



Endothelial dysfunction: developmental mechanisms and therapeutic strategies

Dmitry V. Shcheblykin¹, Anton A. Bolgov¹, Mikhail V. Pokrovskii¹, Julia V. Stepenko¹,
Julia M. Tsuverkalova¹, Olesya V. Shcheblykina¹, Polina A. Golubinskaya², Liliya V. Korokina¹

¹ Belgorod State National Research University, 85 Pobedy St., Belgorod 308015, Russia

² Budgetary Healthcare Institution of the Voronezh Region “Voronezh Regional Clinical Ophthalmological Hospital”, 22 Revolutiitsii 1905 goda St. Voronezh 394000, Russia

Corresponding author: Olesya V. Shcheblykina (sheelvi31@gmail.com)

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Abstract

Introduction: Every year the importance of the normal functioning of the endothelial layer of the vascular wall in maintaining the health of the body becomes more and more obvious.

The physiological role of the endothelium: The endothelium is a metabolically active organ actively involved in the regulation of hemostasis, modulation of inflammation, maintenance of hemovascular homeostasis, regulation of angiogenesis, vascular tone, and permeability.

Risk factors for the development of endothelial dysfunction: Currently, insufficient bioavailability of nitric oxide is considered the most significant risk factor for endothelial dysfunction.

Mechanisms of development of endothelial dysfunction: The genesis of endothelial dysfunction is a multifactorial process. Among various complex mechanisms, this review examines oxidative stress, inflammation, hyperglycemia, vitamin D deficiency, dyslipidemia, excess visceral fat, hyperhomocysteinemia, hyperuricemia, as well as primary genetic defect of endotheliocytes, as the most common causes in the population underlying the development of endothelial dysfunction.

Markers of endothelial dysfunction in various diseases: This article discusses the main biomarkers of endothelial dysfunction currently used, as well as promising biomarkers in the future for laboratory diagnosis of this pathology.

Therapeutic strategies: Therapeutic approaches to the endothelium in order to prevent or reduce a degree of damage to the vascular wall are briefly described.

Conclusion: Endothelial dysfunction is a typical pathological process involved in the pathogenesis of many diseases. Thus, pharmacological agents with endothelioprotective properties can provide more therapeutic benefits than a drug without such an effect.

Keywords

endothelium, endothelial dysfunction, biomarkers, therapeutic strategies.

Introduction

Since the discovery in 1980 that acetylcholine-mediated vasodilation requires the presence of endothelial cells (Furchgott and Zawadzki 1980), the importance of the endothelial layer of the vascular wall for vascular homeostasis has become increasingly apparent. Endothelial dysfunction is an integral part of the pathophysiology of various diseases, including hypertension, atherosclerosis, chronic heart failure, coronary heart disease (CHD), diabetes mellitus, chronic renal failure, oncological diseases and even mental disorders. Therefore, in order to develop therapeutic strategies, it is necessary to understand the key factors involved in maintaining endothelial function and the signaling pathways affecting endothelial dysfunction (ED).

The purpose of this article is to describe the function and main signaling pathways of oxidative stress, inflammatory factors, as well as metabolic disorders leading to the development of ED, to consider currently available biochemical markers of ED, as well as promising therapeutic strategies for the prevention and treatment of this pathology.

The physiological role of the endothelium

Blood vessels consist of connective tissue, fibroblasts, endothelial cells, and vascular smooth muscle cells. The inner surface of the blood vessel wall is covered with endothelium, which is a semi-permeable continuous monolayer of flat cells of mesenchymal origin between the bloodstream and the vessel wall. Due to dense specialized intercellular connections, the endothelium forms a barrier that selectively restricts the movement of macromolecules (Rahimi 2017). The barrier plays an important role in maintaining vascular tone, fluid homeostasis, and body protection (Zhang et al. 2018).

For many years, the endothelium was considered only to be a cellular barrier. But numerous studies have shown a much more complex role of the endothelium. The endothelium is not only a highly selective barrier, but also a metabolically active system, not least involved in maintaining vascular homeostasis, regulating the balance between vasodilation and vasoconstriction (Kasprzak et al. 2006). Vasoconstriction is provided by the following factors: endothelin-1 (ET-1), angiotensin II, prostaglandin H₂, and thromboxane A₂ (Bonetti et al. 2003). Nitric oxide (NO) (formerly known as endothelial relaxation factor), endothelin depolarization factor (EDHF), prostacyclin or natriuretic peptides are responsible for vasodilation (Busse and Fleming 2006; Moncada and Higgs 2006; Spieker et al. 2006). Vasodilating endothelial factors also have antiaggregational properties, inhibit the formation of blood clots, vascular stenosis and, in the case of NO/cGMP (cyclic guanosine monophosphate), also prevent myocardial hypertrophy (Ritchie et al. 2009).

Not so long ago, hydrogen sulfide (H₂S) was identified as a new vasodilator produced by endothelial cells (Yang et al. 2008) that acts in conjunction with NO (Cortese-Krott et al. 2015; Yuan et al. 2015). Regulation of vascular tone by H₂S is carried out both by direct action on vascular smooth muscle cells and by endothelium-dependent pathway (Wang et al. 2015). The main mechanism of H₂S-induced vasodilation is associated with the activation of ATP-sensitive K⁺(ATP) channels of vascular smooth muscle (Zhao et al. 2001). The involvement of K⁺ATP channels in the H₂S-mediated regulation of vascular tone is further confirmed by the effects of vasodilation blockade by the K⁺ATP channel inhibitor glibenclamide (Webb et al. 2008). In addition, H₂S potentiates the NO-mediated vasodilating effect by inhibiting phosphodiesterase-5 (PDE-5), prolonging the half-life of cGMP, which is a key mediator in vasoactive NO signals (Bucci et al. 2010).

Under physiological conditions, due to the controlled synthesis and release of biologically active substances (Table 1) (Melnikova and Makarova 2015), the endothelium has the ability to maintain a balance between its multidirectional functions: regulation of the hemostasis system, modulation of inflammation, maintenance of hemovascular homeostasis, regulation of angiogenesis, vascular tone, and permeability.

Table 1. Factors synthesized in the endothelium determining its functions (Melnikova and Makarova 2015)

Group	Function	Biologically active substances
Factors affecting vascular smooth muscle tone	narrowing of blood vessels	endothelin-1, angiotensin II, thromboxane A ₂ , prostaglandin H ₂
	dilation of blood vessels	nitric oxide, prostacyclin, endothelin depolarization factor, angiotensin I, adrenomedullin, hydrogen sulfide
Hemostasis factors	prothrombotic	platelet growth factor, plasminogen tissue activator inhibitor, Willebrand factor (blood clotting factor VIII), angiotensin IV, endothelin-1, fibronectin, thrombospondin, platelet activation factor
	antithrombotic	nitric oxide, tissue plasminogen activator, prostacyclin, thrombomodulin
Factors affecting growth and proliferation	stimulants	endothelin-1, angiotensin II, superoxide radicals, endothelial growth factor
	inhibitors	nitric oxide, prostacyclin, C-type natriuretic peptide, heparin-like growth inhibitors
Factors affecting inflammation	pro-inflammatory	tumor necrosis factor alpha, superoxide radicals, C-reactive protein
	anti-inflammatory	nitric oxide

The imbalance of these diverse vasoactive factors is fundamental to the development of ED (Frey et al. 2009; Tarafdard and Pula 2018). According to some data, glycocalyx plays an equally important role, located on the surface of endothelial cells facing the vascular bed and participating in the adhesion of leukocytes and platelets and,

consequently, in the function of the endothelium (Van den Berg et al. 2006). It should be emphasized that areas of the damaged endothelium can be renewed thanks to circulating endothelial progenitor cells (EPC), the qualitative and quantitative indicators of which significantly affect the outcomes and prognoses of cardiovascular diseases (Werner et al. 2005) and the functioning of the endothelium as a whole (Hill et al. 2003).

