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Possibility of correction of the blood-heart barrier damage as a consequence of the impact of the SARS-CoV-2 virus on the cardiovascular system in patients with coronary artery disease in combination with COVID-19.

Netiazhenko Vasyl[1,2], Mostovyi Serhii[1,3], Safonova Olga[4], Mikhaliev Kyrylo[2]

[1] Bogomolets National Medical University, Kyiv, Ukraine

[2] State Institution of Science «Research and Practical Center of Preventive and Clinical Medicine»

[3] State Administrative Department, Kyiv, Ukraine
SE «Medbud», Kyiv, Ukraine

[4] Kyiv City Clinical Hospital No. 18, Kyiv, Ukraine

Address for correspondence:

Mostovyi Serhii

E-mail: semostowoy@ukr.net

Abstract: *damage to the blood-heart barrier (BHB) and endothelial dysfunction is a characteristic feature of congestive (cardiopulmonary) chronic heart failure (CHF), the main cause of death in elderly people with CHF caused by new coronavirus variants (SARS-CoV-2), but the mechanism of this phenomenon remains unclear. The aim of this project is to determine the mechanism of BHB damage in coronary artery disease (CAD) with COVID-19, as well as the possibility of its correction with the use of sulodexide. The endocardial endothelium (EE) is a barrier that prevents blood leakage from the endocardium to the interstitium; however, this barrier is impaired during the course of COVID-19 in patients with CAD. Previous studies have shown that one of the pathophysiological mechanisms is the activation of matrix metalloproteinases (MMPs) in CAD with CHF. MMP-9 degrades connexins, which leads to EE dysfunction. One study [Rubens P. et al. 2021] found a juxtacrine connection of EE with the myocyte and mitochondria (Mito), but how this works is still an open question. Materials and methods. We examined 65 patients with coronary artery disease diagnosed with COVID-19. Patients were divided into two groups: Group I (n=35) – patients who had been taking sulodexide at a dose of 500 LE x 2p/day for 6 months against the background of standard therapy of coronary artery disease; Group II (n=30) – patients without sulodexide. Echocardiography and laser Doppler flowmetry were performed at baseline and 6 months later. Echocardiography at the time of inclusion in the study revealed that 30 (50%) patients in group I and 14 (47%) patients in group II had reduced left ventricular ejection fraction (LV EF) values of 40 to 50%. After 6 months of treatment with sulodexide, a tendency to improve LV systolic function and decrease in left ventricular myocardial mass index (LFMMI) was noted in patients of group I. There were no differences between the groups at the time of inclusion in the study in terms of the level of the capillary flow reserve – occlusion test (CFRo) and the capillary flow reserve – nitroglycerin test (CFRn). A repeated study of CFR revealed a significant increase in CFRo and CFRn levels only in group I. In patients of group II, no significant changes in CFRo and CFRn were found. An inverse relationship between the level of CFRo and C-reactive protein (CRP) was found in patients of group I*

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(r=0.52, p<0.05). After 6 months of treatment, plasma CRP concentrations decreased significantly: from 17.7 [1.3; 50.1] to 5.7 [1.0; 12.0] mg/L in group I (p=0.01) and from 14.2 [1.2; 27.0] to 4.2 [1.0; 11.0] mg/L in group II (p=0.01). No significant correlations between CRP level and CFRo after 6 months of treatment were found. There were correlations of CFRo and CFRn with left ventricular systolic function, as well as inverse relationships with the size of the left and right ventricles and systolic pressure in the pulmonary artery. There was a tendency to improve systolic and diastolic left ventricular function in the first group, where sulodexide was used, and no significant changes in echocardiography were noted in the second group. At the initial examination of patients, the ratio of CFRo and CFRn had no significant differences. After 6 months of treatment, a significant increase in the ratio of CFRo and CFRn was observed only in patients taking sulodexide, and no positive dynamics of this ratio was observed in group II. The results indicate that MMP-9 activation, endothelial damage, endothelial-myocyte (E-M) uncoupling, and mitochondrial-myocyte uncoupling in heart failure in patients with CAD combined with COVID-19 were detected to a significant extent; however, treatment with sulodexide successfully mitigated the destructive changes in the heart in CAD with CHF. The results obtained are directly relevant to the range of cardiac manifestations and phenotypes arising from COVID-19 complications in people with CAD. Conclusion. The obtained results confirm the improvement of microcirculation, as well as a tendency to improve systolic function and left ventricular myocardial mass index after 6 months of sulodexide treatment in patients with coronary artery disease with preserved and moderately reduced left ventricular ejection fraction (LV EF) who have undergone COVID-19. The described effects of improving endothelial function, as well as improving the state of the blood-brain barrier due to the use of sulodexide, make it possible to recommend the use of this drug in the category of patients with CAD to reduce the negative impact of COVID-19 on the cardiovascular system.

Keywords: Coronary Artery Disease; COVID-19; Endothelium; Chronic Heart Failure; Sulodexide.

