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НОМЕР СОДЕРЖИТ МАТЕРИАЛЫ МЕЖДУНАРОДНОЙ НАУЧНО-ПРАКТИЧЕСКОЙ КОНФЕРЕНЦИИ «БИОЛОГИЯ, ЭТИОЛОГИЯ И ФИЗИОЛОГИЯ КОРОНАВИРУСА COVID -19»

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ENDOTHELIAL DYSFUNCTION AS A LINK IN COVID-19 PATHOGENESIS

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Introduction

Despite the fact that the attention of a huge number of researchers around the world is focused on the development of effective clinical protocols and recommendations for the management of patients with a new coronavirus infection, the presence of a large number of severe forms of the disease and deaths allows us to count, that to date, doctors have not formed a holistic picture of the pathogenesis of this disease, enabling effective treatment and prevention of critical complications. In a number of studies in patients with severe COVID-19, a statistically significant association was found between the detection of microtrombs in the pulmonary vessels, disorders of the coagulation balance and damage to the vascular endothelium [1, 2, 3]. However, when describing the pathogenesis of COVID-19, as well as the factors involved in the development of complications of a new coronavirus infection, insufficient attention is paid to endothelial dysfunction.

The pathogenesis of intravascular coagulation disorders in coronavirus infection is represented by three interconnected processes that form a vicious pathological circle [6]:

- cytopathic damaging effect of the virus on vascular endothelial cells, which carry molecules of APF2 and CD147 with which the virus is able to interact in the destruction of the aerohematic barrier and developing viremia (Figure 1)

- "cytokine storm," which has a damaging effect on the vascular endothelium and provides an inflammatory reaction with recruitment to the focus of damage to white blood cells, macrophages, lymphoid elements and activation of blood coagulation ("inflammatory coagulation (thrombotic) tornado");

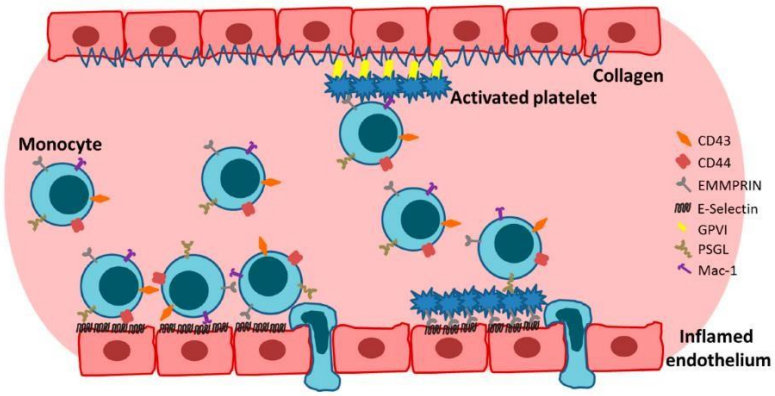

Figure 1. Effect of the CD147 marker (basigin, EMMPRIN, transmembrane serine protease) on the development of endothelial damage in COVID-19 (cite by: [https://medach.pro/post/2300].

- development of systemic vasculitis with small and medium-caliber vascular damage, the role of virus-induced autoimmune reactions is also not excluded.

It should be borne in mind that in the elderly, the most sensitive to coronavirus infection, in many cases, endothelial function is impaired and without additional viral influences. Damage to the endothelium can be caused by many reasons, among which exogenous ones are important - injuries, chronic intoxications with psychoactive substances and heavy metal compounds [7], which, in turn, increase the risk of COVID-19 incidence and affect the severity of the course of infection in the future. In the work of E.E. Ermolaeva et al. it has been shown that vascular endothelium is one of the main targets of organophosphorus compounds under chronic exposure to even subsymptomatic concentrations [8]. Intoxications in interaction with stress factors can initiate activation of lipid peroxidation, products which can damage the membranes of endotheliocytes, causing the development of atherosclerotic processes [9]. In addition to exogenous factors, concomitant oncological diseases, arterial hypertension, neurological pathology, diabetes mellitus, obesity, chronic obstructive pulmonary disease, etc. can have a significant impact on the severity of the course of COVID-19, the complex basis for the development and progression of which also considers endothelial dysfunction [10].

