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ALTERATIONS IN THE PERIPHERAL CIRCULATION IN HEART FAILURE: CURRENT VIEW ON ENDOTHELIAL DYSFUNCTION AND PHARMACOLOGICAL IMPLICATIONS INVOLVING ITS PATHOPHYSIOLOGICAL ASPECTS

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Summary

Introduction. Despite the significant advances in the pharmacotherapy of cardiovascular diseases, the increasing prevalence of heart failure (HF) and its poor prognosis constitute one of the leading medical problems worldwide. The complex pathophysiology of HF involves the alterations in the peripheral circulation, particularly the development of endothelial dysfunction (ED). The deepening of understanding the pathology of ED and the spectrum of pharmacological implications, involving its certain pathophysiological aspects, could favor the optimization of the personalized approach to the management of such challenging HF patients.
Aim: to ***provide*** a literature ***review*** of the ***current*** data on the alterations in peripheral circulation in HF with the focus on ED, and to outline possible pharmacological implications involving certain pathophysiological aspects of ED in HF patients.
Material and methods. The thematic scientific papers, published predominantly during the last decade, constituted the study material. The research methodology involved bibliosemantic method and structural and logical analysis.
Results and discussion. Currently, the ED considered as a stage of a specific continuum, which is initiated in the form of «activation» of the endothelium, and moves through the stage of its actual «dysfunction» to the stage of endothelial «damage». Taking into account the important pathogenetic and prognostic significance of ED in HF, the endothelium is considered as a target of various pharmacological influences, including renin-angiotensin-aldosterone inhibitors and statins. Among the modern approaches to pharmacological treatment of HF, the correction of reduced nitric oxide (NO) bioavailability by modulating the «NO-soluble guanylate cyclase-cyclic guanosine monophosphate» signaling pathway is a perspective option in terms of preventing the occurrence and progression of ED.
Conclusion. The deepening of knowledge about the pathophysiological features of ED in HF allows both to improve the understanding of the pharmacodynamic effects of already approved cardiovascular drugs, and to outline the perspectives for pharmacological direct or indirect impact on endothelium.

Key words: **peripheral circulation, heart failure, endothelial dysfunction, pathophysiology, pharmacological implication**

INTRODUCTION

Despite the significant advances in the pharmacotherapy of cardiovascular diseases, the increasing prevalence of heart failure (HF) is one of the leading medical problems worldwide [1-5].

At present, HF is still a condition associated with a poor prognosis. Even with the existence of several classes of drugs with a proven effect on clinical events, patients with HF have a high risk of adverse outcomes, especially if they have a history of a recent decompensation episode [2, 6, 7].

In spite of repeated attempts to create a unifying hypothesis that clarifies the pathophysiology of HF, no single conceptual model has passed the test of time. According to the cardiovascular continuum concept, the risk factors, related to myocardial damage, cause the activation of compensatory neurohormonal mechanisms, that, inherently, contribute to HF decompensation from the very beginning of their launch. At the same time, despite the importance of the neurohormonal model in explaining the mechanisms of myocardial remodeling, development and manifestation of HF, the results of numerous clinical trials suggest that this concept cannot fully explain the progression of HF syndrome [1-3, 8].

Currently available pharmacological treatment can stabilize the clinical course of HF or, in some cases, cause the reversal of some aspects of its progression. However, in the vast majority of patients, HF still progresses, albeit more slowly. Moreover, as HF progresses, many patients become resistant to conventional treatment regimens and require their revision [8].

The search for new «levers» of pharmacological influence in patients with HF, obviously, is impossible without the comprehensive consideration of interaction between structural and functional biological changes occurring in the failing heart. These biological changes are influenced by the multiple factors, all of which add to the complexity of understanding the HF pathophysiology [1-3].

Considering the complex pathology of HF, one should account the importance of the changes that occur in the peripheral circulation. Among the important findings from the studies on the peripheral circulation in HF is that endothelial dysfunction (ED) plays a significant role in the pathogenesis, clinical manifestation and prognosis in HF. Specifically, it contributes to the impaired coronary and systemic perfusion and reduced exercise capacity in HF patients [2, 9].

The deepening of understanding the nature of peripheral circulatory disorders in HF, including the pathology of ED, as well as the spectrum of pharmacological implications, involving its certain pathophysiological aspects, will allow to identify the areas, where further refinement of current paradigms may be needed, and will promote the development of additional treatments for this population, in particular to further reduce the risk of recurrence episode after recently decompensated HF, favoring the optimization of the personalized approach to the management of such challenging patients [2, 7, 8].

AIM

This *paper aims* to p*rovide* a literature *review* of the *current* data on the alterations in peripheral circulation in HF with the focus on ED, and to outline possible pharmacological implications involving certain pathophysiological aspects of ED in HF patients.

MATERIAL AND METHODS

The thematic scientific papers, published predominantly during the last decade, constituted the study material. While performing literature search, we also analyzed the data from particular landmark scientific works, published earlier than the pre-specified search period. The literature search was conducted by the use of Google Web Search and PubMed search engines by the following keywords: peripheral circulation, heart failure, endothelial dysfunction, pathophysiology, pharmacological implications, as well as their combinations. The research methodology involved bibliosemantic method and structural and logical analysis.

REVIEW AND DISCUSSION

ED as one of the key elements in the peripheral circulation alterations in HF. It is generally accepted that ED plays an extremely important role in the pathogenesis of cardiovascular pathology, including HF. It has been proven that there are two types of endothelial cells in the heart – in the coronary arterial bed and endocardium. Despite the many commonalities between the endocardial and capillary endothelium, many differences have been shown, especially in signaling to adjacent cardiomyocytes [1-3, 9-12].

The biological features of endothelium can be considered in the context of positioning each endothelial cell as an «input-output» system. Input signals are formed in the extracellular environment, include biochemical and biomechanical factors, including the following: growth factors, cytokines, chemokines, lipopolysaccharides, reactive oxygen (and nitrogen) species (RO(N)S), nucleotides, acetylcholine, adrenaline, lipoproteins, serpins, hypoxia, shear stress, pH, temperature etc. At the output, the transformation of input signals is summed in the form of cellular phenotype, which is characterized by the specific features of protein biosynthesis, gene and mRNA expression, differentiation, proliferation, migration, permeability, apoptosis, regulation of leukocyte trafficking, extracellular matrix effects, angiogenesis, vasomotor function, and, inherently, the endothelial heterogeneity in different vascular pools. Each endothelial cell has its own unique properties – the so-called «set point», which is controlled by epigenetic factors. The differences in these input signals and the state of the «set point» determine the phenotypic heterogeneity and vascular diversity of the endothelium [9-13].