According to many researchers, just assessing the function of the endothelium may not be enough, since the functioning of the vascular wall cannot be considered in isolation from the functional state of the smooth myocytes that make it up (for example, a degree of activity of soluble guanylyl cyclase) (Stasch et al. 2006). Moreover, it is currently proven that the adipose tissue surrounding the vessels contributes to vascular homeostasis by producing vasoactive compounds such as adipokines, reactive oxygen species (ROS) and NO (Brown et al. 2014; Jankovic et al. 2017).

Risk factors for ED development

The clinical characteristic of ED is a violation of endothelium-dependent vasorelaxation in response to factors such as exposure to **acetylcholine** and **bradykinin**, or changes in blood flow. Although the mechanisms leading to ED are numerous, the main one, nevertheless, is a decrease in the bioavailability of NO. The

diagram (Fig. 1) shows that the reason for a decrease in the bioavailability of NO may be a decrease in the availability of **L-arginine** (Schlaich et al. 2004), the accumulation of **asymmetric dimethylarginine (ADMA)** (Gamil et al. 2020), changes in the interaction with heat shock protein 90 (Hp90) (Ou et al. 2003), and phosphorylation of endothelial NO synthase (eNOS) (Smith and Hagen 2003), as well as an increase in NO uptake due to an excessive amount of ROS accumulated due to the activity of NADPH and xanthine oxidases (Frey et al. 2009; Tarafdar and Pula 2018), and the separation of eNOS. In addition, it should be noted that changes in caveolin-1 (Darblade et al. 2001), tetrahydrobiopterin (BH4) (Topal et al. 2004), S-glutathionylation of eNOS (Chen et al. 2010; Kavoussi et al. 2019), and oxidation of low-density lipoproteins (oxLDL) (Fleming et al. 2005) are also involved in the separation of eNOS. It is important that a decrease in the expression of the eNOS protein also leads to a violation of the activity of eNOS and the production of NO, which are often observed in such cardiovascular diseases as atherosclerosis, acute myocardial infarction and heart failure in animals and humans (Fujii et al. 2002; Damy et al. 2004; Tonduangu et al. 2004).

The mechanisms underlying a decrease in the bioavailability of nitric oxide include both a decrease in the production of nitric oxide and increased absorption of nitric oxide. A decrease in NO production may be the result of:

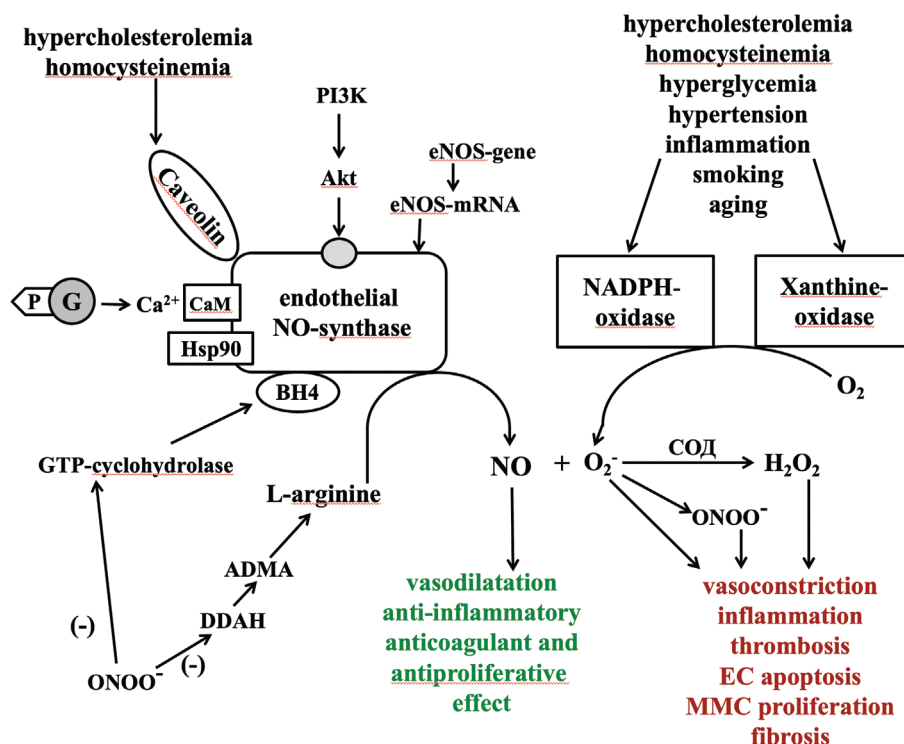


Figure 1. Mechanism of reducing the bioavailability of nitric oxide (Su 2015). **Notes:** NO – nitric oxide, eNOS – endothelial NO-synthase, CAM – calmodulin, ADMA – asymmetric dimethylarginine, DDAH – dimethylarginine dimethylaminohydrolase, BH4 – tetrahydrobiopterin, P – receptor, G – G-protein, Hsp90 – heat shock protein 90, PI3K – phosphatidylinositol-3-kinase, Akt – protein kinase B, NADPH is the reduced form of nicotinamide adenine dinucleotide phosphate, SOD – superoxide dismutase, ONOO – peroxynitrite, O₂⁻ – superoxide, O₂ – oxygen, H₂O₂ – hydrogen peroxide, EC – endothelial cells, MMC – smooth muscle cells (Su 2015).

- reduced availability of **L-arginine** due to its deficiency, disturbances in its transporter, or due to a combination of these phenomena;
- accumulation of **ADMA**, which is an endogenous eNOS inhibitor;
- deficiency of the BH4 cofactor or its modification;
- increases in caveolin-1, leading to a change in the interaction between it and eNOS;
- changes in G-proteins associated with the receptor;
- changes in the interaction of eNOS with Hsp90 due to changes in the content of Hsp90;
- changes in calcium-independent phosphatidylinositol-3-kinase (PI3K) / protein kinase B (Akt) – mediated activation of eNOS due to tyrosine or serine phosphorylation;
- as well as a decrease in eNOS expression as a result of a decrease in the transcription of the eNOS gene and/or a decrease in the stability of the eNOS mRNA.

Increased absorption of NO by ROS and reactive forms of nitrogen (RFA) may be associated with:

- separation of eNOS associated with changes in BH4, caveolin-1 and oxLDL;
- increased expression of NADPH and its activity;
- and increased expression and activity of xanthine oxidase.

The mechanisms underlying ED in various diseases may vary according to the factors contributing to the development of each specific disease.

Mechanisms of ED development

Under physiological conditions, vasodilation, synthesis of aggregation inhibitors, coagulation and fibrinolysis activators, anti-adhesive substances by endothelial cells prevail. ED implies a violation of the production of various messengers produced by the endothelium (as well as smooth muscles, perivascular adipose tissue), which leads to a vasoconstrictor, proinflammatory and proathrombotic phenotype, leading to a violation of the regulation of vascular tone and vascular permeability.

The development of ED is a multifactorial process. Among the many complex mechanisms, oxidative stress is probably the most common cause underlying the development of ED. Oxidative stress develops with excessive formation of free radicals and insufficient mechanisms of antioxidant defense systems. Most risk factors for cardiovascular diseases also contribute to the development of intracellular oxidative stress and increased production of ROS, which contributes to the activation of NADPH oxidase, inactivation of NO, formation of peroxynitrite (ONOO⁻), inhibition of eNOS activity, stimulation of endothelin expression, etc. (Förstermann and Münzel 2006).