Introduction

SARS-CoV-2 has a negative impact on the microcirculation (MC), causing endothelial damage, microthrombosis, and microvascular occlusion (E. Cenko et al. 2021). Microvascular changes are considered not only as a pathophysiological aspect of acute SARS-CoV-2 infection, but also as a factor associated with an increased risk of developing long-term postinfectious consequences in COVID-19 convalescents (Xu S.W. et al. 2023). Patients with concomitant cardiovascular disease are more susceptible to complications associated with COVID-19 and have higher concomitant mortality (Mondini L. 2023). Coronary artery disease cooperates with SARS-CoV-2 infection on the principle of mutual reinforcement (Rudyk Y.S. 2021). Microvascular changes, including endothelial dysfunction and damage, are factors that contribute to the mutual worsening of the course of the 2 diseases. The methodology of non-invasive study of MC, in particular in patients or those who have recovered from COVID-19, involves the use of nail (video) capillaroscopy (NC) (Natalello G. et al. 2021; Karahan S. et al. 2022) and laser Doppler flowmetry (LDF) (Sabioni L. et al. 2021; 2023).

There are data on the targeted assessment of microvascular dysfunction in coronary vessels in patients with COVID-19 and survivors of COVID-19 (Malahfji M. et al. 2022; Çalışkan M. et al. 2022; Rola P. et al. 2022), which, however, are not readily available in routine clinical settings. Considering that COVID-19 causes systemic endothelial damage, we extrapolated the laser Doppler flowmetry (LDF) values of the background recording on the left forearm (Fullerton A. et al. 2002), as well as the ECHO values to assess the state of the BHB.

Patients with coronary artery disease (CAD) have an increased risk of severe COVID-19 and death. Oedema, myocardial inflammation, fibrosis, and related complications are observed in patients recovering from COVID- 19, as well as in patients with post-COVID syndrome. Cardiac lesions are present in 80% of patients, and prolonged myocardial inflammation persists in 60% of cases with an average time interval of 71 days in COVID-19, even in asymptomatic patients (Jia-Fu Wei. et al.

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2020; Rudyk Y.S. 2021). The 45-day cumulative risk of venous thromboembolism after discharge was 0.2%. In another cohort, it was 4.8 per 1000. The incidence of thrombosis (pulmonary embolism, intracardiac thrombus, and ischemic stroke) within 30 days was 2.5%. The risk of thrombotic events in the post-COVID-19 period may correlate with the severity of hyperinflammation (E. Cenko et al. 2021). Acute myocardial injury (AMI) was detected in 15.8% of 110 patients, half of whom had high troponin T levels that were 5 times higher than normal. Patients with AMI were older and more likely to require hospitalization in the intensive care unit, mechanical ventilation, and treatment with vasoactive drugs. Troponin T levels were associated with disease severity, and 3 deaths occurred in COVID-19 patients with AMI (Jia-Fu Wei, 2020).

Numerous studies have focused on CAD with CHF, but only a few have determined the function of the BHB (Rubens P. et al. 2021). The endothelium, whether it is located in the endocardium, coronary or capillary vessels, is the main barrier against BHB dysfunction (Brutsaert, D.L. 1998; 2003; Smiljic, S. et al. 2017). As for the tight junction proteins, such as connexin-37 between endothelium and endothelium, connexin-43 between endothelium and myocyte, myocyte and other myocyte, and mitochondria (mito)-myocyte, they are primary connexins (Dbouk, H.A. et al. 2009; Boengler, K. et al. 2017). In this context, researchers have begun to explore that it is important to determine the mechanism of leakage of BHB if they are involved in various diseases, including viral infections, including COVID-19, which infect vital organs such as the heart (Rubens, P. et al. 2021; Adeghate, E.A. et al. 2021; Bader, F. et al. 2021; Liu, J. et al. 2021; Mehra, M.R. et al. 2020; Shchendrygina, A. et al. 2021; Abbasi, J. 2021).

Indeed, remodeling by its nature involves the synthesis and degradation of the extracellular matrix (ECM). Thus, matrix metalloproteinases (MMPs) play a significant role in vascular leakage and interstitial edema (Bauer, A.T. et al. 2010, Rosenberg, G.A. et al. 2007). The basement membrane between the endothelium and muscles contains ECM, encompassing latent MMPs and tissue inhibitor of metalloproteinases (TIMP)/ nitric oxide; NO in the form of a triple complex. However, oxidative stress during IHD activates MMPs and inactivates TIMP through peroxynitrite and nitration of tyrosine/arginine (Hunt, M.J. et al. 2007). Disruption of the endothelial-myocyte (E-M), myocyte-myocyte (M-M), and mitochondria (mito)-myocyte junctions are signs of heart failure (Zima, A.V. et al. 2013; Pabbidi, M.R. et al. 2013; Rodriguez, W.E. et al. 2008).

In our study, we investigated the mechanism of myocardial damage in patients with IHD combined with COVID-19. According to Rubens P. et al. 2021, connexin-43, which connects myocytes and mitochondria (mito)-cardiomyocytes, and connexin-37 connects endothelial-cardiomyocytes. The role of MMPs in the degradation of connexins leading to cardiac dysfunction remains unclear when E-M, M-M, and mito-cardiomyocyte junctions are disrupted. We expanded on the hypothesis of Rubens P. et al. 2021, suggesting that stimulation of AT2 receptors by SARS-CoV-2 also contributes to leukocyte-dependent release of MMPs (including matrix metalloproteinase I and others), leading to disruption of the spatial configuration of the C-terminal tail and N-terminal domain of connexin-43 and connexin-37. COVID-19 through AT2 receptors also activates leukocyte-dependent release of MMP9, causing dysfunction of connexin proteins through the expression of A2A and A2B receptors, which are associated with Gαs and mediate adenylyl cyclase activation, leading to increased levels of cyclic adenosine monophosphate (cAMP) – one of the intracellular secretory stimulators. Elevated cAMP levels lead to the release of a large amount of isotonic fluid with low protein content and high concentrations of sodium, potassium, chloride, and bicarbonate into the interstitium. The presence of increased cAMP leads to the inactivation of connexins (by disrupting the spatial conformation of connexins 37 and 43) and dysfunction of E-M and M-M gap junctions. Loss of bicarbonate and potassium leads to the development of metabolic acidosis and hypokalemia (Haskó G. et al. 2016). Adenosine receptors A1 and A3 are associated with Gαi, which inhibits adenylyl cyclase activity. In addition, A1 receptors are associated with Gαo, which mediates adenosine inhibition of calcium conductivity. Meanwhile, A2B and A3 receptors are associated with Gαq and stimulate phospholipase activity. The extracellular concentration of

