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The Effectiveness of the Diagnosis of Endothelial Dysfunction and its Pharmacological Correction with a Focus on Angiotensin-Converting Enzyme Inhibitors

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Abstract

The vascular endothelial lining is a kind of unique endocrine system, which is located around the perimeter of absolutely all organs of the vascular system. Why endocrine: in modern cardiology, the main importance in the occurrence and development of almost all pathologies is assigned to neurohormonal breakdowns in the form of an imbalance between vasoconstrictors and vasodilators. On one side of the hormonal balance are neurohormones that cause vasoconstriction, remodeling and antidiuresis. These are components of the renin-angiotensin-aldosterone and sympathoadrenal systems, endothelin, vasopressin. They are counteracted by hormones with vasodilating and diuretic effects that block remodeling processes, the main of which are nitrogen monoxide, as well as natriuretic peptides, the kallikreinkinin system and prostacyclin. Endotheliocytes play the role of an effective buffer between the blood flow and the tissues of the body, performing a number of regulatory functions, producing a large variety of biologically active substances. The strategic location of the endothelium allows it to be sensitive to the slightest changes in the hemodynamic system and not only in it. Thus, the vascular endothelium plays a key role in maintaining homeostasis. This review article presents the main pathogenetic aspects of endothelial dysfunction, methods of diagnosis and its correction.

Disciplinary: Medicine.

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1 Introduction

In classical histology and physiology, the vascular endothelium layer is a layer of flat cells of mesenchymal origin lining the inner surface of blood and lymphatic vessels [1]. The endothelium is not just a semipermeable membrane, but an active endocrine organ. After discovering and studying the functions of nitrogen monoxide as a signaling molecule of the vascular system, scientists were able to pave a new direction in understanding the involvement of the endothelium in the pathogenesis of hypertension and other cardiovascular pathologies, as well as ways to effectively correct its dysfunction [2].

The most important functions of the endothelium are the maintenance of hemovascular homeostasis, regulation of hemostasis, modulation of inflammation, regulation of vascular tone and vascular permeability. In addition, the endothelium has its own renin-angiotensin system. The endothelium secretes mitogens and participates in angiogenesis, fluid balance, and the exchange of intercellular matrix components [3-5]. The vascular endothelium performs these functions by synthesizing and isolating a large number of various biologically active substances (Table 1) [6-10].

Table 1: Factors synthesized in the endothelium and determining its functions

Factors affecting vascular smooth muscle tone	
Vasoconstrictors	Vasodilators
Endothelin	Nitrogen monoxide
Angiotensin II	Prostacyclin
Thromboxane A2	Endothelin depolarization factor
Prostaglandin H2	Angiotensin I Adrenomedullin
Hemostasis factors	
Prothrombogenic	Antithrombogenic
Platelet growth factor	Thrombomodulin
Inhibitor of tissue plasminogen activator	Nitrogen monoxide
Angiotensin IV	Tissue Plasminogen activator
Platelet activation factor	Prostacyclin
The Willebrand Factor	
Endothelin I	
Fibronectin	
Thrombospondin	
Factors affecting growth and proliferation	
Stimulants	Inhibitors
Endothelin I	Nitrogen monoxide
Angiotensin II	Prostacyclin
Superoxide radicals	Natriuretic C-type peptide
Endothelial Growth Factor	Heparin-like growth inhibitors
Factors affecting inflammation	
Pro - inflammatory	Anti-inflammatory
Tumor necrosis factor alpha	Nitrogen monoxide
Superoxide radicals	
C-reactive protein	

2 Pathophysiological Aspects of the Development of Endothelial Dysfunction

The main task of the endothelium is the balanced release of biologically active substances that determine the holistic work of the circulatory system [11]. In the physiological state, the

endothelium has the ability to maintain a balance between its multidirectional functions: synthesis of pro- and anti-inflammatory factors, vasodilating and vasoconstrictive substances, pro- and antiplatelet agents, pro- and anticoagulants, pro- and antifibrinolytics, proliferation factors and growth inhibitors [12-14]. Under physiological conditions, vasodilation, synthesis of aggregation inhibitors, coagulation and fibrinolysis activators, anti-adhesive substances prevail. Vascular cell dysfunction disrupts this balance and predisposes vessels to vasoconstriction, leukocyte adhesion, platelet activation, mitogenesis and inflammation [13]. Thus, the endothelial function is a balance of oppositely acting principles: relaxing and constrictive factors, anticoagulant and procoagulant factors, growth factors, and their inhibitors [14].