In the light of the «input-output» model, the endothelium should not be considered as a «black box», but as a multi-organ cell with a large number of nonlinear signaling networks. Moreover, considering the endotheliocytes each being a matter of nonlinear input and output relationships, the properties of one cell cannot predict the behavior of the entire capillary or vascular pool [10-14].

The cardiomyocytes synthesize many factors that affect the endothelial cell phenotype. At the output, the endothelium expresses a unique pattern of genes and proteins that affect the function of cardiomyocytes. This reciprocal interaction between cardiomyocytes and endothelium plays an extremely important role not only in myocardial performance, but also in regulation of numerous processes, including the cells migration, apoptosis and hemostasis [15-17].

It has been long recognized that ED occurs under the influence of numerous changes in the extracellular environment and leads to the progression of myocardial remodeling [1-3, 8, 18]. A reference should be made to the fact that the vast majority of scientific data on ED in HF have focused on HF with reduced left ventricular ejection fraction (HFrEF). However, the evidence for the role of ED in HF with preserved left ventricular systolic function is growing [19].

Although the endothelium serves as a critical regulator of many aspects of vascular biology, such as hemostasis and inflammation, its ability to produce nitric oxide (NO) is a «pivot» for a variety of endothelium-dependent processes, related to HF development and progression. In parallel with the regulation of hemodynamics, NO acts as a potent modulator of myocardial oxygen consumption in the failing heart [1-3, 8-13, 17].

It is well known that NO is synthesized from L-arginine by the enzyme NO-synthase (NOS). All the isoforms of NOS are represented in the heart: NOS1 – neuronal, NOS2 – inducible (iNOS), and NOS3 – constitutive (endothelial [eNOS]). Once formed, NO binds to the corresponding intracellular receptor, namely the Fe^{2+}-heme active site (β-subunit) of soluble guanylate cyclase (sGC), activating the enzyme and converting guanosine triphosphate to cyclic guanosine monophosphate (cGMP). The cGMP is an intracellular second messenger, interacting with the following three effector pathways: cGMP-dependent protein kinases I and II, cGMP-gated ion channels and cGMP-regulated phosphodiesterases. In general, cGMP is involved in the regulation of vascular tone, cardiac contractility and cardiac remodeling. The physiological effects of cGMP include relaxation of leiomyocytes with the consequent vasodilation, inhibition of platelet activation and proliferation of leiomyocytes, modulation of endothelial adhesion molecule expression, regulation of leukocytes migration, as well as anti-inflammatory and anti-fibrotic properties [1-3, 7-9, 13, 20-24].

The decrease in NO bioavailability in HF is based on both the reduction of its production by eNOS, as well as the intensification of NO degradation due to enhanced oxidation. Besides, the increased inflammation, oxidative stress and ED lead to higher conversion of sGC from its native heme-Fe^{2+}-containing form, for which NO has a high affinity, to the oxidized, dysfunctional heme-free-Fe^{3+}-form. Under such conditions, the impairment of NO-sGC-cGMP signaling pathway activity occurs, contributing to the adverse effects on the heart, kidneys and vasculature, promoting further HF progression [2, 21].

Paradoxically, the chronic production of NO by iNOS in HF adversely affects ventricular contractility and circulatory function. However, as of today, the data on the pathogenic role of iNOS in HF are lacking. The use of iNOS inhibitors does not affect the contractility of the failing heart or β-adrenoceptor sensitivity of ventricular myocytes [2].

ED as a stage of the specific continuum. Nowadays, ED is considered as a stage of a specific continuum, which is initiated in the form of «activation» of the endothelium, and moves through the stage of its actual «dysfunction» to the stage of endothelial «damage» [2].

Endothelial «activation» is positioned as a process of physiological response of endothelial cells to various stimuli, which pursues the goal of maintaining homeostasis (i.e., being essentially a protective phenomenon). In particular, at the stage of «activation» the endothelium can express a number of cell adhesion molecules, as well as release von Willebrand factor and fibrinolytic factors. A key aspect of endothelial «activation» is its reversibility upon termination of the activating agent(s) impact.

In contrast to «activation», the «dysfunction» of endothelium refers to the cases of its long-term excessive (e.g., increased ROS production) or depressed functioning (e.g., in the form of impaired vasodilation). Given that «dysfunction» of the endothelium may be the next step after its chronic «activation» (for example, by prolonged and inappropriate activation of proinflammatory cytokines), there is a clear overlap between these two stages of the «endothelial continuum». In the scope of blood flow control, the leading pathophysiological feature of ED (in the context of cardiovascular diseases) is the functional deficiency of eNOS, which leads to a reduced NO bioavailability and excessive ROS production in the vascular wall, which, in turn, deepens the endothelial functional alterations.

«Dysfunction» may be reversible, while «damage» of the endothelium occurs against the background of excessive ED, and is characterized by premature apoptosis/death of endothelial cells. With the progression of myocardial remodeling and HF, the studies demonstrated the elevated levels of circulating endotheliocytes, as well as the ability of apoptotic endothelial cells to activate platelets by increasing phosphatidylserine expression. Increased shedding of the circulating endothelial cells and high plasma concentrations of von Willebrand factor are considered as markers of endothelial damage, which is unlikely to be reversible [1-3, 8-14].

The systemic nature of ED in HF. In most patients with HF, ED does not occur in a single arterial pool, but rather demonstrates a systemic pattern of distribution in peripheral arteries (e.g., brachial or radial arteries), with

the parallelism observed in myocardial vessels. The systemic nature of endothelial dysfunction extends beyond the arterial bed. There is a growing body of evidence that ED in HFrEF also involves the venous and capillary endothelium. Endothelium-dependent venodilation is impaired in chronic HF, but it is especially noticeable in the case of acute decompensation of the disease.

