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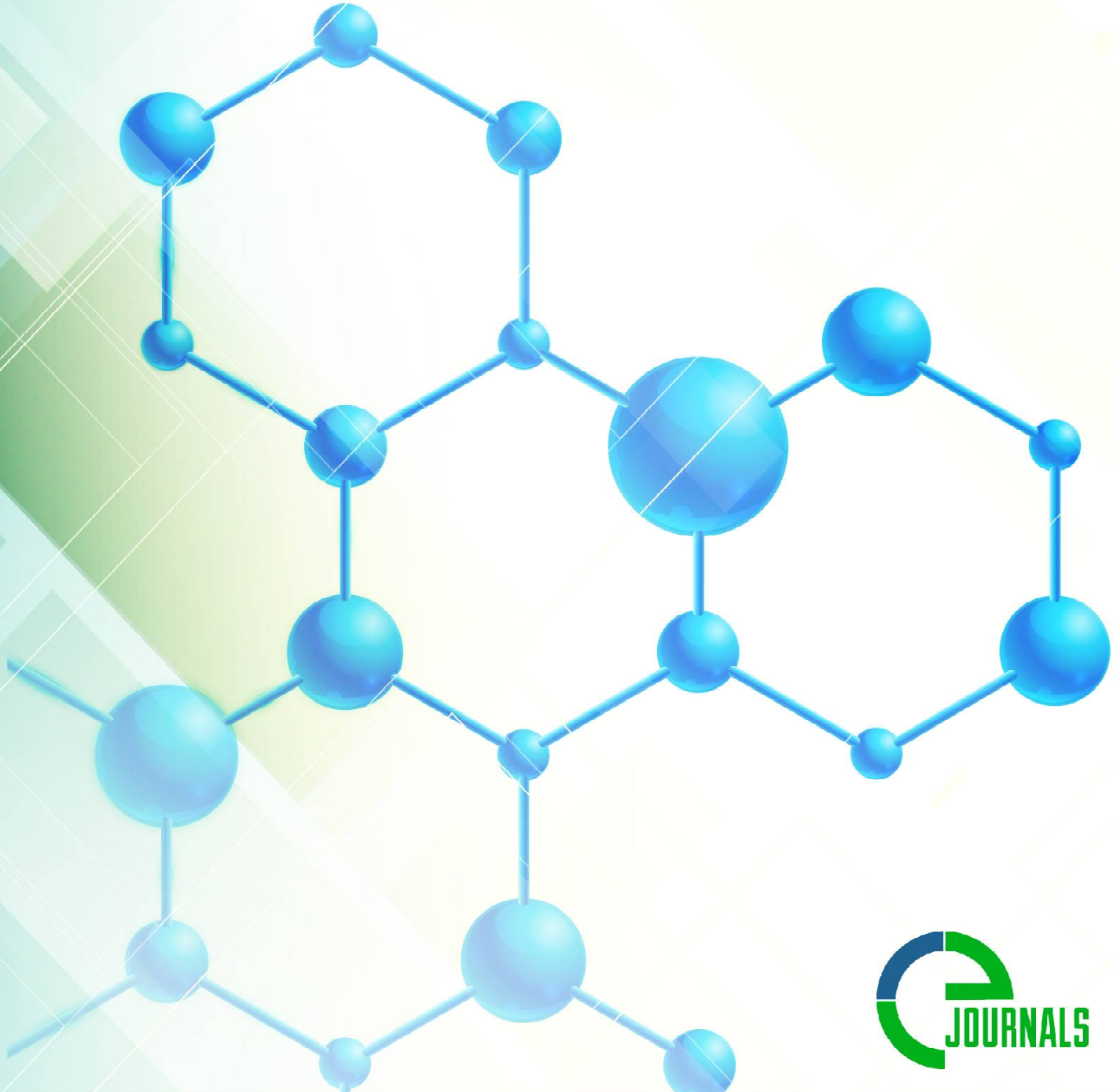

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CONTENT

PLACE OF ENDOTHELIAL DYSFUNCTION IN THE FORMATION OF OBSTRUCTIVE PULMONARY DISEASE IN ARTERIAL HYPERTENSION

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Abstacrt.Chronic obstructive pulmonary disease and arterial hypertension are common diseases with the formation of cardiorespiratory comorbidity, which mutually aggravates the condition of patients, forming certain features of the course of the disease due to the commonality of some links of pathogenesis. The article presents literature data on the role of endothelial dysfunction in the progression of chronic obstructive pulmonary disease in arterial hypertension.

Keywords: chronic obstructive pulmonary disease, arterial hypertension, endothelial dysfunction.