Another common mechanism for the development of endothelial dysfunction is inflammation, and there is a

high probability that there is a direct relationship between the inflammatory process and oxidative stress (Karbach et al. 2014). Under normal conditions, the endothelium regulates vascular inflammation by releasing NO. However, the damaged endothelium contributes to the formation of ROS and thereby exacerbates vascular inflammation, which adversely affects the vascular wall. Oxidative stress can increase inflammation of the vascular wall, and inflammatory cells increasingly secrete superoxide radicals (Karbach et al. 2014), potentiating oxidative stress. There are many inflammatory markers associated with ED. C-reactive protein (CRP) is an acute-phase inflammatory protein, which is released in response to various types of inflammation. Experimental studies have shown that CRP directly contributes to the early phase of atherosclerosis due to deposition on the intima, even before the appearance of monocytes (Torzewski et al. 2000). In addition, CRP directly affects the bioavailability of NO, which leads to the development of oxidative stress, and as a consequence of ED and intimal hyperplasia. CRP acts directly through a lectin-like oxidized low-density lipoprotein receptor, which plays a crucial role in oxLDL-induced ED in human aortic endothelial cells (Li et al. 2004). Inflammation is also associated with overexpression of tumor necrosis factor- α (TNF- α) and interleukin-1, which contribute to the attachment and migration of leukocytes (Barton 2013). In addition, these inflammatory cytokines induce endothelial cells and leukocytes to express adhesion molecules such as vascular cell adhesion molecules (VCAM) and intercellular adhesion molecules (ICAM), chemotactic monocyte protein-1, E-selectin, P-selectin and interleukin-6, which leads to increased ED (Blake and Ridker 2001).

The endothelial function can also be disrupted by infectious agents and immuno-mediated damage developing due to their effects (Epstein et al. 2000). According to population studies, infectious agents can cause predisposition of patients to cardiovascular diseases and their clinical manifestations. Viruses, such as cytomegalovirus and herpes simplex virus-1 and bacteria such as *Chlamydia pneumoniae* and *Helicobacter pylori*, are reported to be associated with the development of various forms of coronary heart disease in humans (Pothineni et al. 2017). It was shown that the titers of immunoglobulin-G antibodies to cytomegalovirus, hepatitis A virus, herpes simplex virus-1, *Chlamydia pneumoniae* and *Helicobacter pylori* were independent risk factors for ED and the presence of coronary heart disease. Therefore, it is possible that due to infection with these pathogens, common significant immunological pathways may develop, as a result of activation of which endothelial damage occurs and the development of pathological conditions mediated by ED (Grabczewska et al. 2006).

In light of recent events, there are more and more reports that COVID-19 affects organs other than the lungs, primarily the heart and kidneys (Fanelli et al. 2020; Yang et al. 2020). Due to the tissue tropism of SARS-CoV-2 for cells expressing angiotensin converting enzyme 2 (ACE2), another major important target for infection is the

vascular endothelium (Monteil et al. 2020). Studies show that APF2 is abundantly expressed on vascular endothelial cells of both small and large arteries and veins (Hamming et al. 2014) demonstrated the structures of virus inclusion in the endothelial cells of glomerular capillary loops and signs of widespread endotheliitis in the heart, lungs, kidneys, liver and gastrointestinal tract in pathological samples from patients with severe COVID-19 (Varga et al. 2020). Damage to the endothelium and its dysfunction in coronavirus infection may be the result of direct infection with SARS-CoV-2 (for example, by induction of intracellular oxidative stress (Khomich et al. 2018), as well as due to a deep systemic inflammatory reaction.

In addition, hyperglycemia is known to disrupt endothelial function (Avogaro et al. 2008). Interestingly, even in subjects with normoglycemia who have a high risk of diabetes and insulin resistance, ED was observed during an oral glucose tolerance test (Title et al. 2000). The mechanisms of ED in patients with diabetes mellitus are associated with a decrease in NO synthesis and increased production of vasoconstrictors (Johnstone et al. 1993). The results of scientific studies show that in patients with diabetes, oxidative stress, NADPH oxidase and eNOS dissociation play an important role in the development of ED (Hsueh et al. 2004). Hyperglycemia also leads to the formation of advanced glycation endproducts (AGE), which are products of non-enzymatic glycation of proteins and lipids. AGEs accumulate in the vessel wall, alter the structural integrity of the endothelium and basement membrane and are able to interfere with the activity of NO. This significantly contributes to the development of ED. In addition, AGEs bind to specific surface receptors that are expressed on cells such as monocytes, macrophages and vascular smooth muscle cells, which leads to an increased inflammatory response, increased vascular permeability and oxidative stress (Soldatos et al. 2005; Avogaro et al. 2008). Vitamin D deficiency (1 α , 25-dihydroxycholecalciferol) becomes a new candidate among the causes of ED development. Vitamin D appears to be indirectly involved in the development of endothelial dysfunction and systemic inflammation. The presence of vitamin D receptors on the surface of endothelial cells has been shown (Kassi et al. 2013). In patients with sub-clinical atherosclerosis and slow coronary blood flow, a strong association was found between vitamin D deficiency and ED (Oz et al. 2013). There are reports in scientific papers that vitamin D stimulates the production of NO in endothelial cells by activating eNOS (Wong et al. 2010; Khan et al. 2018). Recent experimental studies in vivo and in vitro allow us to say with confidence that the vitamin D analog (22-oxacalcitriol) significantly suppresses the increased expression of NADPH oxidase, while increasing eNOS binding, thereby reducing oxidative stress in the endothelium (Oz et al. 2013). Moreover, vitamin D protects endothelial cells from oxidative stress, preventing the formation of superoxide radicals, and apoptosis.

Also, some studies say that high cholesterol, LDL and low HDL levels are independently associated with ED and

inflammation (Mineo et al. 2006). In patients with hypercholesterolemia, a violation of the activation of the metabolic pathway of L-arginine (substrate NO) was found (Hadi et al. 2019). In patients with coronary artery disease and dyslipidemia, it was suggested that increased degradation of NO under the action of ROS, since the infusion of L-arginine partially normalized the impaired function of the coronary endothelium (Czirák et al. 2020). Possible mechanisms underlying dyslipidemia-induced ED include: 1) activation of NADPH oxidase, development of oxidative stress and increased production of superoxide radicals (O₂⁻); 2) increased plasma ADMA levels; and 3) LDL oxidation. ADMA is an endogenous eNOS inhibitor, which competes with L-arginine for the same binding site on eNOS, which leads to eNOS dissociation. As a result, O₂ production increases and NO production decreases (Antoniades et al. 2009). OxLDL cause vasoconstriction by suppressing the action of endothelium-dependent vasodilators and increasing endothelin expression; stimulate proliferation and migration of smooth myocytes, proliferation and subendothelial infiltration of monocytes; increase the production of adhesive molecules by endothelial cells (ICAM, VCAM), stimulate aggregation and adhesion to endothelial cells of leukocytes and platelets, increase coagulation activity of the endothelium, inducing the release of tissue factor and inhibiting fibrinolysis; stimulate the formation of ROS, increase apoptosis, etc. (Markov 2005).

Excess visceral fat is also one of the most important factors in the occurrence and progression of ED. The idea of adipose tissue as an organ of accumulation and storage of energy substrates has finally become a thing of the past. Today, adipose tissue is considered as an important organ that synthesizes many hormone-like proteins. Among the adipocytokines synthesized by visceral fat, which play an important role in the pathogenesis of metabolic syndrome, TNF- α is known to disrupt the function of endothelial cells by increasing insulin resistance and its pro-inflammatory effect (Oz et al. 2013). Also, a number of clinical studies have shown that excess visceral fat is accompanied by a decrease in adiponectin synthesis. Adiponectin is a protein with antiarteriosclerotic activity, the receptor of which is located in vascular endothelial cells. NO is released when endothelial cells are stimulated by adiponectin, which is realized by activation of eNOS by adiponectin via AMP-activated protein kinase and the PI3K/Akt system (Deng et al. 2010). In patients with visceral obesity, as well as with diabetes mellitus, in whom the concentration of adiponectin is reduced, the endothelial function is weakened (Szydelko et al. 2020).

