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ASSOCIATION BETWEEN COVID-19, STENT THROMBOSIS, AND RESTENOSIS

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Abstract

Introduction. COVID-19 is not just a respiratory infection, but a systemic disease that harms the entire body, including the heart and blood vessels. The cause of occlusion, in most cases, is not atherosclerosis, but fibrosis or thrombosis in the area of coronary artery stenting. Early detection of restenosis and its prevention are important tasks for the healthcare system which causes great interest in this issue.

The aim is to study the problems of restenosis and thrombosis of the coronary arteries after coronavirus infection according to the literature data.

Materials and methods. For the search and analysis of scientific data, we used databases and web resources: MEDLINE, Pubmed, Google Scholar, Cyberleninka, and eLIBRARY. For the literature review, we used sources published from 2019 to 2022. Scientific articles were used that correspond to the topic and the basic context of the study.

Results. COVID-19 contributed to a change in the course of myocardial infarction in patients with previous myocardial revascularization. The frequency of stent thrombosis has a positive correlation with the severity of the coronavirus infection. Previous myocardial revascularization procedures significantly increase the risk of death in patients with coronavirus infection.

Conclusion. SARS-CoV-2 infection activates inflammatory mechanisms that potentially create a prothrombotic environment and increase the risk of local microthromboembolism and all types of stent thrombosis. Patients after percutaneous coronary intervention with active COVID-19 infection and symptoms of the acute coronary syndrome are more likely to have stent thrombosis.

Keywords: *Coronary stent thrombosis, Myocardial revascularization, COVID-19.*

Резюме

ВЗАИМОСВЯЗЬ МЕЖДУ COVID-19, ТРОМБОЗОМ СТЕНТА И РЕСТЕНОЗОМ.

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Введение. COVID-19 — это не просто респираторная инфекция, а системное заболевание, поражающее весь организм, включая сердце и сосуды. Причиной окклюзии в большинстве случаев является не атеросклероз, а фиброз или тромбоз в области стентирования коронарных артерий. Раннее выявление рестеноза и его профилактика являются важной задачей практического здравоохранения, что вызывает большой интерес к данному вопросу.

Цель: изучить проблемы рестеноза и тромбоза коронарных артерий после коронавирусной инфекции по данным литературы.

Материалы и методы. Для поиска и анализа научных данных использовались базы данных и веб-ресурсы: MEDLINE, Pubmed, Google Scholar, Cyberleninka и eLIBRARY. Для обзора литературы использовались источники, опубликованные с 2019 по 2022 год. Использовались научные статьи, соответствующие теме и основному контексту исследования.

Результаты. COVID-19 способствовал изменению течения инфаркта миокарда у пациентов с предшествующей реваскуляризацией миокарда. Частота тромбоза стента имеет положительную корреляцию с тяжестью течения коронавирусной инфекции. Ранее проведенные процедуры реваскуляризации миокарда значительно повышают риск летального исхода у пациентов с коронавирусной инфекцией.

Заключение. Инфекция SARS-CoV-2 активирует воспалительные механизмы, которые потенциально создают протромботическую среду и повышают риск локальной микротромбоэмболии и всех типов тромбоза стента. У пациентов после чрескожного коронарного вмешательства с активной инфекцией COVID-19 и симптомами острого коронарного синдрома чаще развивается тромбоз стента.

Ключевые слова: *Тромбоз коронарного стента, Реваскуляризация миокарда, COVID-19.*

Түйіндеме

COVID-19, СТЕНТ ТРОБОЗЫ ЖӘНЕ РЕСТЕНОЗ АРАСЫНДАҒЫ БАЙЛАНЫС

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Кіріспе. COVID-19 - бұл жай ғана респираторлық инфекция емес, бүкіл денеге, соның ішінде жүрек пен қан тамырларына әсер ететін жүйелі ауру. Көп жағдайда окклюзияның себебі атеросклероз емес, коронарлық артерияларды стентациялау аймағындағы фиброз немесе тромбоз болып табылады. Рестенозды ерте анықтау және оның алдын алу денсаулық сақтау тәжірибесінің маңызды міндеті болып табылады, бұл мәселеге үлкен қызығушылық тудырады және осы мәселе бойынша әдебиеттерді шолу үшін негіз болады.

Зерттеу мақсаты әдебиеттерге сәйкес коронавирустық инфекциядан кейінгі коронарлық артериялардың рестенозы мен тромбозы мәселелерін зерттеу.