The data on the systemic nature of ED in HF are also supported by the results of the studies that revealed an impairment of the endothelium-dependent vasodilator response in the microvascular bed. Microvascular ED, along with reduced capillary network density in HFrEF, can significantly affect the occurrence of chronic peripheral tissue hypoxia, fatigue, and reduced exercise tolerance.

Chronic ED in HF contributes to the remodeling of peripheral arteries, leading to hypertrophy and reduced elastic properties. To date, there is an evidence of a correlation between impaired endothelium-dependent vasodilation and vascular wall hypertrophy and abnormalities of local arterial elastic characteristics, such as distensibility and compliance.

The systemic nature of ED in HF allows to position the endothelium as a single unique organ. However, this concept also recognizes the significant heterogeneity of the phenotype and function of endothelial cells, located in different compartments of the vascular bed. At present, there is a need for further research aimed at forming a holistic approach to understanding the systemic and local aspects of the alterations in structural and functional state of the endothelium as the progression of HF [2, 9-14, 17-19].

Particular pathophysiological aspects of ED in HF: focus on «endothelium-red blood cells (RBCs)» interactions. A comprehensive understanding of the ED in HF demands to account the physiological and pathophysiological aspects of the interactions between endothelium and the formed elements of blood, in particular RBCs. The wide spectrum of «endothelium-RBCs» relationships include their interactions at the level of NO system; while formation of atherosclerotic lesions of the arterial wall; and while the implementation of various mechanisms of thrombosis [10, 20, 25-27].

The biological system of endothelium-released NO plays an outstanding role in the regulation of vascular tone and cardiac performance in HF [1-3, 8, 9]. At the same time, a number of researchers have been able to detect eNOS and reveal its activity in RBC. RBCs eNOS was detected in their cytoplasm and the inner layer of the plasma membrane. RBCs eNOS activity, being heterogeneous in different compartments of the vascular bed, is important for the regulation of the RBCs and platelets functional state. The series of conditions, such as atherosclerosis and HF, contribute to RBCs eNOS dysfunction and the reduction of NO bioavailability. In general, both RBCs and endothelium make a significant contribution to the level of circulating NO pool [20, 25].

According to the recent study by F. Leo et al. [28], both endothelial and RBCs eNOS contribute equally to blood flow and blood pressure regulation. The authors mention that RBCs eNOS expression levels are clearly lower than in endothelium. However, the massive abundance of RBCs and extensive surface area appear to provide sufficient NO to contribute to blood flow and blood pressure regulation. These data complement the existing knowledge of endothelium-RBCs interactions, allowing for a better understanding of the specific role of RBCs eNOS under normal conditions and in the pathogenesis of different diseases [20, 28]. Among them one should mention coronary artery disease and chronic kidney disease, where RBCs eNOS is decreased [28].

When considering the interaction between the endothelium and RBCs in the context of the atherosclerotic process, one should deserve attention in the problem of plasma membrane microvesicles (MVs) (or microparticles) formation, which has been of scientific and practical interest in recent years. Plasma membrane MVs are microscopic (0,1-1 μm in diameter) non-nuclear extracellular phospholipid structures of various origins (originated from many cells and non-nucleated cell elements, including endothelium, platelets, leukocytes and RBCs), which form as a result of activation, apoptosis or aging, promote athero- and thrombogenesis due to the anionic phospholipid surface, expression of tissue factor and impaired eNOS activity [26, 27, 29].

Membrane blebbing and formation of RBCs-derived MVs results from the loss of phospholipid asymmetry by the plasma membrane, causing MVs to carry phosphatidylserine at their surfaces. Disturbances of membrane-cytoskeleton interactions underlies the formation of MVs from RBCs. Although MVs have been positioned as an undesirable byproduct of these processes, they have now been shown to be the means of intercellular interactions *in vivo* (including the transport of inflammatory molecular species), to serve as an important regulatory link in various pathophysiological processes, and to constitute a pathogenetic component of many disorders of the hemostasis system, including thrombosis. Moreover, the formation of MVs is also facilitated by enhanced RBCs adhesion to the endothelium, being characteristic of a wide range of pathological conditions, including atherosclerosis and diabetes mellitus [26, 27, 29, 30].

It is now known that RBCs are able to mediate the formation and destabilization of atherosclerotic plaques by interacting with innate and adaptive immune cells, macrophages and T-lymphocytes. For example, immune cells can be activated by a variety of endogenous, chemically or structurally changed molecules. These may include hemoglobin, released from lysed RBCs, or contained in RBCs-derived MVs. In addition, RBCs-originated exosomes bind to monocytes, favoring proinflammatory cytokines to boost the T-cell response. One should note that RBC activity may be increased due to the oxidation process as well [26].

Under physiological conditions, the antioxidant systems from RBCs are able to neutralize RONS, being formed in the process of hemoglobin deoxygenation. On the other hand, the balance of redox reactions in RBCs could be altered, when their passing through the tissues with intensive production of RONS, including the atherosclerotic vessels. Under such conditions, oxidative damage to RBCs outweighs their protective capabilities, while oxidatively modified RBCs becomes a kind of prooxidant «bullet» for the tissues, that are remote from the primary site of injury. A hemoglobin, being among such damaging agents, is released into the vascular bed from hemolyzed RBCs, reacting with peroxides and promotes further oxidation. In this case, RBCs, instead of being scavengers, behave as the generators of RONS. In other words, RBCs can act as a kind of «sensors» of the level of oxidative stress of a particular organ or tissue [30-32].

As outlined in the comprehensive review by R. Asaro and P. Cabrales [26], oxidatively damaged RBCs can augment mitogen-driven T-cell proliferation and apoptosis, along with enhancing the Th1 cells proinflammatory and proatherogenic cytokine response. Besides, oxidatively stressed RBCs promote the dendritic cells maturation, thereby inciting proinflammatory Th1 cell response. A mechanism for this is the loss of CD47 at the RBCs surface due to vesiculation, since CD47 appears to be critical to the RBCs to prevent the dendritic cells maturation. Finally, oxidatively damaged RBCs may polarize macrophages toward M1 pathways, thus promoting proinflammatory cytokine response. On the whole, oxidatively compromised RBCs promote those cell phenotypes that trigger vesiculation and can lead to atherosclerotic progression [26, 33].