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adenosine near normal cells is approximately 300 nM. However, in response to cell damage (e.g., in inflamed or ischemic tissues), the concentration of adenosine quickly increases to 600-1200 nM. Thus, in response to stress or injury, adenosine mostly exhibits cytoprotective action, protecting tissues from damage in cases of hypoxia, ischemia, or seizures. Activation of A2A receptors elicits a wide range of responses that can generally be classified as anti-inflammatory (Haskó G. et al. 2004).

Although randomized clinical trials are needed to verify potential treatment methods including Sulodexide (S), when the pharmacokinetics and pharmacodynamics of Sulodexide will be fully understood, to determine an effective and safe therapeutic regimen for patient treatment, we decided to study the potential mechanism(s) in patients with the anticipation of any benefits, if any, regarding reprofiling S in the treatment of viral infections such as COVID-19 (Alejandro Gonzalez-Ochoa et al. 2020; Sam Schulman, Job Harenberg 2021). Sulodexide is a highly purified mixture of glycosaminoglycan consisting of fast-acting heparin and dermatan sulfate, which has a positive impact on the fibrinolytic system, platelets, endothelial cells, and inflammation (Sadykov D.V. 2008). The endothelial protection of sulodexide includes an influence on the glycocalyx and endothelial cells. The glycocalyx is a thin layer consisting of proteoglycans, glycosaminoglycans, and glycoproteins that covers the endothelium of all blood vessels and performs several important physiological functions (Shen D. et al. 2019 Dogné S, 2018) and its disruption can worsen endothelial function (Lasierra-Cirujeda et. all 2010). Endothelial glycocalyx is damaged in acute respiratory distress syndrome induced by endotoxemia in mice. Protection against endothelial damage by accelerating glycocalyx synthesis weakens glycocalyx damage, reduces the level of IL-6, and improves survival in animal models (Lauver DA. et al. 2006). Sulodexide inhibits disruption of glycocalyx permeability and oxidative stress in experimental ischemia-reperfusion injury (Femiano F. et al. 2008). In cultured endothelial cells, sulodexide restores the glycocalyx barrier (Bilinska M. et al. 2009). In a model of balloon-induced injury to the carotid artery in rats, intraperitoneal injections of sulodexide restore the endothelial glycocalyx, increase the level of endothelial nitric oxide synthase, attenuate endothelial hyperplasia, and suppress platelet aggregation, decrease the expression of CD31 and intercellular adhesion molecule-1 (ICAM-1), normalize the level of osteopontin and vascular cell adhesion molecule-1 (VCAM-1), and prevent inflammatory infiltration of the vessel wall CD68 (Li T. et al. 2017). In patients with diabetes with reduced endothelial glycocalyx thickness, oral administration of sulodexide has been shown to restore glycocalyx thickness (Broekhuisen LN. et al. 2014). In cultured endothelial cells exposed to high glucose concentrations, sulodexide suppresses the inflammatory phenotype by reducing levels of reactive oxygen species (ROS), monocyte chemoattractant protein-1 (MCP-1), and interleukin-6 (IL-6), as well as increasing the rate of wound layer cell repair (Ciszewicz M, et al. 2009). Similar studies on experimental aging human endothelial cells have shown that sulodexide reduces age-related changes (Suminska-Jasinska K. et al. 2011). Sulodexide improves endothelial dysfunction in streptozotocin-induced diabetic rats, while in cultured human umbilical vein endothelial cells, sulodexide opposes inflammation and endothelial dysfunction induced by patient serum with progressive chronic venous diseases, metabolic stress (methylglyoxal), or radiation. In these studies, the cytoprotective effects of sulodexide led to a decrease in ROS production, reduced synthesis and release of pro-inflammatory cytokines such as IL-1, IL-6, IL-18, tumor necrosis factor-alpha (TNF-α), MCP-1, ICAM-1, and DNA damage (Urbanek T. et al. 2016; De Felice F. 2019). Sulodexide also prevents apoptosis of endothelial cells undergoing oxygen-glucose deprivation. This protective effect appears to be mediated by a reduction in oxidative stress (Gabryel B. et al. 2016).

It is known that Sulodexide (S) exhibits antithrombotic effects on platelet aggregation, plasma coagulation, and fibrinolysis. It inhibits platelet aggregation in response to cathepsin G, thrombin, and tissue factor. It counteracts plasma coagulation factors Xa and IIa, thus showing an antithrombin effect similar in vitro to enoxaparin (Rajtar G et al. 1993; Adiguzel C, Iqbal O, Hoppensteadt D. et al. 2009; Cosmi B.et al. 2003). Thrombolytic activity was first demonstrated upon the addition of sulodexide to clots formed 6 hours prior (Barbanti M, et al. 1992)

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When administered orally, sulodexide reduces the level of plasminogen activator inhibitor-1 (PAI-1) and increases the level of tissue plasminogen activator (tPA) (Mauro M. et al. 1992; Crepaldi G. et al. 1990). The antithrombotic activity of sulodexide when administered orally has been confirmed in clinical studies showing its effectiveness in preventing recurrent venous thromboembolic events (Errichi BM. et al. 2004; Andreozzi GM. et al. 2015).