Материалдар мен әдістер. Ғылыми деректерді іздеу және талдау үшін мәліметтер базасы мен веб-ресурстар пайдаланылды: MEDLINE, Pubmed, Google Scholar, Cyberleninka және eLIBRARY. Әдебиетті шолу үшін 2019-2022 жылдар аралығында жарияланған дереккөздер пайдаланылды. Тақырыпқа және зерттеудің негізгі контексіне сәйкес келетін ғылыми мақалалар пайдаланылды.

Нәтижелері. COVID-19 бұрын миокард реваскуляризациясы бар науқастарда миокард инфарктісі ағымының өзгеруіне ықпал етті. Стент тромбозының жиілігі коронавирустық инфекцияның ауырлығымен оң корреляцияға ие. Бұрынғы миокардты реваскуляризациялау процедуралары коронавирустық инфекциясы бар науқастарда өлім қаупін айтарлықтай арттырады.

Қорытынды. SARS-CoV-2 инфекциясы протромботикалық ортаны тудыратын және жергілікті микротромбоэмболияның және стент тромбозының барлық түрлерінің қаупін арттыратын қабыну механизмдерін белсендіреді. Белсенді COVID-19 инфекциясы және жедел коронарлы синдром белгілері бар тері арқылы коронарлық араласудан кейінгі науқастарда стент тромбозының даму ықтималдығы жоғары.

Түйінді сөздер: *Коронарлық стент тромбозы, миокардтың реваскуляризациясы, COVID-19.*

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Introduction

Cardiovascular disease (CVD) still occupies a leading position in the list of causes of death worldwide [10, 33]. Nearly 12 million people die each year from coronary heart disease (CHD) and stroke. According to the forecasts of the World Health Organization (WHO), over the next 10 years, this figure will increase to 23.6 million people.

To date, the leading position among invasive techniques for the treatment of CHD is occupied by percutaneous coronary interventions (PCI). Despite the modernization of PCI technology, the incidence of restenosis and thrombosis in the area of coronary artery stenting remains very high [35]. The cause of occlusion, in most cases, is not atherosclerosis, but fibrosis or thrombosis in the area of coronary artery stenting. Early detection of restenosis and its prevention are important tasks for practical health care, which causes great interest in this issue and serves as the basis for a literature review on this issue [23].

COVID-19 is not just a respiratory infection, but a systemic disease that harms the entire body, including the heart and blood vessels. According to statistics, cardiovascular complications occur in more than 70% of people who have had COVID-19. Even six months after recovery, doctors diagnose serious cardiovascular consequences in patients: acute coronary syndrome, arrhythmias, increased blood pressure, thrombosis, and other serious complications. Today, the impact of a previous COVID-19 infection on long-term consequences in people with cardiovascular pathology remains not fully understood. The issue of the course of diseases of the cardiovascular system and the choice of therapy after suffering from COVID-19 is also acute.

In a tense epidemiological situation, patients who have undergone myocardial revascularization are the least protected, as they are at risk of restenosis and thrombosis of the stand. In addition to clinical factors, COVID-19 affects various aspects of the quality of life of such patients; therefore, it is important to study the quality of life and the influence of various factors on the physical and emotional state of patients with coronary artery disease who underwent ACS in the long-term period after myocardial

revascularization against the backdrop of the COVID-19 pandemic.

Aim: to study the problems of restenosis and thrombosis of the coronary arteries after coronavirus infection according to the literature.

Search strategy

For the search and analysis of scientific data, we used databases and web resources: MEDLINE, Pubmed, Google Scholar, Cyberleninka, and eLIBRARY. For the literature review, we used sources published from 2019 to 2022. Scientific articles were used that correspond to the topic and the basic context of the study. During the selection of literature for writing an article, preference was given to publications in peer-reviewed publications. During the primary analysis, a general array of articles was selected, which was filtered for compliance with keywords and context. As a result of the primary selection, 124 literary sources were identified, of which 28 publications were the basis of the analytical material for this article. *Inclusion criteria:* reports of randomized and cohort studies, systematic reviews and meta-analyses, diagnostic and treatment protocols, and articles in English and Russian. *Exclusion criteria:* personal communications, newspaper publications, abstracts, and articles with fuzzy conclusions.

Results and discussion.

Myocardial revascularization is the restoration of the coronary arteries using a surgical operation. Such operations include percutaneous coronary intervention (stenting and angioplasty). As a result of improvements in the technology of percutaneous coronary interventions, mortality from coronary artery disease has decreased. At the same time, the widespread use of PCI has led to the formation of the problem of repeated adverse cardiovascular events, regardless of the quality of the intervention [13]. The main causes of recurrent myocardial ischemia after PCI are restenosis, stent thrombosis, incomplete revascularization, and progressive atherosclerosis of the coronary arteries [2; 47].

