assistant, Faculty Therapy Department, N.N. Burdenko VSMU, Voronezh, s.feygelman@gmail.com, <https://orcid.org/0000-0003-4128-6044>

Shishkina Victoria V. – Cand. Sci. (Med.), Associate Professor, Senior Researcher, Research Institute of Experimental Biology and Medicine, Head of Histology Department, N.N. Burdenko VSMU, Voronezh, 4128069@gmail.com, <https://orcid.org/0000-0001-9185-4578>

Pervееva Inna M. – Cand. Sci. (Med.), Senior Researcher, Research Institute of Experimental Biology and Medicine, N.N. Burdenko VSMU, Pulmonologist, Voronezh Regional Clinical Hospital No. 1, Voronezh, pervееva.inna@yandex.ru, <https://orcid.org/0000-0002-5712-9302>

Chernik Tatiana A. – Cand. Sci. (Med.), Associate Professor, Faculty Therapy Department, Deputy Head of the Center for Scientific Research, Development and Transfer of Medical Technologies, N.N. Burdenko VSMU, Voronezh, ch01@mail.ru, <https://orcid.org/0000-0003-1371-0848>

Arkhipova Ekaterina D. – Postgraduate Student, Faculty Therapy Department, N.N. Burdenko VSMU, Voronezh, e.pavlykevich@bk.ru, <https://orcid.org/0009-0002-4960-334X>

Budnevskaya Sofia A. – Student of the Faculty of Medicine, N.N. Burdenko VSMU, Voronezh, sofa_budnevskaya@mail.ru, <https://orcid.org/0009-0000-0623-0243>

(✉) **Feigelman Sofia N.**, s.feygelman@gmail.com

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