Sulodexide exhibits anti-inflammatory action: The anti-inflammatory effects of sulodexide have been demonstrated in several in vitro studies, animal models, and in humans. Sulodexide acts on the regulatory inflammatory response, reducing such inflammatory mediators as interleukins (IL) IL-6, IL-8, IL-1b, IL-2, IL-10, IL-13, interferon β, macrophage inflammatory protein-1β (MIP-1β), transforming growth factor-β1 (TGF-β1), vascular endothelial growth factor (VEGF), monocyte chemoattractant protein-1 (MCP-1), tumor necrosis factor-α (TNF-α), granulocyte colony-stimulating factor, and granulocyte-macrophage colony-stimulating factor. Sulodexide reduces oxidative stress by decreasing reactive oxygen species (ROS) and increasing superoxide dismutase (SOD) activity, as well as reducing matrix metalloproteinase-9 activity, which can cause tissue damage (Mattana P et al. 2012; Mannello F. et al. 2014; Munari ACF. et al. 2015).

Sulodexide is safe: It is noteworthy that sulodexide does not have serious side effects. Long-term treatment (two years) did not show a higher incidence of bleeding than placebo. Additionally, a meta-analysis showed lower cardiovascular and overall mortality compared to comparator drugs: Direct oral anticoagulants, vitamin K antagonists, aspirin, and placebo (Bikdeli B. et al. 2020; Pompilio G. et al. 2020).

Sulodexide, when used in the early stages of COVID-19, was associated with limiting disease progression, reducing the need for oxygen support and hospitalization (Frati AC, et al. 2021). It is known that Sulodexide inhibits MMP activity, endothelial hyperpermeability, and thus prevents glycocalyx damage (Munari ACF. et al. 2015). The mechanisms of action of Sulodexide or its derivatives are still being developed as they are not fully understood (Salma Charfeddine et al. 2022). MMPs play a crucial role in tissue damage that occurs during remodeling (Arthur Melkumyants et al. 2022).

Aim: to determine the possibility of correcting the damage to the blood-heart barrier (BHB) as a consequence of the impact of the SARS-CoV-2 virus on the cardiovascular system using sulodexide by assessing intracardiac hemodynamics and microcirculation in patients with coronary artery disease with concomitant COVID-19.

Materials and methods

A prospective study was conducted on 65 patients with coronary artery disease (CAD) and laboratory-confirmed COVID-19 (verified by a positive PCR test for SARS-CoV-2 RNA), with the U07.1 code according to ICD-10. CAD was confirmed based on the criteria of the European Society of Cardiology: previous myocardial infarction, interventional procedures on coronary arteries (stenting or coronary artery bypass grafting), and a positive stress test (exercise stress test or dobutamine stress echocardiography). The study was conducted upon admission of patients to the hospital and 6 months after discharge at the Kyiv City Clinical Hospital No. 18 and Medbud, a subsidiary of Kyivmiskbud (Kyiv) from December 2019 to December 2022.

Inclusion criteria: age 50-80 years, existing CAD, positive COVID-19 test, heart failure with preserved or slightly reduced ejection fraction (phenotypes B and C, according to the European Society of Cardiology, 2020). Exclusion criteria: acute myocardial infarction, acute bleeding, terminal oncology, severe anemia, pregnancy, lack of informed consent. An allergic reaction was a criterion for discontinuation from the study.

Patients were divided into two groups: Group I (n=35) – patients with CAD combined with COVID-19 who, in addition to standard medical therapy for chronic heart failure (CHF), received sulodexide at a dose of 500 LU twice daily for 6 months after discharge from the hospital; Group II (comparison group, n=30) – patients who received standard medical therapy without additional sulodexide.

The study was approved by the local Ethics Committee of Bogomolets National Medical University (protocol No. 631 dated 07.12.2022). All patients provided informed consent before partic-

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ipating in the study. The clinical characteristics of the patients are presented in Table 1.

The investigated groups were similar in age, gender, extent of lung tissue involvement, oxygen saturation level, presence of hypertension, diabetes mellitus, obesity, and severity of heart failure. The degree of blood pressure elevation did not differ significantly between the groups: stage 1 hypertension was diagnosed in 12 (34%) patients in Group I and 10 (30%) patients in Group II, stage 2 hypertension in 10 (29%) and 8 (27%) patients, stage 3 hypertension in 13 (37%) and 12 (40%) patients, respectively.

The treatment prescribed to the patients did not differ significantly; ACE inhibitors were received by 22 (63%) patients in Group I and 20 (67%) patients in Group II, angiotensin receptor blockers by 13 (37%) and 10 (33%) patients, beta-blockers by 31 (88%) and 24 (80%) patients, antiplatelet agents and statins by 35 (100%) and 30 (100%) patients, respectively. After discharge from the hospital, all patients received antithrombotic agents (new anticoagulants or aspirin) for 30 days as part of the treatment for COVID-19 and prevention of thromboembolic complications.