The purpose of the study: To substantiate the feasibility and possible directions of influence of the means of pharmacological correction of endothelial dysfunction for the prevention of the development of a cascade of pathological reactions accompanying the course of a new coronavirus infection.

Main part

The vascular endothelium is a unique "endocrine tree" that lines absolutely all organs of the body's vascular system. According to the classical definition, the vascular endothelium is a single-layer layer of flat cells of mesenchymal origin, lining the inner surface of blood and lymphatic vessels, as well as heart cavities. According to modern ideas, the endothelium is not just a semi-permeable membrane, but an active endocrine organ, the largest in the human body. Endothelial cells create

a barrier between blood and tissues, perform a number of important regulatory functions, synthesizing and isolating a large number of various biologically active substances - nitric oxide, prostacycline, von Willebrand factor, tissue plasminogen activator, endothelin-1, thrombomodulin, protein C receptor, etc.

The strategic location of the endothelium allows it to be sensitive to changes in the hemodynamic system, blood-borne signals, and signals from underlying tissues. The most important functions of the endothelium include the maintenance of hemovascular homeostasis, regulation of hemostasis, modulation of inflammation, regulation of vascular tone and vascular permeability. Intact endothelium has the ability to maintain a balance between its multidirectional functions: the synthesis of pro- and anti-inflammatory factors, vasodilating and vasoconstrictive substances, pro- and antiplatelet agents, pro- and anticoagulants, pro- and antifibrinolytics, proliferation factors and growth inhibitors. The endothelium secretes mitogens, participates in angiogenesis, fluid balance, exchange of intercellular matrix components, and presents its own elements of the renin-angiotensin system [10]. In physiological conditions, vasodilation, synthesis of aggregation inhibitors, coagulation and fibrinolysis activators, antiadhesive substances prevail. Endothelial cell dysfunction disrupts this balance and predisposes vessels to vasoconstriction, leukocyte adhesion, platelet activation, mitogenesis, and inflammation.

Endothelial dysfunction is considered as a pathological state of the endothelium, which is based on a violation of the synthesis of endothelial factors, as a result of which the endothelium is unable to correctly regulate the hemorheological balance of blood, the violation of which inevitably leads to organ damage and the development of polymorphic pathology [11]. Major factors that stimulate endothelial secretory activity include changes in blood flow rate, circulating and/or "intrastenal" neurohormones (catecholamines, vasopressin, acetylcholine, bradykinin, adenosine, histamine, etc.), platelet factors (serotonin, adenosine diphosphate, thrombin) and hypoxia. Leading risk factors for endothelial damage contributing to changes in the physiological balance in the body include hypercholesterolemia, hyperhomocysteinemia, increased levels of cytokines (interleukin- 1β and -8, tumor necrosis factor alpha), increased processes of lipid peroxidation, microcirculation disorders, increased systemic and intraocular pressure, hypoxia [4, 9]. Endothelial dysfunction can lead to structural damage in the body: acceleration of apoptosis, necrosis, desquamation of endotheliocytes.

Endothelial dysfunction markers are considered to be reduced endothelial synthesis of nitric oxide (NO), increased levels of endothelin-1, circulating von Willebrand factor, plasminogen activator inhibitor, homocysteine, thrombomodulin, soluble vascular intercellular adhesion molecule B1, C-reactive protein, microalbuminuria. The main role in the development of endothelial dysfunction is played by oxidative stress, the synthesis of powerful vasoconstrictors, as well as cytokines and tumor necrosis factor, which suppress the production of nitric oxide (NO) [9]. The starting mediator of oxidative stress in the vascular bed is