Predictors of thrombosis and restenosis of the stent.

Approximately 5 million percutaneous coronary interventions are performed worldwide every year. Complications associated with stenting are relatively rare but represent a serious problem for the patient's life. One of the formidable complications is thrombosis and restenosis of the stent. Mortality, in this case, is 5-45%, and the recurrence rate is 15-20% within 5 years [48].

Stent thrombosis is a rare, severe complication of coronary interventions with high mortality. Stent thrombosis is considered to be the presence of acute myocardial ischemia after stent implantation in the presence of angiographic signs of occlusive and non-occlusive thrombosis [32, 39]. Factors leading to thrombosis of the stand are individual for each patient. These include endothelial structure, hypersensitivity, inflammatory reactions, blood rheology, platelet reactivity, coagulation factors, physical and mechanical properties of the stent, and the influence of these various factors on blood flow hydrodynamics. The conducted studies show that the elimination of risk factors leads to a significant reduction in the incidence of stent thrombosis both in the early and late periods after stent implantation. Most stent thromboses develop within the first 30 days after PCI. The expected incidence of early stent thrombosis is ~1%, late stent thrombosis is 0.2% - 0.6%. Most alarming is the fact that acute stent thrombosis has a mortality rate of 20% to 45% and an incidence of myocardial infarction (MI) of 50% to 70%. In addition, about 20% of patients with stent thrombosis will have a second episode within 2 years [42]. The incidence of early and late stent thrombosis in non-drug-eluting and drug-eluting stents are similar, but the incidence of very late stent thrombosis is more common in first-generation drug-eluting stents [17].

Restenosis is a narrowing in the stented area with difficulty in coronary blood flow during control coronary angiography [38]. After stent implantation, restenosis develops mainly during the first three months [1]. Restenosis occurs due to intimal hyperplasia in the stent, which leads to myocardial ischemia. With the introduction of coronary drug-eluting stents, the likelihood of restenosis and, consequently, re-interventions has decreased significantly [27]. The prevalence of restenosis after stent implantation of bare metal coronary stents is approximately 20-35%, on the contrary, the use of drug-eluting stents has led to a further decrease in the occurrence of restenosis to 5%-10% [41].

Studies based on the obtained angiographic data show that neointimal hyperplasia after implantation of bare metal coronary stents (Bare Metal Stent - BMS) reaches its maximum 6 months after implantation of the stent. After stenting a drug-eluting stent (DES), the dynamics of restenosis development look somewhat different. In a significant series of observations based on the evaluation of angiographic results, the researchers found that the process of endothelialization of the drug-eluting stent continues in the long-term follow-up period from 6-8 months to 2 years and is manifested by the presence of areas of the metal structure of the stent that is not covered by endothelium [9]. As a rule, in the zone of implantation of the coronary stent, the endothelial layer is exposed, hemorrhage under the intima, rupture of the intima, and barotrauma of the inner membrane of the elastic layer [4, 45].

At the same time, in some patients, the severity of damage to the arterial wall during stent implantation differs, which is due to the morphological features of the structure of the vessel wall. The most pronounced damage is observed in the case of significant atherosclerotic changes in the coronary arteries with fibrosis and calcium inclusions. As a result, inflammation develops in the area of damage to the arterial wall, installed by the coronary stent. Further, in the places of microdamage of the artery, cells migrate - inflammation mediators - neutrophils, monocytes and at the same time the accumulation of a large number of platelets, and in a later phase - macrophages and lymphocytes [3, 14]. The accumulation of activated leukocytes in the stent implantation zone causes the secretion of inflammatory cytokines: interleukins, which, in turn, induce the migration of smooth muscle cells from the media to the intima, as well as their accumulation and proliferation [20,44, 49].

The pathogenesis of COVID-19-associated cardiovascular complications.

With coronavirus infection, the pathophysiological mechanisms of damage to the cardiovascular system are

chronic inflammation, autoimmune reactions, dysregulation of the renin-angiotensin-aldosterone system, vascular damage, and hypercoagulability with thrombus formation in the vessels [28, 31]. Consider several reasons for the development of heart complications after COVID-19:

- Damage to the heart and blood vessels directly by the SARS-CoV-2 virus.
- Damage to the heart and blood vessels against the background of a general inflammatory response.
- Failure of the cardiovascular system due to respiratory failure, and lack of potassium and magnesium.
- Negative effects on the cardiovascular system of drugs used to treat coronavirus [37, 46].