All patients underwent transthoracic echocardiography (TTE) using an ultrasound system (HD11XE, Philips, USA; multiphase transducer S4-2 [2-4 MHz]). Cardiac remodeling parameters, systolic and diastolic left ventricular (LV) function were assessed according to ASE guidelines. LA – left atrium (anterior-posterior dimension, cm); EDV – left ventricular end-diastolic volume, ml; ESV – left ventricular end-systolic volume, ml; LVEF – left ventricular ejection fraction; Left ventricular myocardial mass index, g\m2; RVWT, right ventricular wall thickness (diastolic), ms; RVD, right ventricle diameter (anteroposterior dimension, cm); SBP, systolic pulmonary artery pressure, mm Hg. The state of microvascular blood flow and mechanisms of its regulation were assessed using laser Doppler flowmetry (LDF), LAKK-02 hardware complex, London, UK, according to European guidelines. The following parameters were determined: baseline microvascular blood flow (perfusion index [PI, p.u.] p.u. – perfusion units.) – the average value of microcirculation and functional tests – capillary flow reserve (CFR) [endothelium-dependent and endothelium-independent mechanisms of microcirculatory regulation] (occlusion test [CFR,%]; nitroglycerin iontophoresis [CFRn,%]).

Repeated examination of patients was performed after 6 months of treatment for all patients included in the study. The concentration of C-reactive protein (CRP) was measured by enzyme-linked immunosorbent assay (ELISA) using Biomerica reagents (USA). The results of the study

Table. 1. Clinical characteristics of patients

Clinical data	1 group, n=35	2 group, n=30	p
Age, years	62 (55-69)	60 (49-67)	0,083
Males	24 (69%)	22 (73%)	0,062
Proportion of lung damage			
CT Imaging -1	16 (46)	11 (37)	0,173
CT-2	14 (40)	16 (53)	0,081
CT-3	5 (14)	3 (10)	0,182
The level of saturation	92±12	93±8	0,094
Arterial hypertension, %	35 (100%)	30 (100%)	0,072
Myocardial infarction has been suffered.	15(43)	9 (30%)	0,067
Diabetes mellitus	12(34)	8 (27)	0,239
body mass index	28,9 (25,1-31,8)	28,2 (24,9-333,9)	0,175
CHF, NYHA.			
phenotype B, NYHA 2 FC (functional class)	23 (65%)	20 (67%)	0,064
phenotype C, NYHA 3 FC	12 (35%)	10 (33%)	0,261

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were entered into an electronic database for statistical processing using the Statistica v. 14.0.0.15 program. In the case of a normal Gaussian distribution, quantitative indicators are presented in the form of M (mean) ± SD (standard deviation), in the case of a distribution other than normal – in the form of median (Me) and interquartile range [Q25; Q75]. Variables were compared using Fisher or Mann-Whitney tests. Correlation analysis was used to study the relationship between two variables using the Spearman or Pearson correlation coefficient. The statistical significance of differences between qualitative indicators was assessed using the $\chi 2$ criterion. The results were considered reliable if the probability of error was <0.05, which meets the criteria accepted in biomedical research.

Results

Echocardiography at the time of enrollment in the study revealed that 30 (50%) patients in group I and 14 (47%) patients in group II had reduced LV EF values of 40 to 50%. After 6 months of treatment with sulodexide, a tendency to improve LV systolic function and decrease in LV MMI was noted in patients of group I. There were no significant differences between the groups at the time of enrollment in the study in terms of CFRo and CFRn levels. A repeated study of CFRo activity revealed a significant increase in CFRo and CFRn levels only in group I. In patients of group II, no significant changes in the levels of CFRo and CFRn were found (Table 2).

During the inclusion of patients in the study, an inverse relationship of moderate strength between plasma CRP and CFRo in patients of group I was found (r=0.52, p<0.05).

After 6 months of treatment, plasma concentrations of CRP significantly decreased: from 17.7 (1.3; 50.1) to 5.7 (1.0; 12.0) mg/l in Group I (p=0.01) and from 14.2 (1.2; 27.0) to 4.2 (1.0; 11.0) mg/l in Group II (p=0.01). There were no significant correlations between the level of CRP and CFRo after 6 months of treatment. Moderate correlations were observed between CFRo and CFRn with left ventricular systolic function, as well as inverse correlations with the sizes of the left and right ventricles and systolic pressure in the pulmonary artery. There was a tendency towards improvement in the systolic and diastolic function of the left ventricle in the first group, where sulodexide was used, while no significant changes in intracardiac hemodynamics were observed in the second group.

One of the most important indicators that allows us to judge the activity of the L-arginine NO system in improving endothelium-dependent vasodilation and its impact on microcirculation system remodeling is the ratio of CFRo to CFRn (CFRo / CFRn). Upon initial examination of patients, the CFRo / CFRn ratio did not show significant differences. After 6 months of treatment, a significant increase in the CFRo/CFRn ratio was observed only in patients taking sulodexide, while there was no positive dynamics of this ratio in Group II (Figure 1).

Discussion

Clinical studies have shown that severe cases of COVID-19 lead to significant inflammation and necrosis of cardiomyocytes in the myocardium. The changes triggered by the SARS-CoV-2 virus intervention contribute to significant fibrotic changes (Bader F. et al 2021).