An unconventional factor leading to endothelial dysfunction is hyperhomocysteinemia. This is evidenced by animal models of hyperhomocysteinemia (Viridis et al. 2003). There are scientific data on the development of ED in patients with hyperhomocysteinemia without hypertension (Baszczuk et al. 2014). Studies on cells (Zhang et al. 2000), animals (Viridis et al. 2003; Khadieva et al. 2019) and humans (Salvio et al. 2021) show that homocysteine reduces the bioavailability of NO due to oxidative excess.

Through inhibition of **NO**, production of prostanoid vasoconstrictors, inhibition of EDHF (Heil et al. 2004; Cheng et al. 2011), homocysteine causes activation of the angiotensin 1 receptor (AT1) and generation of ROS (Cheng et al. 2009). It also inhibits ENOS by increasing **ADMA** production by reducing dimethylargininodimethylaminohydroxylase (DDAH) activity (Stühlinger et al. 2001) and eNOS dissociation by reducing intracellular synthesis of BH4 (Topal et al. 2004), which leads to a decrease in bioavailability of **NO** and an increase in ROS formation. In addition, homocysteine suppresses eNOS expression in human endothelial cells (Zhang et al. 2007), causes endothelial damage, vascular deendothelization, and increases platelet adhesion (Harker et al. 1976). Homocysteine also increases the formation of ROS due to phosphorylation of NADPH oxidase (Siow et al. 2006), as well as due increasing the activity of ACE as a result of homocysteinylolation of ACE with the formation of angiotensin II, which activates NADPH oxidase (Huang et al. 2015). Increased cardiovascular risk in patients with hyperhomocysteinemia may be explained by the mechanisms described above. This is especially important for patients with chronic renal failure, who often have elevated homocysteine levels, which, as shown in recent studies, makes it possible to predict cardiovascular outcomes (Zhang et al. 2020; Shih et al. 2021).

Impaired endothelial cell function is also associated with high plasma uric acid levels (Tomiya et al. 2011; Maruhashi et al. 2018). The pathological effect of uric acid on endothelial cells is apparently promoted by a number of different surface membrane carriers of urates, such as Glut-9 and URAT-1 (Price et al. 2006; Liu et al. 2017). As a result, the formation of chemokines and ROS is stimulated, as well as the activation of adhesion molecules in combination with increased activity of NF- κ B (kappa-B nuclear factor) and a decrease in **NO** production, which contributes to the development of ED (Cai et al. 2017; Afonasyeva 2019; Yang et al. 2019).

To date, there is a lot of evidence that the cause of ED may be a primary genetic defect, as indicated by structural changes in the eNOS gene in Japanese patients with essential hypertension (Markov 2005), as well as a decrease in the synthesis of **NO** in the vessels and their endothelium-dependent dilation in adolescents with primary hypertension long before the first symptoms of the disease (Markov 2005) (apparently due to a genetic defect of endotheliocytes) (Panza et al. 1993). In addition, it became known that a violation of L-arginine-dependent synthesis of **NO** can be observed in individuals with normal blood pressure levels, which is interpreted as a primary genetic defect underlying the development of ED. According to some authors, a defect in the genes responsible for the production and intensity of degradation of endothelium-relaxing factors may potentiate the formation of ED. Thus, the nature of the primary factor contributing to the occurrence of ED is not completely clear.

There is a judgment that endothelial dysfunction, especially in hypertension, is probably associated with a

violation of the phosphatidylinositol signaling pathway/ Ca^{2+} . Since calcium ionophores stimulate the synthesis of **NO** by increasing the entry of calcium into endothelial cells regardless of the activation of membrane receptors, the presence of a structural defect or functional failure of these receptors or signaling mechanisms activated by these receptors in patients with arterial hypertension cannot be ruled out (Markov 2005).

Thus, the literature data indicate a complex pathogenesis of ED. All these factors are closely interrelated, and their effect on the endothelium is difficult to separate. The clinical significance of ED is associated with its role in the development and/or progression of many diseases, not only of the cardiovascular system (Sun et al. 2020; Little et al. 2021), but also rheumatological (Murdaca et al. 2012), oncological (Toya et al. 2020; Ching et al. 2021), mental disorders (Morris et al. 2020) and many others (Vairappan 2015; Ekeloef et al. 2020; Joffre et al. 2020). This prevalence of endothelial dysfunction suggests that it is a common link in the pathogenesis of almost all diseases. Probably, from these positions, ED can be put on a par with such universal damage mechanisms as activation of the immune system and inflammation, formation of ROS and oxidative stress, and some others. There are practically no diseases in which the above mechanisms are not activated to a greater or lesser extent. In addition, they are closely interrelated, including being the cause of ED.

Markers of endothelial dysfunction in various diseases

To assess ED, functional diagnostic methods have been developed, such as flow-mediated dilation, laser Doppler flowmetry, occlusive plethysmography, pulse wave propagation velocity measurement, and in vitro methods using endothelial cell cultures and isolated organs (Storch et al. 2017; Soldatov et al. 2018; Martins-Filho et al. 2020). However, functional methods are very time-consuming compared to laboratory methods for measuring the concentration of biomarkers in blood serum.

Currently, for the purpose of laboratory diagnosis of ED, a number of factors synthesized by endotheliocytes are being considered. The change in the level of these factors in biological fluids reflects a violation of the main functions of the endothelium: vasomotor, regulation of angiogenesis, barrier, adhesion and thromboresistance.

Obviously, to assess the function of the endothelium, it is possible to measure the concentration of **NO** metabolites, which is constantly released and metabolized into stable nitrite and nitrate ions. However, when studying the **NO** level in systemic arterial hypertension, ambiguous results were obtained (Vasina et al. 2017). The next marker of endothelial dysfunction is **ADMA**, which is a structural analog of **L-arginine** and inhibits the activity of all isoforms of NO synthase, disrupting the formation of **nitric oxide** in the endothelium (Zhang et al. 2017).

It is known that ADMA is a competitive analog of arginine; therefore, a decrease in the L-arginine/ADMA ratio is also very significantly associated with an increase in cerebrovascular risk (Tousoulis et al. 2015).

ET-1, a biologically active broad-spectrum peptide, can serve as another marker of ED reflecting the state of vasomotor function of the endothelium (Stepanova et al. 2019). ET-1 is expressed mainly in the endothelium (Davenport et al. 2016), and it is a factor that intensively stimulates vasoconstriction and mitotic activity of vascular muscle cells, fibroblasts, and cardiomyocytes. It also plays the role of a regulator of endothelial proliferation, stimulating endotheliocyte hyperplasia in low concentrations and their production of NO and prostacyclin. ET-1 serves as one of the significant markers of ED in a number of diseases: chronic and acute ischemic lesions of the brain and myocardium (Sapira et al. 2010), diabetes mellitus and its vascular complications (Sánchez et al. 2014; Sorrentino et al. 2018; Efimenko et al. 2022). In addition, this peptide is considered as a predictor of the severity and outcome of these pathological conditions.

Vascular Endothelial Growth Factor (VEGF) is known for its role in angiogenesis, promoting proliferation and migration of endothelial cells and increasing vascular permeability. VEGF is produced by endothelial and some other cells. The selective mitogenic activity of VEGF against endothelial cells suggests that its level in the blood can serve as one of the criteria for ED (Gershtein et al. 2015). At the same time, VEGF is a vital factor in the trophism of endothelial cells (Polverino et al. 2018), and an increase in its level in the blood can be compensatory, thereby indicating a favorable course of the pathological process, for example, in stroke (Gontschar et al. 2013).

Expression of the VEGF type 2 receptor (VEGFR-2) is limited to vascular endothelial cells. VEGFR-2 plays an important role in cell migration, endothelium-dependent vasodilation and angiogenesis, which makes it a good candidate for an ED marker (Lange et al. 2016).

