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Pathogenetic Features of Acute Coronary Syndrome in Patients with Covid-19

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Abstract: The development of acute coronary syndrome (ACS) is caused by an acute discrepancy between the myocardial oxygen demand and its delivery. This mechanism is more associated with the progression of coronary atherosclerosis in combination with an inflammatory response, hypoxemia, procoagulant state of blood plasma and platelets. Patients with the new coronavirus infection COVID-19 (COronaVIrus Disease 2019), burdened by cardiovascular diseases and comorbid pathology, represent a high risk group for ACS.

The purpose of study: To analyze the published literature, which reflects data on the development of ACS in patients with COVID-19, its pathogenesis, and features of the clinical course?

Material and methods. The search for literary data was carried out using Google Scholar, PubMed, ScienceDirect and Cyberleninka services. The analysis included data from clinical guidelines for the management of patients with COVID-19, data from clinical trials, reports and systematic reviews.

Results. This literature review summarizes and systematizes the data presented in modern scientific publications, highlights aspects of the clinical course and features of the pathogenetic mechanisms underlying ACS in patients with COVID-19.

Conclusion. The pathogenesis of COVID-19 is inextricably linked with the widespread cytopathic effect of SARS-CoV-2 (Severe Acute Respiratory Syndrome CoronaVirus 2, coronavirus 2, causing severe acute respiratory distress syndrome), the generation of a pathological uncontrolled immune response that causes systemic inflammation, as well as the implementation of procoagulant activation of the hemostasis system. In patients with COVID-19, along with the atherosclerotic process, these mechanisms significantly increase the risk of developing ACS and may worsen its course at the hospital stage.

Keywords: COVID-19, acute coronary syndrome, myocardial infarction, postcovid syndrome.

The purpose of this review is to analyze and systematize current literature data on the relationship of the new coronavirus infection COVID-19 with ACS, its pathogenesis and clinical course.

The penetration of SARS-CoV-2 into the cell is due to the complementarity of its S-protein domain to human angiotensin converting enzyme-2 (APF2) receptors [9].

APF2 is a membrane protein whose key role is the conversion of angiotensin II into angiotensin 1-7. APF2 is most widely expressed in pneumocytes, endotheliocytes, macrophages, and myocytes. Increased expression of APF2 on the surface of cell membranes, on the one hand, can increase the risks of infection with SARS-CoV-2, and on the other hand, it is also a compensatory mechanism that occurs in response to pressor effects with increased production and excess of angiotensin II [10][11]. The activity of APF2 significantly increases in people with myocardial infarction (MI), hypertension and DM [10]. Virus invasion significantly reduces the number of APF2 receptors on the cell surface, which also leads to destabilization of the renin-angiotensin-aldosterone system, decompensation of chronic forms of coronary heart disease, increased severity of hypertension and progression of atherosclerosis, and also increases the risk of developing MI. Dysfunction and death of virus-affected cells leads to the emergence of new and decompensation of chronic diseases.

According to a retrospective analysis conducted at Tongji Hospital [12] on 150 patients with mild and severe COVID-19, 20% showed signs of myocardial damage, which was accompanied by an increase in the level of NT-proBNP (N-terminal fragment of the precursor of the brain natriuretic peptide) and cardiac troponin (Tn) I, which subsequently they were identified as independent markers of the severity of the clinical course of the disease. These data have been confirmed in a number of other studies [13][14][15].

One of the most severe cardiovascular complications (CVD) of COVID-19 is ACS, which can manifest itself with or without elevation (STEMI) of the ST segment, as well as unstable angina. The pathophysiology of MI in COVID-19 currently raises many questions due to the complex of mechanisms that can lead to myocardial damage.

The key role in the pathogenesis of COVID-19 is played by the inflammatory process. One of its most important links, along with a severe systemic uncontrolled response, is endothelial dysfunction. The mechanism causing endothelial dysfunction, and, as a consequence, damage and thrombosis in the lung tissue, myocardium, brain, kidneys, is virus-induced endotheliitis associated with COVID-19 [16]. Activation and maintenance of endotheliitis is associated with the production of pro—inflammatory cytokines - interleukins-6, -2 (IL-6, IL-2), tumor necrosis factor α, chemokines from damaged endotheliocytes, increased activity of von Willebrand factor and factor VIII, and an increase in their concentration in the bloodstream [17]. All this, in turn, contributes to the activation of leukocytes and directly leads to an imbalance of anticoagulants and procoagulants, which leads to the potentiation and maintenance of the pro-inflammatory and procoagulant state.