Causes such as impaired blood flow, hypoxia, increased systemic and intrarenal pressure, hyperhomocysteinemia, and increased lipid peroxidation processes can lead to changes in the physiological balance in the body [15-17]. Vascular endothelium is extremely vulnerable, but, on the other hand, researchers note its huge compensatory capabilities in violation of physiological conditions [18].

Currently, endothelial dysfunction is understood as an imbalance between the formation of vasodilating, atrombogenic, antiproliferative factors, on the one hand, and vasoconstrictive, prothrombotic and proliferative substances synthesized by the endothelium, on the other. Endothelial dysfunction can be an independent cause of circulatory disorders in the organ, since it often provokes angiospasm or vascular thrombosis. On the other hand, disorders of regional blood circulation (ischemia, venous congestion) can also lead to endothelial dysfunction [19]. Hemodynamic causes, age-related changes, free radical damage, dyslipoproteinemia, hypercytokinemia, hyperhomocysteinemia, exogenous and endogenous intoxication can contribute to the formation of endothelial dysfunction [20]. Endothelial dysfunction can lead to structural damage in the body: acceleration of apoptosis, necrosis, desquamation of endotheliocytes. However, functional changes in the endothelium, as a rule, precede morphological changes in the vascular wall [21].

There are four forms of endothelial dysfunction: vasomotor, thrombophilic, adhesive and angiogenic [22]. The vasomotor form of endothelial dysfunction is caused by a violation of the relationship between endothelial vasoconstrictors and vasodilators and is important in the mechanisms of both systemic increases in blood pressure and local angiospasm. The thrombophilic form of endothelial dysfunction is caused by a violation of the ratio of thrombogenic and atrombogenic substances formed in the endothelium and involved in hemostasis or affecting this process. Under physiological conditions, the formation of atrombogenic substances in the endothelium prevails over the formation of thrombogenic substances, which ensures the preservation of the liquid state of the blood in case of damage to the vascular wall. The thrombophilic form of endothelial dysfunction can lead to the development of vascular thrombophilia and thrombosis. The adhesive form of endothelial dysfunction is caused by a violation of the interaction of leukocytes and endothelium. Increased adhesion of the endothelium

and uncontrolled adhesion of leukocytes are of great importance in the pathogenesis of inflammation in atherosclerosis and other pathological processes. The angiogenic form of endothelial dysfunction is associated with a violation of neoangiogenesis. Therefore, endothelial dysfunction as a typical pathological process is a key link in the pathogenesis of many diseases and their complications [23,24].

3 Diagnosis of Endothelial Dysfunction

Direct determination of NO in the blood is difficult due to its short half-life. NO production is evaluated by the content in blood plasma and urine of the end products of NO metabolism (nitrite, nitrate) during chemiluminescence analysis or gas chromatography/mass spectrometry [25,26]. The determination of cyclic guanosine monophosphate (cGMP) makes it possible to estimate the proportion of NO that had a functional effect on endothelial cells and to distinguish reduced NO production from increased degradation. The concentrations of these substances are extremely low, there is a significant dependence on other sources of nitrite and nitrate, including food, and therefore the clinical use of this method is limited. Endothelin-1 is an endothelial peptide with strong vasoconstrictor, mitogenic properties. It is believed that an increased level of endothelin-1 is associated with endotheliocyte damage and can be considered a marker of ED [27]. Due to large fluctuations in people, regardless of vascular status, the use of endothelin-1 as a separate marker is highly inaccurate. Willebrand factor is a glycoprotein synthesized mainly by endothelial cells. Its level correlates with the severity of risk factors for atherosclerosis, the elimination of which is accompanied by its decrease. An increased level of the Willebrand factor indicates either endothelial damage or, more likely, increased activation of endotheliocytes [28]. Tissue plasminogen activator, plasminogen activator inhibitor-1: with endothelial dysfunction and an increased risk of atherosclerosis or its complications, an increase in the level of both of these markers is observed. Adhesive molecules include vascular cellular adhesive molecule 1 (VCAM 1), endothelial-leukocyte adhesive molecule 1 (E-selectin), inter-cellular adhesive molecule 1 (ICAM 1), and P-selectin. Circulating soluble forms of adhesive molecules are detected in plasma, their levels are elevated in inflammatory diseases, and they are measured by immunological methods.