Mechanisms of damage to the immune system in COVID-19: induction of the production of interferon, interleukin 2 and 7, stimulation of granulocyte activity, and production of tumor necrosis factor [7], which leads to uncontrolled intravascular hyperinflammation with impaired angiogenesis and hypercoagulability. COVID-19 may be a trigger for the development of secondary diseases associated with immunosuppression and the presence of the virus, as well as autoimmune reactions. Immune patterns associated with disease progression and severity in patients with COVID-19 have been described.

Dysregulation of the immune response also affects the physiological functions of the vascular endothelium (development of endothelium) and underlies many complications of COVID-19, mainly of a thromboembolic nature. Accordingly, the persistence of endothelial inflammatory mechanisms may contribute to chronic symptoms. The pathogenesis of damage to the cardiovascular system in coronavirus infection is associated with the expression of angiotensin-converting enzyme 2 (ACE2) receptors in the cells of the cardiovascular system, especially in the vascular endothelium. ACE2 is vital for the cardiovascular and immune systems to maintain homeostasis. It is assumed that the mechanisms of development of cardiovascular complications are associated with the consequences of the interaction of viral S-protein with ACE2, with a decrease in ACE2 activity and resulting damage to the immune and cardiovascular systems. ACE2 plays a key role in the regulation of angiotensin II (AII) and bradykinin metabolism. A decrease in ACE2 activity is associated with the development of a cytokine and bradykinin storm. Suppression of the effects of ACE2 leads to an increase in the level of AII with the development of systemic vasoconstriction, inflammation, and fibrosis. The significance of the renin-angiotensin-aldosterone system and kinin-kallikrein system dysregulation in the development of cardiovascular complications of coronavirus infection is beyond doubt. In the pathogenesis of coronavirus infection, vascular damage and hypercoagulability play an important role [24, 25].

Myocardial injury with COVID-19 in patients with previous revascularization.

Studies show that patients with previous myocardial revascularization who have had a coronavirus infection have a higher risk of developing severe complications. So Polish scientists in there study concluded that stent thrombosis is more common in patients with multiple concomitant diseases and in patients with complex atherosclerotic lesions, diabetes mellitus, chronic kidney disease, diffuse and bifurcation lesions of small arteries, requiring more than one stent. During SARS-CoV-2 infection, a cytokine storm occurs 5-10 days after symptom onset, resulting in endothelial damage, platelet activation, and a coagulation cascade. The presence of a stent in a coronary artery should be considered as a local stasis factor that completes the Virchow triad.

According to the results of the study by *Giustino G et al.,* which included 305 patients with prior revascularization who underwent coronavirus infection, myocardial damage was observed in 190 patients (62.3%). Compared with patients without myocardial injury, patients with myocardial injury had more electrocardiographic abnormalities, higher inflammatory biomarkers, and an increased prevalence of major echocardiographic abnormalities, which included left ventricular wall motion abnormalities, global left ventricular dysfunction, grade II or III left ventricular diastolic dysfunction, and pericardial effusions [22].

In a study by scientists from Italy, which included more than 1000 hospitalized patients with confirmed COVID-19 infection: 54.8% of patients had arterial hypertension as one of the risk factors for cardiovascular pathologies, 44.6% of patients had a history of coronary heart disease, 2. 3% were with prior surgical myocardial revascularization. Subsequently, patients with a history of myocardial revascularization were excluded from the analysis, as their in-hospital mortality was higher than in patients without coronary stents (41.0% vs. 19.3%, $p<0.001$). Based on this, it can be concluded that among hospitalized patients with confirmed coronavirus infection, in-hospital mortality was higher in patients with previous myocardial revascularization than in patients without previous revascularization. [21].

Turkish scientists in 2020 in their study of 50 patients found that there were no significant differences between survivors and non-survivors in terms of coronary artery bypass surgery, percutaneous coronary intervention, and coronary stenting history. They concluded that prothrombotic coagulopathy mediated by endothelial interaction with SARS-CoV-2 may also play a role in poor prognosis in COVID-19 [6].

The systematic review of cases reported worldwide by *Wojciech Jan Skorupski et al.* (Poland) included all published cases of COVID-19 stent thrombosis from the start of the coronavirus pandemic until the end of 2021. The review included 17 patients. All types of stent thrombosis were presented in patients: acute (4 patients; 23.5%), subacute (4 patients; 23.5%), late (1 patient; 5.9%) with a clear predominance of the very late type (8 patients or 47.1%). By the nature of the localization of thrombosis of the stand: in more than half of the patients in the left anterior descending artery (ADA), 5 (29.4%) in the right coronary artery (RCA), 3 (17.6%) in the left circumflex artery. In one case, there was a rare case of double coronary stent thrombosis in LAD and RCA. Mortality in this analysis was 35.3%. Based on their results, they concluded that COVID-19 triggers several inflammatory mechanisms, which in turn create a prothrombotic environment, leading to an increased risk of local microthromboembolism and stent thrombosis [43].