The systemic inflammatory response in COVID-19 is currently recognized as a key link that determines the severity of the disease. As a result of excessive uncontrolled synthesis of cytokines, a phenomenon previously referred to in the literature as a “cytokine storm" develops. A similar state of hyperactivation of the immune system was observed in a number of neoplastic and autoimmune processes, as well as in the complicated course of influenza and severe acute respiratory syndrome caused by the previous coronavirus SARSCoV [18].

Cytokine storm in patients with severe COVID-19 is directly associated with the development of acute respiratory distress syndrome (ARDS) and secondary hemophagocytic lymphohistiocytosis [19].

In a study conducted in China, in all patients with a confirmed diagnosis of COVID-19, a marked increase in such pro-inflammatory cytokines as IL-1B, IL1RA, IL-7, IL-8, IL-9, IL-10, γ-interferon, β-chemokines, tumor necrosis factor α was detected in the blood, fibroblast growth factor, granulocyte-macrophage colony stimulating factor, vascular endothelial growth factor. In addition, it was proved that high levels of IL-6 correlated with increased mortality [8][20]. Other studies indicate the presence of a direct correlation of the level of cardiac Tn I and D-dimer with the severity of the disease, as well as non-specific cytokine-mediated cardiotoxicity [13].

Currently, atherosclerosis is considered as a chronic inflammatory process characterized by the accumulation of lipids in the subendothelial space of the arterial wall as a result of increasing its permeability to low-density lipoproteins and monocytes, which then differentiate into macrophages. The intensity of plaque growth directly correlates with the intensity of the inflammatory process, more pronounced infiltration, production of cytokines, proteases and accumulation of free radicals. All this can provoke the rupture of the fibrous covering of the plaque and, as a result, lead to atherothrombosis and the development of ACS.

An important role in the maintenance of inflammation and the development of atherosclerosis is played by dipeptidylpetidase-4 (DPP-4), a glycoprotein presented both as a membrane protein and a soluble enzyme. In addition to regulating the function of pancreatic beta cells, DPP-4 is widely expressed on the surface of the endothelium, endocardium, as well as myeloid cells, has a pro-inflammatory effect that can contribute to the progression of atherosclerosis [20-22].

Inflammation caused by direct damage to endothelial cells as a result of the penetration of SARS-CoV-2 through APF2 causes prothrombotic changes in the blood. Also, DPP-4 can serve as a

functional receptor for SARS-CoV-2 and facilitate the penetration of the virus into the cell. All this leads to increased migration of monocytes, increased production of chemokine SDF-1 (stromal cell-derived factor-1), rapid growth of plaque, its destabilization and, ultimately, to the development of ACS. In turn, systemic inflammation significantly increases thrombotic activity and, together with the above factors, also contributes to the development of thrombosis at the site of damage to the endothelium of the coronary arteries [17][23].

A number of studies have found that elevated levels of C-reactive protein (CRP) and IL-6 are independent risk factors for the development of ACS, as well as factors determining the severity of MI [24][25][26][27][28][29]. Despite the proven pathogenetic relationship between inflammation and the development of atherosclerosis, as well as pathohistological evidence of the cytopathic effect of SARSCoV-2, there is currently no convincing data on the direct effect of COVID-19 on the progression of atherosclerosis.

The manifestation of coagulopathy in COVID-19 is the development of both arterial and venous thrombosis and thrombosis at the level of the microcirculatory bed.

The multi-compound complex nature of coagulopathy is represented by a combination of the phenomena of disseminated intravascular coagulation, antiphospholipid syndrome, thrombotic microangiopathy, hemophagocytic syndrome, which gives prerequisites for the isolation of such a concept as COVID-19-associated coagulopathy [30][31]. In the future, as research continues, the list of syndromes and mechanisms of coagulopathy development will undoubtedly expand. Currently, the direct effect of the SARS-CoV-2 virus on the coagulation system remains unproven. A study conducted by Huazhong University of Science and Technology during the spread of SARS-CoV infection in 2008 revealed a significant shortening of blood clotting time due to the direct activation of HFGL2 prothrombinase and other cytokines by the SARS-CoV nucleocapsid protein, which, in turn, significantly increased the risk of thrombotic complications in infected patients [32]. The implementation of such mechanisms in SARS-CoV-2 has also yet to be proven in the future.