Analyzing the available literature, the authors of the above review [26] discuss the role of RBCs and hemoglobin in the development of atherosclerotic lesions, emphasizing the process of plaque neovascularization, and pointing that such kind of effects implement via the mechanisms of coagulation, inflammatory response, as well as cell adhesion *per se*. It is important to note that RBCs may generate MVs more readily within the oxidative environment of atherosclerotic plaques. This is related, in part, to the existing hypoxic conditions, being the background for a switch from aerobic to anaerobic metabolism, characterized by glucose and adenosine triphosphate (ATP) depletion, conditions that are known to promote RBCs vesiculation. RBCs-derived MVs can then release hemoglobin, arousing the generation of such substances as methemoglobin and oxyhemoglobin. As a result, local production of MVs during the blood flow through the affected artery region, may indeed contribute to the atherosclerotic plaque progression and destabilization [26, 29-31].

Additionally, it should be noted that F. Jenny et al. [34] and D. Tziakas et al. [35, 36] have hypothesized that cholesterol and hemoglobin, released by RBCs within atherosclerotic plaques, are important contributors to plaque instability via the mechanism involving the «breakdown of RBCs» releasing cholesterol. The release of hemoglobin-containing MVs may be partially related to the process of plaque destabilization, although the number of MVs would be most likely quite large to account for the cholesterol levels estimated.

The review by V. Loyer et al. [37] further analyzed the possible and probable roles of RBCs-derived MVs in destabilizing plaques. The authors outlined the general trends of increased MVs levels with a range of cardiovascular risk factors and conditions, such as dyslipidemia, diabetes mellitus, hypertension and atherosclerosis [37]. In the context of these parallels it is worth noting that RBCs participate in the transport of lipids in the circulation. Their lipidome is determined by exchange with blood components, and is altered in lipotoxic diseases, such as fatty liver disease, HF and diabetes. Moreover, ceramide, lysophosphatidylcholine, lysophosphatidic acid, palmitic acid and free cholesterol induce RBCs malfunction [38].

The newer findings by D. Tziakas et al. [39] suggest that intraplaque hemorrhage with RBCs extravasation and lysis promotes osteoblastic differentiation of smooth muscle cells and vascular/valvular lesions calcification. Discussing the clinical implications, researchers [39] point that membranes of extravasated, lysed RBCs appear to play an important role in this process, and RBCs eNO synthase-derived NO is involved, at least in part, in mediating the effects of RBCs on vascular and valvular calcification.

Thus, the current body of actual data suggests, that oxidatively stressed RBCs, containing oxidized hemoglobin, exposing phosphatidylserine at their external surface, and having compromised membrane-skeleton connectivity, may undergo increased endothelial cell adhesion and vesiculation, consequently impacting the progression of atherosclerosis [26, 33]. In this context it is also worth noticing that, according to the long-known facts and recent research, RBCs are characterized by both aging and a process similar to apoptosis (eryptosis, erythroptosis). It is initiated by the increase of cytosolic calcium, which causes the «shrinkage» of RBCs, formation of MVs, binding of annexin to the surface of RBCs, along with aforementioned alterations of the plasma membrane phosphatidylserine asymmetry. These effects lead to the adhesion of RBCs to the endothelium and the development of microcirculation disorders [40].

Although the prothrombotic state in HF has a multifactorial in nature, namely due to the low cardiac output, dilatation of heart chambers, and peripheral blood stasis, endothelial damage/dysfunction is also positioned as an important factor in pathogenesis of thrombotic complications in such patients. The antithrombotic properties of the intact endothelium are significantly impaired in case of ED. For example, excessive exposure to proinflammatory cytokines in HF induces the expression of tissue factor, which is a trigger of the extrinsic coagulation cascade. Additionally, it should be noted, that tissue factor is a significant predictor of poor prognosis in chronic HF [1-3].

In disease states, leading to HF development and progression, such as arterial hypertension, coronary and extra-coronary atherosclerosis, diabetes mellitus, abnormal RBCs and RBCs-derived MVs may adhere to the endothelium or extracellular matrix, activate platelets and other cells, and enhance local thrombin generation, favoring thrombus formation. At the same time, the antithrombotic RBCs-related influences could be mediated by RBCs modulation of endothelial cell activation (through release of NO, NO equivalents and ATP). However, the relationship between RBCs and the physiological and pathological aspects of the hemostasis system is more complex, which warrants further research, in particular to elucidate the clinical implementation of the obtained results [27, 41].

Pharmacological implications involving certain pathophysiological aspects of ED in HF: classic and modern approaches. Taking into account the important pathogenetic and prognostic significance of ED in HF, the endothelium is considered as a target of various pharmacological influences [2, 9]. In the context of classical neurohormonal model of HF pathogenesis, that activation of the renin-angiotensin-aldosterone axis adversely affects the functional state of endothelial cells and disrupts the NO signaling pathway [1-3, 8]. In HF patients, the clinical efficacy of renin-angiotensin-aldosterone inhibitors, such as angiotensin-converting enzyme inhibitors (ACEis) and mineralocorticoid receptor antagonists (MRAs), is at least in part due to their positive effect on the vascular endothelium [2].

The ACEis provide favorable modulation or recovery of the ED in HF via the series of mechanisms, including the suppression of ROS generation, reduction in production of vasoconstrictor prostanoids, upregulation of eNOS and inhibition of endothelial cells apoptosis [2, 9]. An advantageous effect of ACEis on the functional state of the endothelium in the form of improvement the endothelium-dependent vasodilation has been demonstrated in a number of studies [42], although the ability of different ACEis molecules to restore endothelial function may differ significantly [2]. At the same time, one should bear in mind that current evidence is lacking to justify the preference of particular ACEis based on their endothelial effects [2].

Statins constitute another classic group of cardiovascular drugs, with an endothelium being one of their treatment targets. According to the results of the majority of reported trials, statins improve the functional state of endothelium in HF regardless of its cause. Statins possess a plenty of pleiotropic properties, but the exact mechanisms of the action on ED are not clearly defined, and appear to be independent of their cholesterol-lowering effects. Given the current evidence for the use of statins in HF, the presence of ED cannot be an independent indication for statin therapy in such patients [2, 4, 5].