Vasogibin-1 (VASH1) is a new, currently actively studied marker of ED, which is formed in endothelial cells under the action of VEGF and the main fibroblast growth factor. It has been experimentally proven that VASH1 prevents premature aging of endothelial cells and increases their resistance to stress (Miyashita et al. 2012), and with replicative aging of endotheliocytes, VASH-1 expression is significantly reduced (Takeda et al. 2016). For example, with the instability of atherosclerotic plaques of the carotid arteries, the production of this protein increases, reflecting active vascularization and inflammation and indicating the risk of ischemic stroke.

Endothelial cells play a key role in the transport of other cell types and metabolic substrates between the blood and the interstitial space. When these cells are activated by pro-inflammatory proteins, such as C-reactive protein, bacterial endotoxins, interleukin 1B, TNF- α , the expression of cell adhesion molecules, such as ICAM-1, VCAM-1 and E-selectin, increases. Transendothelial migration of leukocytes is realized through these molecules.

ICAM-1 is a member of the supergene family of immunoglobulins and a ligand for integrin β 2 molecules present on leukocytes (Hubbard and Rothlein 2000), and is highly expressed in endothelial cells and subendothelial macrophages (de Lemos et al. 2000). ICAM-1 mediates a number of intercellular interactions, including adhesion and migration of leukocytes to the vascular endothelial wall. Literature data support the hypothesis that ICAM-1 expression activates endothelial cells and leads to inflammation, which, in turn, is an important stage for the initiation and progression of atherosclerosis (Marzolla et al. 2017).

VCAM-1 expression is limited to endothelial cells (but sometimes to spindle cells). Unlike ICAM-1, which is produced in low concentrations, VCAM-1 is not expressed in healthy endothelial cells. It is assumed that VCAM-1 expression can lead to endothelial activation, since it increases monocyte recruitment and improves monocyte-endothelial interaction at the initial stages of atherosclerotic lesion formation (Habas and Shang 2018).

E-selectin belongs to the lectin family, participates in the attraction of leukocytes to the site of inflammation and is expressed by vascular endothelial cells, due to which it is a specific marker of endothelial activation (Hidalgo et al. 2007).

Markers of inflammation of CRP, CD40 ligand (CD40L), IL-18, chemotactic protein of monocytes 1, leading to endothelial activation, can act as markers of ED (Straface et al. 2010), since inflammation is an integral part of the development of atherosclerosis.

The endothelial damaging factor, in addition to CRP, is homocysteine, an amino acid formed in the body during methionine metabolism. Elevated homocysteine content is currently considered as an independent risk factor for the development of cardiovascular diseases (Afonasyeva 2019). Hyperhomocysteinemia is also noted in stroke (Murmu et al. 2018) and other pathological conditions, causing the development of ED.

8-hydroxy-2'-deoxyguanosine is a modified nucleoside that is a product of oxidative DNA damage caused by the action of ROS. Recent studies suggest that this compound can be considered as a fairly sensitive and specific early marker of ED in many pathological conditions, including malignant neoplasms, atherosclerosis, cardiovascular diseases and diabetes mellitus (Mahat et al. 2018).

Scientists suggest a direct relationship between elevated levels of circulating endothelial cells (CEC) in peripheral blood and a degree of endothelial damage in patients with atherosclerotic disease and vascular inflammation (Szmítko et al. 2003). Consequently, the amount of CEC measured by flow cytometry can serve as a marker of ED.

The enzyme myeloperoxidase can bind to glycosaminoglycans in the walls of blood vessels and disrupt the release of endothelial NO, which leads to local ED. Scientists have also recognized the role of this enzyme in the occurrence and development of atherosclerosis (Penathur and Heinecke 2007).

Markers of endothelial thromboresistance disorders include Willebrand factor and thrombomodulin, which are synthesized directly in the endothelium (Leite et al. 2020).

Endocan, or endothelial cell-specific molecule-1 (biomarker of ED), is a proteoglycan dermatan sulfate and is secreted in response to inflammation not only by vascular endothelial cells, but also by epithelial cells that line the distal tubules of the kidneys and bronchi (Zhang et al. 2012). On the one hand, endoxane increases VEGF-A expression and the interaction between VEGF-A and its VEGFR 2, increasing vascular permeability (Lee et al. 2014), and on the other hand, VEGF directly induces endoxane expression (Sun et al. 2019).

Another marker of ED is free fatty acids (FFA). FFA can increase ROS levels by increasing cytokine production in mononuclear cells. In addition, FFA can induce activation of the proinflammatory pathway NF- κ B in human endothelial cells. In this regard, FFA is considered an early biomarker of ED and atherosclerosis, which is important for the prevention and treatment of cardiovascular diseases (Badimon et al. 2012).

Along with the well-known role of the endothelium in the pathogenesis of cardiovascular diseases, it has been demonstrated that the proper functioning of the endothelium plays a role in human fertility (Santi et al. 2021). Since polycystic ovary syndrome is associated with the risk of cardiovascular diseases, early detection of ED is of clinical importance. In this case, scientists consider increased VEGF, matrix metalloproteinase 9, visfatin, pentraxin-3, and soluble lectin-like oxidized low-density lipoprotein receptor-1 as markers of ED (Dambala et al. 2019).

Thus, the assessment of ED using various markers should be complex, since not all of the compounds listed above have equally valuable prognostic significance. Therefore, the development of an optimal protocol for the diagnosis of ED is an urgent task for fundamental medicine at the present time. As ED indicators become clinically applicable, this may lead to an improved risk assessment methods that will help predict, prevent and treat cardiovascular diseases.

Therapeutic strategies

Evaluation of ED as a result of an imbalance in the formation of vasoactive messengers requires the development of new therapeutic approaches to the effect on the endothelium in order to prevent or reduce a degree of damage to the vascular wall.

Currently, it has been proven that the modification of a person's lifestyle and habits lead to an improvement in endothelial function. ED is one of the main damages caused by cigarette smoke (as well as vapors of electronic cigarettes and hookahs (Münzel et al. 2020)). Toxic substances that enter the bloodstream during smoking (for example, free radicals and reactive glycation products) can react with endothelial and cause various vascular damage (Prasad et al. 2015; Münzel et al. 2020). Cigarette smoking causes inflammation and also increases ROS production and lipid peroxidation (Yamaguchi et al. 2005; Barbieri et al. 2011). Cigarette smoke extracts

inhibit the activity of eNOS endothelial cells of the pulmonary artery by changing the pattern of phosphorylation of eNOS (Wagner et al. 2007), which leads to a decrease in the bioavailability of NO. Quitting smoking leads to an improvement in endothelial function (Delgado et al. 2020; Fukumoto et al. 2021).

Physical activity improves the condition of the endothelium (Hirata et al. 2013). Physical exercise causes an increase in NO production, both in normotensives and in patients with hypertension (Nystoriak and Bhatnagar 2018).

Weight loss also contributes to the restoration of endothelial function in obese patients. This is probably facilitated by the normalization of the production of cytokines released from visceral fat (Ziccardi et al. 2002).

Daily monitoring of blood glucose levels is one of the most important factors in ED correction (Chen et al. 2021). In turn, compensation for hyper- and dyslipidemia contributes to normalization of endothelial function (Kim et al. 2012) and reduction of cardiovascular risk (Chen et al. 2021).

An excessive amount of fat consumed daily in food stimulates the development of the initial signs of ED in practically healthy individuals. It has been experimentally shown that a high-fat diet stimulates the formation of oxygen free radicals (superoxide anions) that inactivate NO (Roberts et al. 2000). High salt intake suppresses the effect of NO in peripheral resistive vessels in animal hypertension modeling (Kurtz et al. 2018). A link between reduced NO production and high salt intake in clinical studies in patients with hypertension has also been demonstrated (Li et al. 2009; Boegehold 2013).