The fact remains indisputable that the coagulation system is directly involved in the development of COVID-19 complications, including ACS. Reports from a number of clinical studies link the severe course of infection and deaths of COVID-19 with significantly elevated levels of ferritin, D-dimer and other fibrin breakdown products, which potentially predisposes to thromboembolic complications, as well as increases the risk of ACS [19][33][34].

As the number of publications grows, there is more and more data on the direct ability of SARS-CoV-2 to infect myocardial tissue. This is evidenced by an increase in the level of cardiac Tn in blood plasma, the development of arrhythmias, ST segment deviation, including in the absence of obstructive lesions of the coronary arteries [35]. An increase in the level of cardiac Tn I in patients with COVID-19 correlates with a severe course of infection, and its increase in dynamics is a predictor of fatal outcomes [36], however, these data cannot reliably indicate the direct cytopathic effect of the virus on myocardial cells.

Published data from pathohistological studies indicate that, along with lung tissue, a high titer of SARS-CoV-2 RNA was detected in the myocardium, kidneys and liver [37][38]. Despite this, the issue of virus invasion directly into cardiomyocytes remains controversial. In their report, Chen L, et al. [11] presented the results of the analysis of the intercellular substance of myocardial samples, on which the study of potential damage mechanisms was carried out. The highest degree of APF2 expression was found in myocardial pericytes, which makes them a potential target for SARS-CoV-2 and may cause the course of COVID-19.

A multicenter study conducted in the USA describes the results of autopsy of 23 patients who revealed viral invasion not only in perivascular cells, but also in interstitial and endothelial cells. The development of microvascular dysfunction, endotheliitis, myocarditis, pericarditis, as well as direct and indirect damage to cardiomyocytes is described. Such morphological changes corresponded to changes characteristic of viral myocarditis [16]. COVID-19-associated myocarditis can occur both latently and have a fulminant course, which determines a significant decrease in the contractility of the heart and an increase in the phenomena of circulatory insufficiency [35]. Clinically, the

development of viral myocarditis can be masked by the ACS clinic and infarct-like changes on the electrocardiogram, which complicates diagnosis and can lead to incorrectly chosen primary therapeutic tactics and the development of severe complications.

Along with COVID-19, the published research data on the course of viral infections of the past years confirm the high risks of MTR. Thus, the influenza virus significantly increased the risks of developing ACS and sudden cardiac death both in the early and in the delayed period of the course of the disease [39][40][41]. The results of the study of 133562 cases of MI during the seasonal flu epidemic showed a higher incidence of MI during the periods with the largest number of reported cases of influenza. These data correlated with the results of observations for >33 thousand. patients who indicate a significant increase in the risk of developing MI within 3-7 days after contacting a doctor about the appearance of symptoms of acute respiratory viral infection [42]. Another prospective study presents the results of observation of 75 patients with atypical pneumonia caused by SARS-CoV during the outbreak in 2003, of which 2 people died from acute MI on days 13 and 17. diseases [43].

Data from the European retrospective registry ISACS-STEMI (International Study on Acute Coronary Syndromes — ST-segment Elevation Myocardial Infarction) COVID-19, which includes a total of 6,609 patients with STEMI treated in 77 vascular centers from 18 countries, showed a significant decrease in the number of admissions of patients with STeMI and the number of primary percutaneous coronary interventions (PCI) in 2020 compared to the same period in 2019 [44]. On the one hand, this may be a consequence of a possible underestimation of ACS symptoms in a pandemic, unwillingness of patients to come into contact with medical professionals due to the potential danger of infection, decreased physical activity and lack of adequate assessment of the progression of angina symptoms. On the other hand, patients with high cardiovascular risk and comorbid pathology are more likely to be exposed to severe COVID-19. Thus, high-risk patients are more likely to be hospitalized for COVID-19 rather than ACS, in addition, myocardial damage in this category of patients against the background of infection may more often manifest as type 2 MI.