It is known that worsening endothelial function is associated with suppression of the L-arginine NO system, increased concentration of pro-inflam-

Table 2. Dynamics of echocardiography and LVEF in patients with coronary artery disease with concomitant COVID-19

Data M, Q25-75	1 group initially	1 gr. After 6 months	P	2 group initially	2 gr. After 6 months	P
LV EF,%	49 (40; 56)	53 (42; 60) *	0,051	48 (41; 62)	49 (45; 65)	0,063
LV MMI, g\m^2	137 (93; 160)	130 (89; 155)*	0,054	140 (76; 161)	138 (71; 160)	0,071
PI, p.u.	4,11 (2,53; 7,58)	3,88 (2,28; 7,00)	0,081	4,57 (2,14; 9,24)	4,45 (2,32; 9,00)	0,085
CFRo%	136 (88;189)	160 (127; 245)	0,003	146 (80; 250)	164 (75; 304)	0,059
CFRn%.	185 (130; 216)	199 (155; 287)	0,001	193 (124; 242)	202 (85; 460)	0,063

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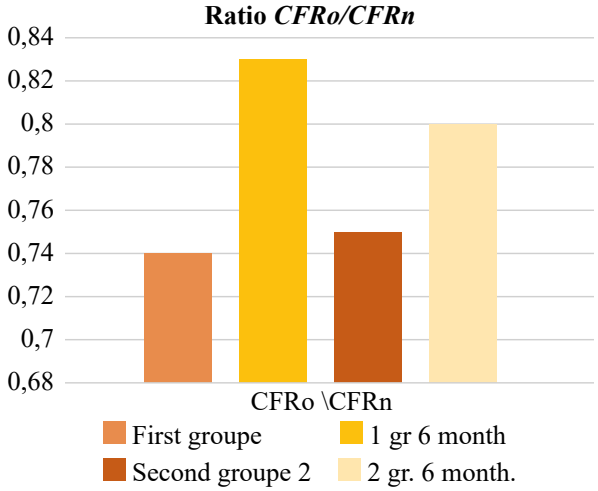

Group 1: patients with coronary artery disease with concomitant COVID-19 who were administered sulodexide.

Group 2 in patients with coronary artery disease with concomitant COVID-19 who were prescribed standard therapy without sulodexide.

Figure 1: Correlation of endothelium-dependent and endothelium-independent vasodilation in patients with coronary artery disease with concomitant COVID-19.

matory cytokines (IL-6, IL-8, IL-1b, IL-2, IL-10, IL-13, TNF-alpha, etc.), increased concentration of MMP-9 and a deficiency of TIMP-1, increased adenylyl cyclase activity, leading to edema and degradation of the intercellular matrix, development of pronounced dilation of the left ventricular cavity, and rapid progression of systolic heart failure. Decreased MMP activity indicates a decrease in the degree of fibrosis. This study demonstrated that additional administration of sulodexide in the comprehensive treatment of patients with ischemic heart disease and preserved or moderately reduced left ventricular ejection fraction who had recovered from COVID-19 led to improvement in endothelial function (enhanced activation of the L-arginine NO system, reduction in pro-inflammatory cytokines, as well as plasma concentrations of MMP-9 and TIMP-1).

According to A. Gonzalez-Ochoa et al. 2020, sulodexide may help restore the integrity of the glycocalyx in venous and arterial endothelium, which can reduce or limit the response to inflammatory molecules. It has an antithrombotic effect, which may help reduce the frequency of thromboembolic complications, which can be beneficial for these patients. We hypothesize that sulodexide, administered in the early symptomatic stages of COVID-19, will improve clinical outcomes, reduce hospitalizations, and decrease morbidity and mortality in patients with IHD. According to S. Charfeddine et al. 2021, sulodexide in patients with long-term COVID-19 may be an effective means of relieving chest pain, palpitations, fatigue, and neurocognitive disorders associated with endothelial dysfunction. The study by Zudina A.M., 2021 convincingly demonstrated the importance of sulodexide in reducing inflammation, anticoagulant effects, and improving endothelial function (Kryvoschekov E.P. 2022). Sulodexide significantly (by 40%) reduced the number of circulating endothelial cells, potentially indicating its antiviral endothelial-protective properties. It also prevented excessive platelet activation and the formation of erythrocyte sludge according to Arthur Melkumyants, 2022.

Sulodexide improves the condition of the glycocalyx barrier and reduces its damage in COVID-19, reducing the level of thrombomodulin, von Willebrand factor (Győző Szolnoky. 2022). Sulodexide, a precursor for the synthesis of glycosaminoglycans (GAGs), may help restore the damaged endothelial glycocalyx and prevent further degradation (J. Gonzalez-Ochoa et al. 2022). Improving the integrity of the glycocalyx not only restores the barrier function of the endothelium but also allows the endothelium to better modulate the production of key inflammatory molecules, such as IL1, IL6, IL8, and TNF, while simultaneously reducing its response to them. The heparin compound adds an αβ-antithrombotic and profibrinolytic effect, which may be important against the procoagulant state caused by SAR-CoV-2; moreover, it may exert additional anti-inflammatory action. Sulodexide is known for its pleiotropic action and protective effect on the endothelium (Shen D. et al. 2019). It exhibits antithrombotic properties by reducing the level of fibrinogen (Dogné S. et al. 2018; Lauver DA. et al. 2018) and plasminogen activator inhibitor-1 (PAI-1) inhibitor (Dogné S. et al. 2018; Bilinska M, et al. 2003) and is believed to have anti-inflammatory properties (Mauro M. et al. 1993; Femiano F. et al. 2003). In various cardiovascular indications, the use of sulodexide has been associated with a reduced risk of venous thrombo-

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embolism, myocardial infarction, cardiovascular mortality, and all-cause mortality (Bilinska M. et al. 2009; Bikdeli B. et al. 2020). Treatment with sulodexide has been associated with a significant increase in CFRo and CFRn, as well as the ratio of CFRo/CFRn, indicating improvement in endothelial function and a slower rate of microcirculatory remodeling (Kryvoschekov E.P. 2022).