The pharmacological manipulation of the NO biological system is one of the oldest concepts in HF treatment, with the huge efforts have been made in this area, but the results have, until now, been disappointing. Nitrates, being the exogenous source of NO and modulators of the NO-sGC-cGMP signaling pathway, are still used in chronic HFrEF, but, except when used in combination with hydralazine (possessed antioxidant properties) in self-identified black patients, do not have robust contemporary evidence demonstrating any effect on outcomes and are badly affected by tachyphylaxis [4, 5, 9, 23, 24].

A number of other classes of medications, such as phosphodiesterase-5 inhibitors (sildenafil), xanthine oxidase inhibitors (allopurinol), tumor necrosis factors inhibitors (etanercept) and growth hormone, have shown favorable effects on ED in HF, but the clinical utility of such effects remains controversial until results of appropriately designed randomized trials are available [2].

An insufficient supply of L-arginine, being a substrate for eNOS to produce NO, is suggested to be a pathophysiological factor in ED development. Additionally, L-arginine supplementation reduces the concentration of asymmetric dimethylarginine, known to be endogenous NO inhibitor, which is elevated in HF. However, the longer-term effects of L-arginine supplementation and its impact on clinical outcomes in HF are the matter of uncertainty. Thus, according to currently available evidence, the routine use of L-arginine supplements is not justified in HF patients [2].

Discussing the modern approaches to pharmacological treatment of HF, it should be noted that the correction of reduced NO bioavailability by modulating the NO-sGC-cGMP signaling pathway is a perspective option in terms of preventing the occurrence and progression of ED [1-3, 6-8, 21-24]. It has also been a challenge to capture the potentially beneficial effects of NO without provoking its potentially cytotoxic effects related to RONS production. In this context, it is important that the beneficial properties of NO seem to be implemented via the sGC-dependent mechanisms, while the adverse effects are independent phenomena. In this regard, sGC *per se* is considered to be a particularly attractive therapeutic target [24].

At present, the preclinical data suggest that the support of sGC activity could be a perspective approach to the problem of cardioprotection by preventing cardiac and vascular remodeling, that develops due to the accumulation of extracellular matrix, fibrosis, ischemic/reperfusion myocardial damage, biomechanical stress, as well as apoptosis of cardiomyocytes and mitochondrial dysfunction [22, 43-45].

The so-called sGC activators were the first synthesized molecules capable of affecting the activity of the enzyme. The pathophysiological prerequisite for their pharmacodynamic properties is that oxidative stress, associated with cardiovascular disease, may change sGC-associated heme from a ferrous to ferric state, weakening its binding to sGC and consequently producing a relatively NO-resistant state. Accordingly, sGC activators, such as cinacig-

uat, can bind to sGC with or without haem and activate it directly, which is suitable when sGC function is impaired by oxidation. This leads to an increase in cGMP production even under conditions of reduced NO bioavailability [6, 8, 21-24, 43]. Cinaciguat has been shown to improve hemodynamics in patients with acute decompensated HF; however, at high doses, it has been associated with significant hypotension, which resulted in the termination of early clinical studies [46].

On the other hand, the sGC stimulation is a fundamentally new approach, which implies a dual mechanism of action: an increase in the sensitivity of sGC to endogenous NO by stabilizing its nitrosyl-heme interaction, as well as direct stimulation of the heme-containing unoxidized native form of sGC through another binding site, irrespective of NO. Thus, such sGC stimulation mechanism allows this class of drugs to promote cGMP production in NO-independent manner, and to act synergistically with NO, which is suitable for use when sGC has normal function, but the concentration of NO is low, i.e. under the conditions of its reduced bioavailability [1-3, 6, 8, 9, 21-24, 43].

Vericiguat is one of the sGC stimulators synthesized to date, with its major pharmacodynamic effect as an increase of cGMP production important for cardioprotection. Vericiguat is characterized by indirect activation of cGMP-dependent protein kinases involved in signaling pathways, which are protective in the context of counteracting myocardial hypertrophy and fibrosis. Preclinical research results suggest that sGC stimulation with veriguat can also activate oxidized forms of protein kinases. In addition to this unique mechanism of action, vericiguat causes smooth muscle relaxation with the consequent vasodilation [43].

Vericiguat has been studied in several phase-II trials (SOCRATES-PRESERVED, SOCRATES-REDUCED and VITALITY-HFpEF), and one phase-III trial, namely VICTORIA [23]. Particularly, the Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction (VICTORIA) [47], enrolled higher risk HF patients with left ventricular ejection fraction <45%, and demonstrated a significant reduction in a composite end point of cardiovascular death or HF hospitalization among those who received vericiguat, as compared to placebo.

Based on the results of VICTORIA [47], the latest European Society of Cardiology guidelines position vericiguat as a treatment option, which may be considered in patients in NYHA class II-IV, who have had worsening HF despite treatment with ACEis (or *angiotensin receptor-neprilysin inhibitor*), beta-blockers and an MRAs, to reduce the risk of CV mortality or HF hospitalization [4]. In like manner, recently published AHA/ACC/HFSA guidelines point that, in selected high-risk patients with HFrEF and recent worsening of HF already on guideline-directed medical therapy, an oral sGC stimulator (vericiguat) may be considered to reduce HF hospitalizations and CV death [5].

In the context of continuing further research regarding vericiguat, two new trials in HF were launched, namely VICTOR (a phase III trial, intending to expand the applicable population of vericiguat in HFrEF patients) and NCT05086952 (a phase I trial of a new liquid formulation of vericiguat) [6].

Thus, vericiguat, as a sGC stimulator, represents a modern approach to harnessing the therapeutic potential of NO pathway. In contrast with the neurohormonal blockers, vericiguat, being an agonist, stands alone in its mechanism of action and complements the existing armamentarium of contemporary HF treatment options. The conceptual approach to medical treatment of HF, used in the development of vericiguat, involves certain pathophysiological aspects of ED, and serves to highlight the importance of efforts to boost the endogenous mechanisms of cardioprotection. In this context, further basic, clinical and translational studies are obviously required to evaluate in more detail the prospects of new classes of drugs in the treatment of various HF phenotypes [7, 8, 24, 48].