A British study conducted on the basis of data analysis of 117,327 patients with STeMI and STEMI included in the national register from January 1, 2017 to May 22, 2020, showed that with the introduction of isolation in the UK, the average number of daily hospitalizations for STEMI decreased significantly — from 69 to 35 (the relative risk of developing the disease was 0.51; 95% confidence interval: 0.47-0.54), compared with STeMI — from 35 to 25 (relative risk = 0.74; 95% confidence interval: 0.69-0.80). In general, patients were younger and significantly less likely to have CVD risk factors, however, the 30-day mortality rate in patients with STeMI decreased from 10.2 to 7.7%, and in the STEMI group increased from 5.4 to 7.5% [45].

The results of the multicenter Italian study also confirm a significant decrease in the total number of hospitalizations of patients with MI, but meanwhile indicate a significant increase in the overall mortality from STeMI compared to 2019 (from 4.1 to 13.7%). Mortality in the group of patients with detected COVID-19 and STeMI was also significantly higher than in uninfected patients — 28.6 vs 11.9%. The authors also cite data on an increase in the time from the onset of symptoms to coronary angiography by 39.2%, and from the first medical contact to PCI by 31.5% compared to 2019, which, in turn, may be one of the reasons for increased mortality [46].

A single-center observational study, including 106 patients admitted with ACS in the period from March 1 to April 20, 2020, and 174 patients for the same period in 2019, indicates that the frequency of STeMI and STEMI was the same among patients with and without verified COVID-19, however, in comparison with the previous period of MI Type 2 was more common in the group of patients with COVID-19 — 29 vs 4% (p=0.0497). All patients with COVID-19 had higher levels of CRP and D-dimer compared to uninfected patients [47].

Based on constantly updated data on the course of ACS in patients with COVID-19, treatment strategies are being developed, but the optimal tactics still remain undetermined. In addition, the question of the justification of the use of thrombolytics in patients with STEMI remains open [50].

Coronary artery stenting in patients with MI and COVID-19 is associated with an increase in thrombotic risks both in the early and late postoperative period. The choice of interventional tactics for the treatment of ACS also requires further study [50, 51]. According to current clinical guidelines, the use of drug-coated stents is a priority when performing PCI on the infarct-responsible artery, however, the use of drug-coated stents is associated with a higher risk of thrombosis in the long term than with the use of holometallic stents [52]. In addition, future studies will determine the efficacy, safety and justification of the use of anticoagulants in combination with classical antithrombotic therapy in patients with coronary heart disease and COVID-19.

Conclusion

Currently, many potential predictors have been identified for the stratification of cardiovascular and thrombotic risk in patients with COVID-19, however, most studies have a number of limitations, the main of which are small sample sizes, as a rule, limited to the region of residence of patients, the endemicity of the region for certain infectious and non-communicable diseases, population features.

According to the literature studied, the course of COVID-19 is inextricably linked with a significant risk of ACS development in patients with and without a previous cardiological history. The observed severe disorders in the hemostasis system in patients with COVID-19 and atherosclerosis have a significant impact on the clinical course of the disease, including due to atherothrombotic complications. Myocardial lesion is realized due to the involvement of a variety of pathological mechanisms that require the involvement of a multidisciplinary medical team and the definition of an integrated approach to the treatment and prevention of possible complications. A special risk group for the development of SSO is persons with comorbid pathology, who are exposed not only to a more severe course of the disease, but also to a potentially high risk of complications in the long term. The analysis of the nature of changes caused by COVID-19, the severity of organ and system damage, as well as possible complications in the period of convalescence is currently one of the most urgent research tasks. Timely immunoprophylaxis, correction and modification of non-infectious risk factors, prevention of the development and compensation of chronic pathologies can contribute to a significant reduction in the frequency of severe course and mortality in COVID-19.

Of particular scientific interest at present is the observation of patients who have undergone COVID-19, the study of changes in their coagulation status in dynamics, the analysis of the frequency of thrombotic complications, as well as the features of the course of chronic and the frequency of detection of new CVD in the long term.

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