Polyunsaturated fatty acids, antioxidants, vitamins (especially, tocopherol and ascorbic acid), folic acid, and L-arginine have been found to have a beneficial effect on vascular endothelial function (Konovalova et al. 2019; Belenichev et al. 2021). They improve endothelium-dependent vasodilation both in patients at high risk of cardiovascular diseases and in healthy people without risk factors (Brown and Hu 2001; Kurtz et al. 2018).

In cases of smokers, diabetics, as well as patients with dyslipidemia and hypertension, vitamin C may be a substance that can improve the endothelium-dependent response (Engler et al. 2003; Sabri et al. 2016). By capturing superoxide, it increases the bioavailability of NO, inhibits lipid peroxidation, activation of platelets and neutrophils, and activation of adhesion molecules, which in turn inhibits endothelial cell damage (Matsumoto et al. 2003). Vitamin C captures RF produced by peroxidase and inhibits the oxidation of LDL mediated by myeloperoxidase/H₂O₂/ nitrite (Cai et al. 2017).

Vitamin E also has a protective effect on the endothelium in smoking and hypercholesterolemia (Engler et al. 2003), but its effect on diabetes remains controversial (Skyrme-Jones et al. 2000; Economides et al. 2005). Vitamin E acts as a fat-soluble antioxidant, trapping hydroperoxyl radicals in the lipid environment (Traber and Stevens 2011). The intake of antioxidants (vitamin E, C) contributes to the correction of endothelial function and

inhibits the thickening of the intima of the carotid artery (Frey et al. 2009).

N-acetylcysteine is an interchangeable amino acid that is mainly used in the treatment of cough. However, in the course of experimental studies, it turned out that it has pronounced antioxidant properties, acting on the production of glutathione, which protects the cardiovascular system from the harmful effects of TNF- α , which causes the production of ROS using NADPH oxidase and ceramide (Adamy et al. 2005; Scioli et al. 2014). Its action has a positive effect on the vessels in relation to the endothelium-dependent response, and it does not matter whether they were affected by atherosclerosis (Andrews et al. 2001). The effect of **N-acetylcysteine** on ED is mediated not only through a decrease in NADPH oxidase expression and suppression of leukocyte adhesion and secretion of inflammatory cytokines (Scioli et al. 2014), but also by inhibition of Willebrand factor-dependent platelet aggregation and collagen binding in human plasma and in mice (Chen et al. 2011), attenuation of expression matrix metalloproteinase in microvascular endothelial cells in rats (Bourraindeloup et al. 2004), as well as inhibition of caveolin-1 activation and improvement of endothelial barrier function in mice (Beauchesne et al. 2010). These multiple effects contribute to the pronounced endotheliotective action of **N-acetylcysteine**. **N-acetylcysteine** interacts with endogenous and exogenous vasodilators. Moreover, in patients with systemic atherosclerosis, **N-acetylcysteine** causes vasodilation (Salsano et al. 2005) and in hypertensive patients it potentiates the hypotensive effects of angiotensin converting enzyme (ACE) inhibitors, thereby exhibiting vasoactive properties (Barrios et al. 2002).

Genistein (soy phytoestrogen) weakens ED in rats with hypertension and rats with hyperhomocysteinemia. This is achieved by increasing the activity and expression of eNOS and reducing the production of cytokines and ROS (Cho et al. 2011; Zhen et al. 2012). **Genistein** also increases the concentration of nitrites/nitrates and reduces the levels of ET-1 in plasma (Ou et al. 2003). Thus, **genistein** may be effective for the treatment of ED that occurs in connection with atherosclerosis and hypertension.

Resveratrol (phytoestrogen with antioxidant properties) is a promising multi-purpose therapeutic agent for the correction of endothelial dysfunction. According to experimental studies, **resveratrol** modulates several processes associated with endothelial dysfunction, such as vasorelaxation disorders, eNOS dissociation, oxidative stress, leukocyte adhesion, endothelial aging, smooth muscle proliferation and vascular remodeling (Gumanova et al. 2007; Kochkarov et al. 2008; Gureev et al. 2010). It was found that the endothelial protective effects of resveratrol are mediated by numerous molecular targets (Li et al. 2019; Parsamanesh et al. 2021) (for example, sirtuin-1 (SIRT1), 5' AMP-activated protein kinase (AMPK), endothelial nitric oxide synthase (eNOS), redox-sensitive transcription factor of nuclear erythroid origin (Nrf2), the receptor activated by the proliferator peroxisome (PPAR), Krüppel-like factor-2 (KLF2) and nuclear factor

“kappa-bi” (NF-kB)). Considering the fact that **resveratrol** is contained in large quantities in grapes and red wine, one of the promising directions may be an another therapeutic approach to the correction of endothelial dysfunction.

It has been experimentally revealed that ACE inhibitors exhibit endotheliotective properties when administered to animals with heart failure (Varin et al. 2000) and those suffering from coronary heart disease (Bots et al. 2007). This effect is associated with both a decrease in the level of angiotensin II and an increase in tissue **bradykinin**. In addition, in animal experiments, ACE inhibitors have been shown to enhance eNOS expression (Bachetti et al. 2001; Fujii et al. 2002). This effect is realized through **bradykinin** B2 receptors (Bachetti et al. 2001; Fujii et al. 2002). ACE inhibitors, as well as AT1 blockers, suppress the production of ROS and vasoconstrictors derived from COX-2, which contributes to the endotheliotective effect of these drugs (Ancion et al. 2019).

There is also evidence that some beta-blockers have an endothelial protective effect. Nebivolol, a β 1-antagonist with the property of a β 2,3-agonist, improves endothelium-dependent vasodilator reactions in patients with hypertension (Zepeda et al. 2012) and in smokers (Vyssoulis et al. 2004). Nebivolol also reduces vascular remodeling and expression of ET-1 and cytokines when modeling pulmonary hypertension in rats (Perros et al. 2015). Nebivolol increases the release of NO and reduces prothrombotic levels of fibrinogen, homocysteine and plasminogen-1 activator inhibitor in the blood, thereby affecting the state of the endothelium, in particular in smokers (Vyssoulis et al. 2004; Zepeda et al. 2012). Carvedilol, which is a non-selective antagonist of β 1 and β 2 with the property of an α -antagonist, also has a positive effect on the endothelium in patients with hypertension, but this effect in this case is explained by its antioxidant properties (Zepeda et al. 2012). The combined use of carvedilol with an ACE inhibitor has the most beneficial effect on the endothelium-dependent response in patients with hypertension and obesity (Kelly et al. 2012). Thus, this group of drugs alone and in combination with some others is suitable for the treatment of ED associated with hypertension, atherosclerosis and possibly diabetes.

Calcium channel blockers of the dihydropyridine series **nicardipine** and **nifedipine** protect endothelial cells from damage caused by exposure to ROS (Velena et al. 2016). **Benidipine** has an endothelial protective effect against oxLDL-induced generation of ROS in human endothelial cells (Matsubara and Hasegawa 2005). Isradipin improves endothelial function in rabbits treated with cholesterol (Habib et al. 1986). Thus, the endotheliotective effect of dihydropyridine calcium channel blockers is realized through their antioxidant effect, namely through the reduction of lipid peroxidation and the associated generation of ROS (Velena et al. 2016). In addition, **amlodipine**, **azelnidipine** and **nifedipine** have been shown to have an anti-inflammatory effect, which was manifested by a decrease in the level of CRP and interleukin-6 and activation of leukocytes (Fukao et al. 2011; Yasu et al.

2013). **Amlodipine** in combination with a renin inhibitor improves ED in patients with arterial hypertension, which is apparently due to its NO-releasing effect and anti-inflammatory effect (Fukutomi et al. 2014; He et al. 2014; Celik et al. 2015). In addition, **amlodipine** in combination with statin has a better effect on the endothelium than the separate use of such drugs in rats with hypertension or diabetes (Okamura et al. 2014; Zhou et al. 2014). Thus, dihydropyridines can be effectively used not only for hypertension, but also for the treatment of ED in diabetes.