According to Rubens P. et al. 2021, activation of MMP-9 induces EMMPRIN (CD147), reduces the level of connexin-37, and causes endothelial endocardial (EE) leakage, and sulodexide mitigates MMP-9 activation, EE leakage, and dysfunction of the muscles of the pulmonary diaphragm. Although MMP-9 degrades collagen/elastin and connexins, collagen metabolism occurs faster compared to elastin or connexins, which in turn are replaced by stiffer collagen (Jiang Q–J. et al. 2018; Rucklidge, G.J. et al. 1993). Therefore, a shift in the collagen/elastin ratio may lead to fibrosis. Increased cardiovascular risk in ischemic heart disease (IHD) essentially linked to fibrosis and MMP-9, which degrades connexins (-37 and -43), causing disconnection of E-E and M-M junctions. Fibrosis caused by collagen degradation by MMP-9 can be reduced by lowering the level of MMP-9. Although sulodexide reduces the level of MMP-9, the mechanism of this effect is unknown. In our opinion, adenosine receptor expression is involved here, so it is necessary to determine whether MMP-9 activation reduces the level of connexin-43 and causes disconnection of endothelial-myocyte (E-M) and myocyte-myocyte (M-M) junctions, and whether sulodexide mitigates them. Connexins in myocytes are important for proper mitochondrial functioning (Rottlaender D. et al. 2012; Boengler, K. et al. 2012).

Elevated levels of mitochondrial MMP-9 disrupt connexin-43, leading to the disconnection of mitochondria and myocytes. In patients with ischemic heart disease and heart failure, there is a disruption in the regulation of mitochondrial fusion and fission (Givvimani, S. et al. 2014; Givvimani S. 2012). The dynamic process of myocyte contraction and relaxation is synchronized with mitochondrial fusion and fission, as mitochondria make a significant contribution to calcium balance and energy production in myocytes (Zima, A.V. et al. 2013). There is a decrease in the Mfn2/Drp1 ratio (Mfn2; mitofusin 2, a mitochondrial fusion protein/Drp1; dynamin-related protein, a mitochondrial fission protein), indicating abnormal predominance of fission over fusion, leading to abnormal mitophagy (Givvimani, S. et al. 2012).

Altered mitochondrial dynamics due to decreased Mfn2/Drp1 ratio result in desynchronization. Sulodexide may mitigate the disconnection of junctional connections between mitochondria and cardiomyocytes, supporting mitochondrial dynamics (Mfn2/Drp1 ratio) and inhibiting connexin degradation mediated by MMP-9. Our study suggests that sulodexide reduces the induction of proteolytic and mitochondrial oxidative stress (Salma Charfeddine. 2022).

Thus, remodeling of the blood-heart barrier (BHB) involves: worsening of endothelial function, degradation of the extracellular matrix (ECM) through hyperproduction of pro-inflammatory cytokines, activation of matrix metalloproteinases, adenylyl cyclase system, which play a significant role in vascular leakage and interstitial edema (Bauer, A.T. et al. 2010, Rosenberg, G.A. et al. 2007), and disrupt junctional connections between endothelial-myocyte (E-M), myocyte-myocyte (M-M), and mitochondria (mito)-myocyte, which are signs of prolonged heart failure (Zima, A.V. et al. 2013; Pabbidi, M.R. et al. 2013; Rodriguez, W.E. et al. 2008) in patients with CAD in combination with COVID-19. Correction of this condition should be carried out using endothelioprotectors such as statins, beta-blockers, ACE inhibitors (angiotensin receptor blockers), antithrombotic agents in combination with sulodexide.

Conclusion

The results obtained confirm the improvement of microcirculation, as well as the tendency to improve systolic function and left ventricular myocardial mass index after 6 months of sulodexide treatment in patients with CAD with preserved and moderately reduced LVEF who have had COVID-19. The described effects of improving endothelial function, as well as improving the state of the hematocardial barrier through the use of sulodexide, make it possible to recommend the use of this drug in this category of patients to reduce the negative impact of COVID-19 on the cardiovascular system.

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ORCID ID and Autor contributions

0000-0001-9697-4421 (A,F) Netiazhenko Vasyl

0000-0002-8783-3819 (A, B, C, D) Mostovyi Serhii

0000-0003-3759-6699 (A,E,F) Mikhaliev Kyrylo

0009-0007-8839-4268 (B, C) Safonova Olga

A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of article

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Корекція ураження гематокардіального бар'єру, як впливу вірусу SARS-CoV-2 на серцево-судинну систему у хворих на ІХС у поєднанні з COVID-19

Нетяженко Василь Захарович[1], Мостовий Сергій[2], Міхалєв Кирило[3], Сафонова Ольга[4]

[1] доктор медичних наук, член-кор. НАМНУ, професор, зав каф. Пропедевтики внутрішньої медицини №1 Національний медичний університет ім. О.О. Богомольця, Київ, Україна

[2] кандидат медичних наук, лікар кардіолог Медичного центру ДП МЕДБУД, м. Київ, Україна

[3] кандидат медичних наук, Державна наукова установа «Науково-практичний центр профілактичної та клінічної медицини» Державного управління справами (Київ), Україна

[4] лікар УЗД, Комунальне некомерційне підприємство «Київська міська клінічна лікарня № 18» (Київ), Україна.