4 Pharmacological Correction of Endothelial Dysfunction Based on Angiotensin Converting Enzyme (ACE) Inhibitors

At least two main mechanisms of aCEI influence on endothelial function are discussed. It is known that ACE inhibitors lead to an increase in the amount of tissue bradykinin. Vasoprotective, antiproliferative, antisclerotic and acute vasodilatory effects of ACE inhibitors can be explained by endothelium-dependent reactions associated with the ability of ACE inhibitors to prevent the breakdown of bradykinin. Bradykinin is a powerful stimulant for the release of endothelium-dependent relaxing factors such as NO, endothelium-dependent hyperpolarization factor and prostacyclin. Endothelial hyperpolarization factor is an unstable metabolite of arachidonic acid, its release depends on the concentration of intracellular calcium and calmodulin, and its effect on endothelium-dependent relaxation is associated with the size of blood vessels and is most

significant in small arteries. Prostacyclin, formed in endothelial cells, activates adenylate cyclase of smooth muscle cells, increasing the formation of cAMP, the relaxing effect of which enhances vasodilation caused by NO. The concept of the possibility of using ACE inhibitors to affect endothelial function, ischemia and atherogenesis has emerged relatively recently. This effect is realized with the help of several mechanisms. The first information that ACE inhibitors contribute to a decrease in the frequency of myocardial ischemic events was obtained as a result of large clinical studies involving patients with left ventricular dysfunction and heart failure. At the end of these studies, it became obvious that the use of ACE inhibitors contributes to a significant reduction in the number of ischemic negative events [29].

Another mechanism of action of ACE inhibitors on endothelial function is the blockade of angiotensin II formation, which is considered an inducer of oxidative stress. An increase in the formation of reactive oxygen species (superoxide anion) has been experimentally demonstrated under the action of angiotensin II. The mechanisms of action of angiotensin II on the production of superoxide anion are associated with the stimulation of NADPH/NADH oxidases [30,31]. Thus, a decrease in the level of angiotensin II leads to a decrease in oxidative stress, the products of which reduce the activity of NO. Angiotensin II in many respects has the opposite effect with respect to NO and is currently recognized as practically its antagonist. ACE inhibition restores the balance between the two vasoactive systems [32].

5 Conclusion

To date, the concept of endothelial dysfunction as a central link in the pathogenesis of many chronic diseases has been formulated. The main role in the development of endothelial dysfunction is played by oxidative stress, the synthesis of powerful vasoconstrictors that suppress the formation of nitrogen monoxide. Endothelial dysfunction precedes the development of clinical manifestations of diseases, therefore, the evaluation of endothelial functions is of great diagnostic and prognostic importance. Further study of the role of endothelial dysfunction in the development of diseases is necessary to develop new therapeutic approaches. Currently, there is an accumulation of new data on the specific mechanisms of endothelial dysfunction in hypertension. The effect of traditional antihypertensive drugs is supplemented and reinterpreted from the point of view of the effect on the endothelium, and the mechanisms of vasoprotective and organoprotective action of cardiovascular drugs due to the modulation of NO production are revealed. Priority endothelium-protective drugs today are ACE inhibitors with the maximum level of lipophilicity.

6 Availability of Data and Material

Data can be made available by contacting the corresponding authors.

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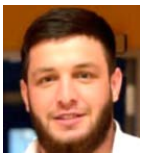

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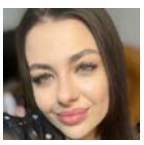

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