Phosphodiesterase-5 inhibitors are of therapeutic interest. Phosphodiesterase-5 (PDE5) is an enzyme that is found in vascular smooth muscles, heart, skeletal muscles, platelets, placenta, brain, kidneys, liver, pancreas, gastrointestinal tract, and lung tissues (Kass et al. 2007). In the vascular network, the main action of PDE5 is the degradation of cGMP and, thus, the induction of vasoconstriction. PDE5 inhibitors are often used to correct erectile dysfunction; they block the degradation of cGMP, which leads to its accumulation in tissues and, consequently, vasodilation (Boolell et al. 1996). PDE5 inhibitors increase the expression of eNOS and thereby increase the release of NO (Salloum et al. 2003; DeYoung et al. 2008), which contributes to a long-term vasodilator effect. PDE5 inhibitors have a number of other properties – in a model of mouse hind limb ischemia, the use of sildenafil has shown that not only does it improve blood flow restoration, but also increases capillary density and mobilization of endothelial progenitor cells (Dussault et al. 2009). In patients with vascular erectile dysfunction, daily use of **ildenafil** reduces arterial stiffness (Aversa et al. 2012). However, PDE5 inhibitors can be used not only in ED conditions for erectile dysfunction. For example, inhibition of PDE5 suppresses platelet activation in patients with coronary artery disease (Halcox et al. 2002) or with chronic heart failure (Bocchi et al. 2002; Lewis et al. 2007). Moreover, under conditions of modeling diabetes mellitus in rats, this group of drugs improves endothelium-dependent vasorelaxation (Schäfer et al. 2008). PDE5 inhibitors also reduce the concentration of ET-1 in plasma (Proietti et al. 2007), thereby improving microcirculation (Rosato et al. 2009). However, the mechanism underlying the action of PDE5 inhibitors to reduce ET-1 has not yet been determined.

The endothelioprotective effect of statins involves several mechanisms. Under the influence of statins, there is a decrease in LDL, which, like oxLDL, reduce the expression of eNOS (Martínez-González et al. 2001) and increase the levels of caveolin-1 (Feron et al. 2001). Statins also have a direct antioxidant effect on LDL, reducing the electronegative form of LDL (Sánchez-Quesada et al. 1999). Statins increase the bioavailability of NO by activating eNOS via the PI3K/Akt signaling pathway (Kureishi et al. 2000), stimulated by the agonists of the eNOS-hsp90 interaction (Feron et al. 2001) and the BH4-mediated binding of eNOS. These properties were demonstrated not only in the model of insulin-resistant diabetes mellitus in rats (Okamura et al. 2014), but also in patients suffering from atherosclerosis (Antoniades et al. 2011). These stud-

ies have shown that atorvastatin promotes an increase in the vascular content of BH4 and bioavailability of NO, as well as a decrease in ROS production by stimulating the expression and activity of the GTP cyclohydrolase I gene (Antoniades et al. 2011). In addition, statins increase eNOS expression by increasing the stability of eNOS mRNA (Rikitake and Liao 2005; Kosmidou et al. 2007). Statins also have an anti-inflammatory effect (Antonopoulos et al. 2012; Denisyuk 2015). For example, treatment with atorvastatin reduces pro-inflammatory cytokines (TNF- α , interleukin-1 and -6), intercellular adhesion molecules and CRP levels in the blood of patients with hypercholesterolemia (Ascer et al. 2004), while rapid discontinuation of statins provokes an increase in proinflammatory and prothrombotic markers (Lai et al. 2005). Statins have also been shown to increase the number of circulating endothelial progenitor cells, probably via the PI3K/Akt pathway (Dimmeler et al. 2001), which may contribute to their longer-term endotheliotropic effect.

One of the promising therapeutic agents in the treatment of ED is Angiotensin-(1-7). It is a metabolite of angiotensin I (Su 2014). It can also be obtained from angiotensin II under the action of prolylcarboxypeptidase (Mallela et al. 2008) and carboxypeptidase APF2 (Zisman et al. 2003). Angiotensin-(1-7) activates endothelial cell eNOS via the PI3K/Akt pathway, thereby inhibiting angiotensin II-induced activation of NADPH oxidase (Sampaio et al. 2007a, 2007b). Long-term angiotensin therapy (1-7) improves renal ED, pathogenetically caused by apolipoprotein E deficiency (Stegbauer et al. 2011) and diet-induced obesity in mice (Beyer et al. 2013) which is probably mediated by an increase in NO release (Traskand Ferrario 2007) and eNOS expression (Zhang et al. 2008; Costa et al. 2010). Angiotensin-(1-7) has also been shown to disrupt the production of ROS activated by the angiotensin receptor AT1 NADPH oxidases in the modeling of hypertension or diabetes mellitus in rats (Fraga-Silva et al. 2013; Pernomian et al. 2014). Angiotensin-(1-7) restores the production and migration of NO/cGMP, and increases the stability and proliferative activity of endothelial progenitor cells in patients with diabetes (Jarajapu et al. 2013). However, there is not enough information about the effectiveness of angiotensin-(1-7) in relation to the human endothelium yet.

In recent years, a new class of drug has appeared – a direct renin inhibitor – aliskiren. The endothelioprotective effect of aliskiren on animals has been experimentally demonstrated. In rabbits with Watanabe hyperlipidemia, the renin inhibitor aliskiren enhanced both an increase in NO concentration in the blood and a decrease in NO release after treatment with L-NMMA (nitric oxide synthase inhibitor) to a degree similar to that obtained with **valsartan**; in addition, it simultaneously reduced the area of plaques in the aorta. These effects were further enhanced by the combined use of aliskiren and **valsartan** (Imanishi et al. 2008), which indicates that the effect of aliskiren is independent of angiotensin II. However, information on the effect of aliskiren on the functional activity of the human endothelium remains insufficient.

Endogenous **bradykinin**, as mentioned above, has many different effects on the functional state of the endothelium. As a pharmacological drug, it protects against the death of microvascular endothelial cells caused by ROS and toxins (Bovenzi et al. 2010). Long-term use of **bradykinin** preserves the expression of eNOS in dogs with cardiac insufficiency caused by pacing (Tondangu et al. 2004), and also enhances the expression of eNOS and nNOS (neuronal nitric oxide synthase) in the vessels and heart of dogs with cardiomyopathy with dystrophin deficiency (Dabiré et al. 2012; Su et al. 2012). However, due to the very short half-life and the involvement of **bradykinin** in inflammation (Chen et al. 2004) and cancer (Montana and Sontheimer 2011; Yu et al. 2013), the use of **bradykinin** in clinical practice remains problematic.

The eNOS transcription enhancer, the chemical compound AVE3085, has certain prospects for ED correction. It stimulates eNOS expression, suppresses oxidative stress and activates platelets, thereby improving endothelium-dependent relaxation and heart function, which was found in animals with various experimental diseases (Cheang et al. 2011; Yang et al. 2011). This compound, among other things, prevents the inhibition of vasodilation by **asymmetric dimethylarginine (ADMA)** in the rings of the human internal thoracic artery and in the rings of the porcine coronary artery (Xuan et al. 2012; Xue et al. 2012). However, its clinical efficacy in relation to humans has not yet been demonstrated.