Address for correspondence:

Сергій Мостовий

E-mail: semostowoy@ukr.net

Анотація: *ураження гематокардіального бар'єру (ГКБ), порушення ендотеліальної функції є характерною ознакою застійної серцевої недостатності (СН), основною причиною смертей людей похилого віку з ІХС, спровокованих новими варіантами коронавірусу (SARS-CoV-2), але механізм цього явища залишається нез'ясованим. Метою цього проекту є визначення механізму ураження ГКБ при ІХС із застійною СН із розвитком в них COVID-19, а також можливість його корекції при використанні сулодексиду. Ендотелій ендокарда (ЕЕ) є бар'єром, що перешкоджає витоку крові з ендокарда в інтерстицій; однак цей бар'єр порушується під час перебігу COVID-19 у хворих на ІХС. Попередні дослідження показали, що одним із патофізіологічних механізмів є активація матриксних металопротеїназ (ММП) при ІХС із ХСН. ММП-9 деградує коннексини, що призводить до дисфункції ЕЕ. В одному дослідженні [Rubens P. et al. 2021] виявлено юкстакринне з'єднання ЕЕ з міоцитами і мітохондріями (Міто), але як цей працює, досі залишається відкритим питанням. Матеріали та методи. Було обстежено 65 хворих на ІХС з діагнозом COVID-19. Хворі були розподілені на дві групи: I група (n=35) – пацієнти, які протягом 6 міс. на тлі стандартної терапії ІХС приймали сулодексид у дозі 500 ЛО х 2р/добу; II група (n=30) – хворі без сулодексіду. Проводили ехокардіографію і лазерну допплерівську флоуметрію на початку дослідження і через 6 місяців. При проведенні ехокардіографії на момент включення в дослідження було виявлено, що 30 (50%) пацієнтів I групи і 14 (47%) хворих II групи мали знижені значення ФВ ЛШ від 40 до 50%. Через 6 міс. лікування сулодексидом була відзначена тенденція до поліпшення показника систолічної функції ЛШ, а також зменшення ІММЛШ у хворих I групи. За рівнем резерву капілярного кровотока оклюзійної проби (РККо) і резерву капілярного кровотока нітрогліцеринової проби (РККн) відмінностей між групами під час включення в дослідження не було. Повторне дослідження після 6 місяців прийому сулодексиду на тлі стандартної терапії виявило значуще збільшення рівня РККо і РККн тільки в I групі. У хворих II групи істотної зміни РККо і РККн виявлено не було. Виявлено зворотну залежність між рівнем СРБ і РККо у хворих I групи (r=0,52, p<0,05). Через 6 міс. лікування плазмові концентрації СРБ істотно знизилися: з 17,7 [1,3; 50,1] до 5,7 [1,0; 12,0] мг/л у I групі (p=0,01) і з 14,2 [1,2; 27,0] до 4,2 [1,0; 11,0] мг/л у II групі (p=0,01). Достовірних взаємозв'язків між рівнем СРБ і РККо через 6 міс. лікування виявлено не було. Відмічено взаємозв'язки показників РККо і РККн*

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з систолічною функцією лівого шлуночку, а також зворотні залежності з розмірами лівого та правого шлуночку і систолічним тиском в легеневій артерії. Виявлена тенденція до поліпшення систолічної та діастолічної функції лівого шлуночка в першій групі, де був використаний сулодексид, в другій групі істотних змін показників ЕхоКГ не було відмічено. При первинному обстеженні пацієнтів співвідношення РККо/РККн не мало значущих відмінностей. Через 6 міс. лікування спостерігалося істотне збільшення співвідношення РККо/РККн тільки в пацієнтів, які приймали сулодексид, позитивної динаміки цього співвідношення в II групі не спостерігалося. Результати свідчать про те, що активація ММП-9, ендотеліальне ураження, ендотеліально-міоцитарне (Е-М) роз'єднання і мітохондріально-міоцитарне роз'єднання при (хронічній серцевій недостатності) ХСН у хворих на ІХС у поєднанні з COVID-19 були виявлені в значній мірі; однак лікування сулодексідом (С) успішно пом'якшило деструктивні зміни стану серця при ІХС із ХСН. Отримані результати мають безпосереднє відношення до гами кардіологічних проявів та фенотипів, що виникають внаслідок ускладнень COVID-19 у людей із ІХС. Висновок. Отримані результати підтверджують покращення стану мікроциркуляції, а також тенденцію до покращення систолічної функції та індексу маси міокарда лівого шлуночка через 6 місяців лікування сулодексидом у хворих на ІХС зі збереженою та помірно зниженою ФВ ЛШ, які перенесли COVID-19. Описані ефекти покращення ендотеліальної функції, а також покращення стану гематокардіального бар'єру завдяки використанню сулодексиду дають змогу рекомендувати використання цього препарату в категорії хворих ІХС із ХСН для зменшення негативного впливу COVID-19 на серцево-судинну систему.

Ключові слова: Ішемічна хвороба серця, COVID-19, ендотелій, хронічна серцева недостатність, сулодексид.

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