CONCLUSION

Despite the successful implementation of current guideline-directed pharmacotherapy, the natural history of HF is characterized by its steady progression, which, at least in part, is related to highly complex and multi-linked HF pathophysiology. Among these links, one should recognize the exceptional role of the alterations in peripheral circulation, in particular the ED development.

Although the problem of disorders in the functional state of endothelium has been known for a long time, the unfading interest in its further study is supported by the understanding of ED as a stage of the so-called «endothelial continuum», as well as by defining the role of endothelium in the complex architecture of interactions both with cardiomyocytes and with components of the blood system, in particular RBCs. In addition, the deepening of knowledge about the pathophysiological features of ED in HF allows both to improve the understanding of the pharmacodynamic effects of already classical cardiovascular drugs (in particular, renin-angiotensin-aldosterone inhibitors and statins), and to outline the perspectives for pharmacological direct or indirect «endotheliotropic» effects.

Among such perspective directions, the effects on various intracellular signaling pathways are of scientific and practical interest, particularly the NO-sGC-cGMP one. To date, the sGC stimulation is a possible pharmacological option regarding the impact on this pathway, which is promising in the context of cardioprotection and its justifiable use under the conditions of ED and reduced NO bioavailability. Vericiguat, being a sGC stimulator, is currently the only representative of this class of drugs that has occupied its «niche» in the current guidelines for the management of HF patients.

Even though the preclinical studies on sGC stimulators demonstrate the attractive results, and the clinical data on vericiguat seem to be promising, one should account for the available armamentarium of effective, prognosis-modifying guideline-directed groups of drugs for the treatment of HF patients, thus there is a strong need for further research, aiming a number of practical issues to be elucidated. In particular, it is essential to identify the additional positive prognostic properties of sGC stimulators, namely vericiguat, as well as to determine their significance for optimizing the personalized treatment of patients with various HF phenotypes. Probably, such an approach, regarding the translation of the existing fundamental pathophysiological concepts into clinical practice, is equally valid for other available or perspective pharmacological options, pretending both to improve the functional state of endothelium and to modulate the endogenous mechanisms of cardioprotection.

FUTURE PERSPECTIVES

In the context of future research in the field of peripheral circulatory disorders in HF, a number of directions deserve attention, in particular the following: 1) the deepening of understanding the role of genetic, molecular and biophysical factors, involved in the interactions between cardiomyocytes, endothelium and the blood system; 2) a comprehensive analysis of the epigenetic mechanisms of regulation of endotheliocytes at various stages of the «endothelial continuum»; 3) the reveal of novel therapeutic approaches for the improvement of microcirculation and boosting the endogenous mechanisms of cardioprotection, based on the findings from the studies of intracellular signaling pathways and intercellular cross-talks in HF; 4) further elucidating the role of extracellular vesicles, derived from endothelium and other cells, in HF development and progression, as well as clarifying their therapeutic potential in such patients; 5) integrating the basic science data with the evidence from large-scale well-conducted clinical trials, with the aim to maximize the potential of novel treatments for patients with different HF phenotypes, and to optimize the individualized HF management, while minimizing the potential risks of polypharmacy.

Conflicts of interest. Nothing to declare.

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REFERENCES

1. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine / Ed. by P. Libby, R.O. Bonow, D.L. Mann, G.F. Tomaselli, D. Bhatt, S.D. Solomon, E. Braunwald. Elsevier, 2022. 2032 p.
2. Heart Failure: A Companion to Braunwald's Heart Disease / Ed. by G.M. Felker, D.L. Mann. Elsevier, 2020. 760 p.
3. Fuster and Hurst's The Heart / Ed. by V. Fuster, J. Narula, P. Vaishnava, M. Leon, D. Callans, J. Rumsfeld, A. Poppas. McGraw Hill/Medical, 2022. 2432 p.
4. McDonagh T.A., Metra M., Adamo M., Gardner R.S., Baumbach A. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021. Vol. 42 (36). P. 3599-3726. doi: 10.1093/eurheartj/ehab368.
5. Heidenreich P.A., Bozkurt B., Aguilar D., Allen L.A., Byun J.J. et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022. doi: 10.1161/CIR.0000000000001063. Epub ahead of print.
6. Xia J., Hui N., Tian L., Liang C., Zhang J. et al. Development of vericiguat: The first soluble guanylate cyclase (sGC) stimulator launched for heart failure with reduced ejection fraction (HFrEF). Biomed Pharmacother. 2022. Vol. 149. P. 112894. doi: 10.1016/j.biopha.2022.112894.
7. Abdin A., Bauersachs J., Frey N., Kindermann I., Link A. et al. Timely and individualized heart failure management: need for implementation into the new guidelines. Clin Res Cardiol. 2021. Vol. 110 (8). P. 1150-1158. doi: 10.1007/s00392-021-01867-2.
8. Mann D.L., Felker G.M. Mechanisms and Models in Heart Failure: A Translational Approach. Circ Res. 2021. Vol. 128 (10). P. 1435-1450. doi: 10.1161/CIRCRESAHA.121.318158.
9. Endothelium and Cardiovascular Diseases: Vascular Biology and Clinical Syndromes / Ed. by P.L. Da Luz, P. Libby, A.C.P. Chagas, F.R.M. Laurindo. Elsevier, 2018. 758 p.
10. Microvascular Research: Biology and Pathology / Ed. by D. Shepro, P. D'Amore. Elsevier, 2006. 1296 p.
11. The Vascular Endothelium I / Ed. by S. Moncada, A. Higgs. Springer, 2006. 348 p.
12. The Vascular Endothelium II / Ed. by S. Moncada, A. Higgs. Springer, 2006. 365 p.
13. Krüger-Genge A., Blocki A., Franke R.P., Jung F. Vascular Endothelial Cell Biology: An Update. Int J Mol Sci. 2019. Vol. 20 (18). P. 4411. doi: 10.3390/ijms20184411.
14. Botts S.R., Fish J.E., Howe K.L. Dysfunctional Vascular Endothelium as a Driver of Atherosclerosis: Emerging Insights into Pathogenesis and Treatment. Front Pharmacol. 2021. Vol. 12. P. 787541. doi: 10.3389/fphar.2021.787541.