Dario Pellegrini et al. in their study found a significant increase in mortality in patients with COVID-19 undergoing myocardial revascularization compared to patients without COVID. Patients with ST-elevation myocardial infarction

after COVID-19 often had severe respiratory failure and concomitant myocardial dysfunction, which were also the most common causes of death. In these patients, urgent myocardial revascularization did not result in the same improvement in survival as in patients without COVID-19. In this study, among hospitalized patients with prior myocardial revascularization with COVID-19, the reported time of death was on average 2 weeks after symptom onset. Evidence confirms that coagulopathy caused by COVID-19 is increasing and microthrombi have already been found in the heart, lungs, and other organs [5, 30]. The higher incidence of persistent thrombosis that they observed during PCI may be further evidence for such a hypercoagulable state [40].

At the moment, the exact causes leading to acute myocardial injury are not fully understood, but there are suggestions that they are associated with the interaction between coronavirus infection and the cardiovascular system, either directly or indirectly.

Treatment approaches in the cases of stent thrombosis and restenosis associated with COVID-19.

The optimal methods of hospital treatment of acute coronary syndrome include percutaneous coronary intervention and thrombolysis. There is evidence that STEMI with concomitant COVID-19 is associated with high rates of multiple coronary and stent thrombosis, as well as the use of glycoprotein IIb/IIIa inhibitors [16], but these results are mainly from small observational studies with small sample sizes. Such findings require a special diagnostic approach and modification of antithrombotic therapy for these patients. Primary PCI is currently the treatment of choice for STEMI, but a balance must be struck between the risk of exposure and the patient benefit of thrombolysis. Early after myocardial infarction, delaying even one hour may reduce the effectiveness of primary PCI compared to thrombolysis [8], so in some Asian countries, such as China and Iran, thrombolytic therapy is recommended instead of primary PCI for the treatment of STEMI if COVID-19 has been confirmed. Previous studies recommend pre-discharge coronary angiography after the patient has stabilized from COVID-19 [36].

In patients with COVID-19, anticoagulant therapy requires changes in dosing regimen due to the high risk of thrombosis complicates the dosing of anticoagulants in hospitalized patients with COVID-19 [11]. Therefore, even when using primary PCI, anticoagulants are given in addition to antithrombotic therapy [26, 15], such as unfractionated heparin and intravenous enoxaparin [26]. The optimal dosing regimen of anticoagulants in such patients must be selected individually depending on the severity of inflammation and the state of hypercoagulability. Patients with STEMI should receive anticoagulant therapy for at least 48 hours after intravenous thrombolysis [15]. The introduction of post-procedural anticoagulant therapy and prolongation of anticoagulant therapy is necessary to balance COVID-19-related systemic hypercoagulability after primary PCI and intravenous thrombolysis in patients with COVID-19. Notably, these therapeutic approaches may increase the risk of heparin-induced thrombocytopenia [18]. In a previous prospective study, summarized reports on thrombosis and bleeding rates were based on early data from the COVID-19 outbreak and reported on the pros and cons of antithrombotic treatment in patients after PCI [50]. In the early stage of COVID-19, platelet inhibition by dual antiplatelet therapy (DAPT) can suppress a state of platelet hyperactivation, likely by inhibiting in situ platelet activation in the pulmonary vasculature [34, 29]. Antiplatelet drugs used at this stage act on intravascular fibrin and thrombus formation, thereby preventing secondary fibrinolysis and depletion of blood clotting factors. Notably, observational studies report that taking aspirin before hospitalization is associated with lower mortality in patients with community-acquired pneumonia (100 mg) [19] and ARDS (75–300 mg) [12].

Conclusion.

Stent thrombosis or restenosis is a life-threatening event, often associated with massive myocardial infarction and death. SARS-CoV-2 infection activates inflammatory mechanisms that potentially create a prothrombotic environment and increase the risk of local microthromboembolism and all types of stent thrombosis. Patients after percutaneous coronary intervention with active COVID-19 infection and symptoms of the acute coronary syndrome are more likely to have stent thrombosis. Further research is needed to determine the optimal antithrombotic therapy for coronary heart disease in COVID-19 survivors. Damage to the cardiovascular system is carried out through various mechanisms that can cause the manifestation of cardiovascular pathology in the long-term period after a coronavirus infection.

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