NADH/NADPH oxidase of the cytoplasmic membrane of macrophages, which produces superoxide anions. In addition, in the presence of hypercholesterolemia in the vascular wall, NO formation is reduced due to the accumulation of NO synthase inhibitors such as L-glutamine, asymmetric dimethylarginine, as well as a decrease in the concentration of the NO synthase cofactor tetrahydrobiopterin [10]. NO is synthesized from L-arginine in the presence of a number of cofactors and oxygen by various NO synthase isoforms (NOS): neuronal, or brain (nNOS), inducible (iNOS), and endothelial (eNOS). Nitric oxide synthesized in endothelium diffuses into vascular smooth muscle cells and stimulates soluble guanylate cyclase there. This leads to an increase in the content of cyclic guanosine monophosphate (cGMP) in the cell, the concentration of calcium in smooth muscle cells decreases, as a result of which relaxation of vascular smooth muscle cells and vasodilation occur. Nitric oxide is released by endothelial cells and represents a chemically unstable compound that exists for several seconds. In the lumen of the vessel, NO is rapidly inactivated by dissolved oxygen, as well as superoxide anions and hemoglobin. These effects prevent NO from acting at a distance from its release site, making nitric oxide an important regulator of local vascular tone.

In the formation of the stages of endothelial dysfunction in a new coronavirus infection [7], four phases can be distinguished: I - the phase of the beginning of viral pneumonia; II - the generalization phase of pulmonary damage to coronavirus; III - phase of expanded respiratory and vascular failure; IV - phase of increasing toxemia.

The main reason for the formation of the first phase is hypercytokinemia. In case of generalized damage by the lung tissue virus (type I and II alveolocytes, pulmonary macrophages), there is a sharp activation of alveolar macrophages and neutrophils, expression of pro-inflammatory cytokines (interleukin-1, interleukin-2, interleukin-6, interleukin-10, tumor necrosis factor), as well as activation of prostaglandin and leukotricin synthesis Hyaluronidase, in turn, begins to break down the interstitial substance of the pulmonary interstitium and reduces the strength of the alveolar-capillary barrier. Under the influence of proinflammatory cytokines and prostaglandins, overexpression of selectins, adhesion molecules (ICAM-1, VCAM-1) occurs, which, participating in interaction with the corresponding ligands of white blood cells, ensure their adhesion to vascular endothelium and alveolar epithelium. At the same time, the expression of endothelial NO synthase decreases, which leads to a decrease in the generation of nitric oxide and the associated vasodilating, anticoagulant and anti-inflammatory function of the endothelium.

The generalization phase of pulmonary damage by the new coronavirus is associated with direct damage to endothelial cells by the circulating SARS-CoV-2 virus in the blood

- there are several types of "gates" for coronavirus on the surface of endothelial cells. This factor is most significant in the formation of endothelial dysfunction in the pulmonary vessels, glomerular apparatus of the kidneys, coronary and cerebral vessels. Damaged endotheliocytes of pulmonary vessels produce a large

amount of endothelin, local spasm of the vessels of the microvasculature of the lung is formed, pulmonary blood pressure increases [11]. Fluid from the vascular bed penetrates the interstitial space, interstitial edema develops, making it difficult to transport gases through the alveolar-capillary barrier. Further, gas exchange function sharply decreases, hypoxemia increases, respiratory acidosis develops, carbon dioxide accumulates in the blood, causing hyperstimulation of the respiratory and autonomic centers of the brainstem. Against this background, respiratory failure progresses. In the kidneys, the generation of vasoconstrictors is more significant prostaglandins H2, which leads to impaired glomerular blood flow and a decrease in excretion and resorptive processes in the distal parts of the nephron.

In the third phase (the phase of expanded respiratory and vascular failure), blood flow reduction, acidosis, hypoxemia and circulatory hypoxia have adverse effects on the endothelium. Endothelial disorders are mainly compensatory in nature and are aimed at improving microcirculation, eliminating increased tone and/or spasm of regional vessels. However, the secretion of vasodilating factors (nitric oxide, endothelial relaxation factor, endothelial depolarizing factor) and procoagulants, especially the tissue plasminogen activator inhibitor and Willebrand factor, can be enhanced. Inhibition of fibrinolysis and activation of the coagulation cascade supports the long-term existence of intravascular microthrombs, which is an important element of the pathogenesis of multiple organ failure syndrome.