15. Sabe S.A., Feng J., Sellke F.W., Abid M.R. Mechanisms and clinical implications of endothelium-dependent vasomotor dysfunction in coronary microvasculature. Am J Physiol Heart Circ Physiol. 2022. Vol. 322 (5). P. H819-H841. doi: 10.1152/ajpheart.00603.2021.
16. Gallo G., Volpe M., Savoia C. Endothelial Dysfunction in Hypertension: Current Concepts and Clinical Implications. Front Med (Lausanne). 2022. Vol. 8. P. 798958. doi: 10.3389/fmed.2021.798958.
17. Segers V.F.M., Brutsaert D.L., De Keulenaer G.W. Cardiac Remodeling: Endothelial Cells Have More to Say Than Just NO. Front Physiol. 2018. Vol. 9. P. 382. doi: 10.3389/fphys.2018.00382.
18. Zuchi C., Tritto I., Carluccio E., Mattei C., Cattadori G., Ambrosio G. Role of endothelial dysfunction in heart failure. Heart Fail Rev. 2020. Vol. 25 (1). P. 21-30. doi: 10.1007/s10741-019-09881-3.
19. Lam C.S.P, Lund L.H. Microvascular endothelial dysfunction in heart failure with preserved ejection fraction. Heart. 2016. Vol. 102 (4). P. 257-259. doi: 10.1136/heartjnl-2015-308852.
20. Gladwin M.T. Endothelium Seeing Red: Should We Redefine eNOS as the Endothelial and Erythrocytic NOS? Circulation. 2021. Vol. 144 (11). P. 890-892. doi: 10.1161/CIRCULATIONAHA.121.055679.
21. Kassis-George H., Verlinden N.J., Fu S., Kanwar M. Vericiguat in Heart Failure with a Reduced Ejection Fraction: Patient Selection and Special Considerations. Ther Clin Risk Manag. 2022. Vol. 18. P. 315-322. doi: 10.2147/TCRM.S357422.
22. Sandner P., Follmann M., Becker-Pelster E., Hahn M.G., Meier C. et al. Soluble GC stimulators and activators: Past, present and future. Br J Pharmacol. 2021. doi: 10.1111/bph.15698. Epub ahead of print.
23. Tran B.A., Serag-Bolos E.S., Fernandez J., Miranda A.C. Vericiguat: The First Soluble Guanylate Cyclase Stimulator for Reduction of Cardiovascular Death and Heart Failure Hospitalization in Patients With Heart Failure Reduced Ejection Fraction. J Pharm Pract. 2022. doi: 10.1177/08971900221087096. Epub ahead of print.
24. Lang N.N., Dobbin S.J.H., Petrie M.C. Vericiguat in worsening heart failure: agonising over, or celebrating, agonism in the VICTORIA trial. Cardiovasc Res. 2020 Oct 1;116(12): e152-e155. doi: 10.1093/cvr/cvaa247.
25. Helms C.C., Gladwin M.T., Kim-Shapiro D.B. Erythrocytes and Vascular Function: Oxygen and Nitric Oxide. Front Physiol. 2018. Vol. 9. P. 125. doi: 10.3389/fphys.2018.00125.
26. Asaro R.J., Cabrales P. Red Blood Cells: Tethering, Vesiculation, and Disease in Micro-Vascular Flow. Diagnostics (Basel). 2021. Vol. 11 (6). P. 971. doi: 10.3390/diagnostics11060971.
27. Weisel J.W., Litvinov R.I. Red blood cells: the forgotten player in hemostasis and thrombosis. J Thromb Haemost. 2019. Vol. 17 (2). P. 271-282. doi: 10.1111/jth.14360.
28. Leo F., Suvorava T., Heuser S.K., Li J., LoBue A. et al. Red Blood Cell and Endothelial eNOS Independently Regulate Circulating Nitric Oxide Metabolites and Blood Pressure. Circulation. 2021. Vol. 44 (11). P. 870-889. doi: 10.1161/CIRCULATIONAHA.120.049606.
29. Lugo-Gavidia L.M., Burger D., Matthews V.B., Nolde J.M., Galindo Kiuchi M. et al. Role of Microparticles in Cardiovascular Disease: Implications for Endothelial Dysfunction, Thrombosis, and Inflammation. Hypertension. 2021. Vol. 77 (6). P. 1825-1844. doi: 10.1161/HYPERTENSIONAHA.121.16975.
30. Thangaraju K., Neerukonda S.N., Katneni U., Buehler P.W. Extracellular Vesicles from Red Blood Cells and Their Evolving Roles in Health, Coagulopathy and Therapy. Int J Mol Sci. 2020. Vol. 22 (1). P. 153. doi: 10.3390/ijms22010153.
31. Misiti F., Carelli-Alinovi C., Rodio A. ATP release from erythrocytes: A role of adenosine. Clin Hemorheol Microcirc. 2022. Vol. 80 (2). P. 61-71. doi: 10.3233/CH-221379.
32. Chiangjong W., Netsirisawan P., Hongeng S., Chutipongtanate S. Red Blood Cell Extracellular Vesicle-Based Drug Delivery: Challenges and Opportunities. Front Med (Lausanne). 2021. Vol. 8. P. 761362. doi: 10.3389/fmed.2021.761362.
33. Buttari B., Profumo E., Riganò R. Crosstalk between red blood cells and the immune system and its impact on atherosclerosis. Biomed Res Int. 2015. Vol. 2015. P. 616834. doi: 10.1155/2015/616834.
34. Jeney V., Balla G., Balla J. Red blood cell, hemoglobin and heme in the progression of atherosclerosis. Front Physiol. 2014. Vol. 5. P. 379. doi: 10.3389/fphys.2014.00379.
35. Tziakas D.N., Chalikias G.K., Stakos D., Boudoulas H. The role of red blood cells in the progression and instability of atherosclerotic plaque. Int J Cardiol. 2010. Vol. 142 (1). P. 2-7. doi: 10.1016/j.ijcard.2009.10.031.
36. Tziakas D., Chalikias G., Kapelouzou A., Tentes I., Schäfer K. et al. Erythrocyte membrane cholesterol and lipid core growth in a rabbit model of atherosclerosis: modulatory effects of rosuvastatin. Int J Cardiol. 2013. Vol. 170 (2). P. 173-181. doi: 10.1016/j.ijcard.2013.10.070.
37. Loyer X, Vion AC, Tedgui A, Boulanger CM. Microvesicles as cell-cell messengers in cardiovascular diseases. Circ Res. 2014. Vol. 114 (2). P. 345-353. doi: 10.1161/CIRCRESAHA.113.300858.
38. Papadopoulos C., Tentes I., Anagnostopoulos K. Lipotoxicity Disrupts Erythrocyte Function: A Perspective. Cardiovasc Hematol Disord Drug Targets. 2021. Vol. 21 (2). P. 91-94. doi: 10.2174/1871529X21666210719125728.
39. Tziakas D.N., Chalikias G., Pavlaki M., Kareli D., Gogiraju R. et al. Lysed Erythrocyte Membranes Promote Vascular Calcification. Circulation. 2019 Apr 23;139(17):2032-2048. doi: 10.1161/CIRCULATIONAHA.118.037166.
40. Dreischer P., Duszenko M., Stein J., Wieder T. Eryptosis: Programmed Death of Nucleus-Free, Iron-Filled Blood Cells. Cells. 2022. Vol. 11 (3). P. 503. doi: 10.3390/cells11030503.