One of the controversial candidates for the treatment of ED is the if-channel inhibitor ivabradine. A number of studies have revealed its positive effect on both endothelium-dependent vasodilation and eNOS expression in both animals and humans (Bolduc et al. 2011; Musikhina et al. 2012; Orea-Tejeda et al. 2013). However, the authors of some studies note that there was no significant improvement in vasodilation under the action of ivabradine in patients with microvascular angina (Villano et al. 2013), as well as in patients with other forms of coronary heart disease (Jochmann et al. 2014) or type II diabetes (Nerla et al. 2012). Moreover, the use of ivabradine (in addition to standard treatment) in patients with stable coronary artery disease without heart failure was associated with an increase in the frequency of atrial fibrillation, which casts doubt on the usefulness of this drug (Fox et al. 2014).

There is evidence of endothelioprotective effects of sphingosine-1-phosphate (C1F). C1F is a signaling sphingolipid formed by sphingosine kinase in blood and tissues, regulates vascular proliferation, their permeability and transport of T- and B-lymphocytes. C1F enhances the function of the endothelial barrier (Wilkerson et al. 2014) stimulates the release of **NO** through Akt-mediated phosphorylation of eNOS (Igarashi et al. 2001) and restores high-density lipoproteins (Tong et al. 2014). C1F also has anti-inflammatory properties and has a protective effect against lung damage caused by endotoxins (Lucke and Levkau 2010). Moreover, C1F has a strong effect on the differentiation of adipose tissue-derived stem cells into endothelial-like cells and the activation of eNOS in

these cells (Arya et al. 2014). All these properties of C1F can contribute to its endothelioprotective effect. Interestingly, FTY720, an oral active analogue of C1F, also demonstrates similar properties (Van der Giet et al. 2008). Thus, C1F and its analogues can be used to improve the functional state of the endothelium, especially in such pathological conditions as atherosclerosis and acute lung damage, when a violation of the function of the endothelial barrier is manifested (Natarajan et al. 2013).

Another promising drug for the treatment of ED is erythropoietin (EPO). EPO activates the PI3K/Akt pathway and promotes the release of **NO**. In addition, there is evidence showing that the concentration of EPO in the blood is directly proportional to the amount of EPC in patients with coronary heart disease (Heeschen et al. 2003). In addition, the introduction of EPO increased the amount of EPC. These data suggest that EPO may play an important role in the production of EPC.

Several authors of large prospective studies report a significant reduction in cardiovascular events in patients with major depressive disorder who responded to antidepressant therapy (Santangelo et al. 2009; Kimmel et al. 2011; Safronenko et al. 2021). In these patients, there was a significant improvement in ED and inflammation markers, which was confirmed by increased endothelial dilation and a decrease in interleukin-6 levels (Pizzi et al. 2009; Tseng et al. 2010; Lopez-Vilchez et al. 2016). There is also evidence to suggest that the effectiveness of low doses of lithium in borderline personality disorder and stroke may be partially associated with improved endothelial function and reduced inflammation in the endothelium (Lyoo et al. 2010; Mohammadianinejad et al. 2014; Li et al. 2018).

Recently, **H₂S** donors have attracted the attention of researchers with the discovery of new therapeutic strategies for the treatment of various ED-related diseases (Benavides et al. 2007; Martelli et al. 2014; Tomasova et al. 2015; Abramavicius et al. 2021). **Sodium thiosulfate** is the main product of **H₂S** oxidation. **Sodium thiosulfate** is an odorless inorganic water-soluble compound with the chemical formula $\text{Na}_2\text{S}_2\text{O}_3$ and a molecular weight of 158.11 g/mol. Recent data show that **sodium thiosulfate** has antioxidant, anti-inflammatory and antihypertensive properties (Roorda et al. 2021), which makes it a potential candidate molecule in the treatment of ED-related diseases. In addition to the fact that thiosulfate is a stable non-toxic metabolite of **H₂S** (Bilska-Wilkosz et al. 2017), it is also sulfane sulfur, which is defined as sulfur atoms covalently bound to other sulfur atoms, which makes it unstable and easily oxidized in air and reduced by thiols (Koike and Ogasawara 2016). It is known that compounds containing sulfane sulfur have cell regulation effects due to activation or inactivation of enzymes and changes in protein activity (Mustafa et al. 2009). The functions of sulfane sulfur include antioxidant regulation, sulfonation of tRNA and the formation of iron-sulfur protein. As an **H₂S** donor molecule, **sodium thiosulfate** has unexplored therapeutic potential in the context of many diseases.

Over the past few years, a number of independent research groups have found positive effects of sodium thiosulfate on animal models of various diseases (Zhang et al. 2021).

Conclusion

ED is a typical pathological process involved in the pathogenesis of many diseases. In some diseases, such as atherosclerosis, ED plays a crucial role in the development of pathology, whereas in others, such as hypertension and type II diabetes mellitus, ED usually occurs as a complication, but subsequently contributes to the development and progression of organ damage. It is obvious that multiple mechanisms are involved in the pathogenesis of ED development, such as inflammation, increased ROS and RFA, cellular apoptosis, increased production of vasocon-

strictors, decreased production of vasodilators and vascular remodeling, and each specific pathology may include them to a greater or lesser extent. However, a decrease in the bioavailability of NO seems to play a crucial role. Thus, pharmacological agents with endothelioprotective properties can provide more therapeutic benefits than a drug without such an effect. Considering the important role of ED in the development and progression of many diseases, it is becoming increasingly attractive to consider ED as a primary therapeutic goal. For this reason, the evaluation of the endothelioprotective effect is becoming increasingly attractive in the development of new drugs.

Conflict of interest

The authors declare that there is no conflict of interests.

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Author contributions

- **Dmitry V. Shcheblykin**, post-graduate student, Department of Pharmacology and Clinical Pharmacology; e-mail: dmitryshchl@gmail.com, ORCID ID <https://orcid.org/0000-0002-2420-2243>. The author was engaged in literature analysis and paper writing.
- **Anton A. Bolgov**, post-graduate student, Department of Pathology; e-mail: toxabolgov@mail.ru, ORCID ID <https://orcid.org/0000-0001-9708-8181>. The author made a contribution to collection, analysis and interpretation of the data for the paper.
- **Mikhail V. Pokrovskii**, Doctor Habil. of Medical Sciences, Professor, Department of Pharmacology and Clinical Pharmacology, e-mail: mpokrovsky@yandex.ru, ORCID ID <https://orcid.org/0000-0002-1493-3376>. The author set the research objectives, motivated the team, conducted a critical analysis of the material, and gave the final approval of the version of the manuscript.
- **Julia V. Stepenko**, postgraduate student, Department of Pharmacology and Clinical Pharmacology, e-mail: aspirj16@gmail.com, ORCID ID <http://orcid.org/0000-0002-7414-7326>. The author was engaged in structuring the article and arranging the references.

- **Julia M. Tsuverkalova**, postgraduate student, Department of Pharmacology and Clinical Pharmacology, e-mail: cvd404@mail.ru, **ORCID ID** <http://orcid.org/0000-0001-8489-247X>. The author was engaged in structuring the article and arranging the references.
- **Olesya V. Shcheblykina**, PhD in Medical Sciences, senior lecturer, Department of Pharmacology and Clinical Pharmacology, e-mail: sheolvi31@gmail.com, **ORCID ID** <https://orcid.org/0000-0003-0346-9835>. The author was engaged in developing the concept and conducting the literature analysis.
- **Polina A. Golubinskaya**, PhD in Medical Sciences, Head of the Clinical Diagnostic Laboratory, Budgetary Healthcare Institution of the Voronezh Region “Voronezh Regional Clinical Ophthalmological Hospital”, e-mail: polinapigeon@gmail.com, **ORCID ID** <http://orcid.org/0000-0002-1765-9042>. The author was engaged in collecting information and writing the article.
- **Liliya V. Korokina**, PhD in Medical Sciences, Associate Professor of the Department of Pharmacology and Clinical Pharmacology, e-mail: korokina@bsu.edu.ru, **ORCID ID** <http://orcid.org/0000-0002-4115-1564>. The author was engaged in developing the concept and conducting the literature analysis.