In the phase of increasing toxemia, endothelial damage is associated with endotoxicosis caused by disorders of the intestinal capillary barrier and resorption of intestinal and microbial toxins, impaired detoxification function of the liver (especially ammonia detoxification in the urea synthesis cycle), as well as impaired elimination of kidney exchange slags as a result of the onset of acute renal failure. Under the influence of endotoxins, the trophics and energy supply of endothelial cells are weakened, their ability to maintain a negative charge on their surface, to maintain hemorheological and coagulation balance. Expression of platelet activation factor and fibronectin is increased. As a result, conditions are formed for intra-organ thrombotic damage, microcirculation disturbance, and inhibition of the function of organs suffering from this. In activated platelets, increased formation and release of platelet growth factor, which is a mitogen of fibroblasts, from granules occurs, as a result of which the formation of procollagen and collagen, hyaline membranes in the lungs is increased, followed by the activation and maintenance of the processes of fibrous transformation of the lung tissue.

Conclusion

Thus, the presented analytical review on the influence of the functional state of the endothelium on the formation of pathological processes initiated by the effect on the body of coronavirus from the SARS-CoV-2 family allows us to distinguish endothelial damage as one of the central links in the pathogenesis of ARDS and the development of other severe complications of COVID-19. Timely differentiated prescribing pharmacological correction of endothelial dysfunction with a high

degree of probability will improve the prognosis for the disease with a new coronavirus infection, especially against the background of concomitant chronic diseases complicating the course of COVID-19.

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Abstract

The main purpose of this work was to substantiate the feasibility and possible directions of influence of the means of pharmacological correction of endothelial dysfunction for the prevention of pathological conditions associated with a new coronavirus infection. An analysis of available literature on endothelial functions was carried out, a study of foreign and domestic experience on possible directions

of pharmacological correction of endothelial dysfunction was carried out. An overview of the information available in the available literature on endothelial dysfunction with justification of the role of vascular endothelial damage as one of the central links in the pathogenesis of acute respiratory distress syndrome is presented. The phases of the formation of the stages of endothelial dysfunction are shown, the mechanisms of endothelial damage in a new coronavirus infection were determined.

Keywords: *new coronavirus infection, COVID-19, pathogenesis, endothelial dysfunction, viral pneumonia, pharmacotherapy.*

Аннотация

Основной целью настоящей работы было обоснование целесообразности и возможных направлений влияния средств фармакологической коррекции эндотелиальной дисфункции для профилактики патологических состояний, сопутствующих новой коронавирусной инфекции. Проведен анализ доступной литературы о функциях эндотелия, выполнено изучение зарубежного и отечественного опыта о возможных направлениях фармакологической коррекции эндотелиальной дисфункции. Представлен обзор имеющихся в доступной литературе сведений о дисфункции эндотелия с обоснованием роли повреждения эндотелия сосудов, как одного из центральных звеньев в патогенезе острого респираторного дистресс-синдрома. Показаны фазы формирования этапов эндотелиальной дисфункции, определены механизмы повреждения эндотелия при новой коронавирусной инфекции.

Ключевые слова: новая коронавирусная инфекция, COVID-19, патогенез, эндотелиальная дисфункция, вирусная пневмония, фармакотерапия.

Ключевые слова: *новая коронавирусная инфекция, COVID-19, патогенез, эндотелиальная дисфункция, вирусная пневмония, фармакотерапия.*

Аннотация

Ушбу илмий изланишнинг асосий мақсади янги коронавирус инфекцияси билан боғлиқ патологик ҳолатларнинг олдини олиш учун ендотелиал дисфункцияни фармакологик тузатиш воситаларининг таъсир қилиш имкониятлари ва мумкин бўлган йўналишларини асослаш еди. Эндотелиал функциялар бўйича мавжуд адабиётлар таҳлили ўтказилди, ендотелиал дисфункцияни фармакологик тузатишнинг мумкин бўлган йўналишлари бўйича хорижий ва маҳаллий тажриба ўрганилди. Ўткир респиратор дистресс синдроми патогенезида марказий бўғинлардан бири сифатида қон томир эндотелиал шикастланишнинг ролини асослаш билан эндотелиал дисфункция бўйича мавжуд адабиётларда мавжуд бўлган маълумотларнинг умумий кўриниши келтирилган. Эндотелиал дисфункция

босқичларининг шаклланиш босқичлари кўрсатилган, янги коронавирус инфекциясида эндотелиал шикастланиш механизмлари аниқланган.

Калит сўзлар: *янги коронавирус инфексияси, СОВИД-19, патогенез, ендотелиал дисфункция, вирусли пневмония, фармакотерапия.*