41. Byrnes J.R., Wolberg A.S. Red blood cells in thrombosis. Blood. 2017. Vol. 130 (16). P. 1795-1799. doi: 10.1182/blood-2017-03-745349.
42. Münzel T., Gori T., Keaney J.F. Jr., Maack C., Daiber A. Pathophysiological role of oxidative stress in systolic and diastolic heart failure and its therapeutic implications. Eur Heart J. 2015. Vol. 36 (38). P. 2555-2564. doi: 10.1093/eurheartj/ehv305.
43. Campbell N., Kalabalik-Hoganson J., Frey K. Vericiguat: A Novel Oral Soluble Guanylate Cyclase Stimulator for the Treatment of Heart Failure. Ann Pharmacother. 2022 May;56(5):600-608. doi: 10.1177/10600280211041384.
44. Park M., Sandner P., Krieg T. cGMP at the centre of attention: emerging strategies for activating the cardioprotective PKG pathway. Basic Res Cardiol. 2018. Vol. 113 (4). P. 24. doi: 10.1007/s00395-018-0679-9.
45. Yu J.D., Miyamoto S. Molecular Signaling to Preserve Mitochondrial Integrity against Ischemic Stress in the Heart: Rescue or Remove Mitochondria in Danger. Cells. 2021. Vol. 10 (12). P. 3330. doi: 10.3390/cells10123330.
46. Erdmann E., Semigran M.J., Nieminen M.S., Gheorghiade M., Agrawal R. et al. Cinaciguat, a soluble guanylate cyclase activator, unloads the heart but also causes hypotension in acute decompensated heart failure. Eur Heart J. 2013. Vol. 34 (1). P. 57-67. doi: 10.1093/eurheartj/ehs196.
47. Armstrong P.W., Pieske B., Anstrom K.J., Ezekowitz J., Hernandez A.F. et al. Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2020. Vol. 382 (20). P. 1883-1893. doi: 10.1056/NEJMoa1915928.
48. Schirone L., Forte M., D'Ambrosio L., Valenti V., Vecchio D. et al. An Overview of the Molecular Mechanisms Associated with Myocardial Ischemic Injury: State of the Art and Translational Perspectives. Cells. 2022. Vol. 11 (7). P. 1165. doi: 10.3390/cells11071165.

Резюме

ПОРУШЕННЯ ПЕРИФЕРІЙНОГО КРОВООБІГУ ПРИ СЕРЦЕВІЙ НЕДОСТАТНОСТІ: СУЧАСНИЙ ПОГЛЯД НА ЕНДОТЕЛІАЛЬНУ ДИСФУНКЦІЮ ТА ПАТОФІЗІОЛОГІЧНО ОБҐРУНТОВАНІ МОЖЛИВОСТІ ЇЇ ФАРМАКОЛОГІЧНОЇ КОРЕКЦІЇ

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Вступ. Незважаючи на суттєві успіхи у фармакотерапії хвороб системи кровообігу, зростання поширеності серцевої недостатності (СН) та її несприятливий прогноз лишаються однією з провідних медичних проблем в усьому світі. Складна патофізіологія СН характеризується залученням порушень периферійного кровоплину, зокрема виникненням ендотеліальної дисфункції (ЕД). Поглиблення розуміння природи ЕД та патофізіологічно обґрунтованих можливостей її фармакологічної корекції потенційно сприятиме оптимізації персоніфікованого підходу до ведення пацієнтів з СН.
Мета: здійснити огляд сучасних літературних даних щодо порушень периферійного кровообігу при СН, з фокусом на ЕД, а також окреслити можливі патогенетично обґрунтовані шляхи її фармакологічної корекції у таких пацієнтів.
Матеріал і методи. Тематичні наукові праці, опубліковані, переважно, впродовж останнього десятиліття, були використані як матеріал для дослідження. Методологія дослідження передбачала застосування бібліосемантичного методу та структурно-логічного аналізу.
Результати та обговорення. На теперішній час ЕД розглядається як стадія специфічного континууму, який ініціюється у вигляді «активації» ендотелію, і в подальшому просувається етапами його «дисфункції» та «пошкодження». Беручи до уваги важливу патогенетичну і прогностичну роль ЕД при СН, ендотелій позиціонується як мішень для різноманітних фармакологічних впливів, включаючи блокатори ренін-ангіотензин-альдостеронової системи і статини. Серед сучасних підходів до фармакологічного лікування СН, перспективним напрямом корекції зниженої біодоступності оксиду азоту (NO) є модуляція сигнального шляху «NO-солюбілізована гуанілатциклаза-циклічний гуанозинмонофосфат», з огляду на можливості такого механізму у попередженні виникнення та прогресування ЕД.
Висновок. Поглиблення уявлень про патофізіологічні особливості ЕД при СН дозволяє поліпшити розуміння фармакодинамічних ефектів уже схвалених до застосування кардіоваскулярних препаратів, а також окреслити перспективні шляхи прямого чи непрямого фармакологічного впливу на ендотелій.

Ключові слова: **периферійний кровообіг, серцева недостатність, ендотеліальна дисфункція, патофізіологія, фармакологічний вплив**