Introduction. Chronic obstructive pulmonary disease (COPD) is a common pathology, leading to death, disability of millions of people. The prevalence of COPD in the world is growing and among people over 40 varies from 7 to 18.2% [14.42]. In the structure of total mortality from respiratory diseases, COPD is the first among the causes of mortality. Each year, COPD is the cause of death of about 3 million people, according to forecasts by World Health Organization experts, by 2030, COPD will take 4th place among other causes of mortality due to the spreading epidemic of smoking and a decrease in mortality from other causes [29].

The combination of COPD and cardiovascular disease, in particular arterial hypertension (AH), is one of the most common aggravating comorbid conditions in the clinic. The prevalence of arterial hypertension (AH) among patients with COPD varies widely and amounts to 76.3% of cases, averaging 34.3% [1.24.33].

In the studies of V. S. Zadiochenko [3], the concept of comorbidity is put forward on the agenda, which implies the formation of interconnections and mutual influences between coexisting diseases, as well as the presence of common pathogenetic mechanisms, such as chronic inflammation of low gradation, oxidative stress and endothelial dysfunction.

COPD is considered as a systemic disease with various extrapulmonary manifestations, which in most cases determines the prognosis and outcome of the disease. Moreover, violations of vascular changes are of no small importance, in particular, cardiovascular complications are among the main systemic manifestations of COPD [44]. Thus, cardiovascular diseases (CVD) are more common in patients with COPD than in the general population.

The development of cardiorespiratory comorbidity, accompanied by a mutual aggravation syndrome, due to the commonality of some links of pathogenesis, forms a special clinical picture that leads to a worsening prognosis of the disease and dictates the consideration of this condition in a special framework and requires new diagnostic approaches to improve therapeutic tactics [7].

Cardiorespiratory comorbidity of COPD and AH is a combination of complex multi-stage pathogenetic processes, among which the leading factor is difficult to identify. The main pathogenetic mechanisms leading to the development and progression of hypertension

in COPD are systemic inflammation and oxidative stress, which causes dysfunction and / or damage to the endothelium [55], which serves as an independent predictor of poor prognosis for most cardiovascular diseases and makes vascular endothelium a vulnerable target.

According to literature, to date, not all mechanisms of the pathogenesis of hypertension in COPD and their relationships have been sufficiently studied. In recent decades, in the pathogenesis of hypertension, as well as in atherogenesis, great importance has been attached to studying the role of endothelium and the development of endothelial dysfunction [23].

In case of vascular disturbances in the combined course of arterial hypertension and COPD, endothelial dysfunction, early disturbances in the ratio of prooxidant and antioxidant systems, high lipoperoxidation syndrome, tissue hypoxia, systemic disorders of vascular-platelet and fibrinolytic hemostasis with depletion of anticoagulant reserve are important [6].

Some common mechanisms in the pathogenesis of COPD and hypertension can be distinguished - this is the development of a systemic inflammatory response, oxidative stress and endothelial dysfunction, which are considered to be a key link in the development of cardiorespiratory comorbidity [20,49].

In this case, the formation of secondary pulmonary arterial hypertension (PAH) with an increase in the load on the right heart and left atrium leads to a deterioration of the coronary reserve, which enhances myocardial ischemia in both ventricles and leads to the progression of both coronary and pulmonary insufficiency.

There is also an inverse relationship, i.e. CVD impact on the development of exacerbations of COPD. So, not only the frequency of exacerbations affects the quality of life, but in most cases determines the prognosis of the disease in these patients. According to the results of the study, the cause of acute exacerbation of COPD requiring hospitalization in more than 40% of cases was the destabilization of CVD [8].

Among patients with bronchial obstructive diseases, not only local inflammation of the bronchi, but also persistent systemic inflammation, which is characteristic of patients with COPD, makes a significant contribution to the pathogenesis of atherosclerosis and other cardiovascular diseases, contributing to the development and progression of endothelial dysfunction. This explains the ongoing interest in the study of this pathology [43].

In recent years, more and more information has been accumulating that assessing the state of the endothelium can be of great clinical importance to expand understanding of the pathogenesis of many diseases and predict the development of complications. All this indicates that the development of ED is currently one of the main components in the pathogenesis of hypertension and COPD.

Endothelial dysfunction is understood to mean a violation of parity between the production of vasodilating, angioprotective, antiproliferative factors, on the one hand, and vasoconstrictor, prothrombotic, proliferative endothelial producers, on the other.

Endothelial dysfunction (ED) and chronic persistent inflammation are interrelated processes that play a key role in the development and progression of both COPD and hypertension. These mechanisms constantly potentiate each other, creating a vicious cycle, and contribute to the formation and progression of hypertension in COPD.

Research data from recent decades indicate the important role of ED in the study of the pathogenesis of diseases with combined pathology, which is an important mechanism for their formation and progression [21,22,25,45].

Endothelial dysfunction affects the severity of the clinical picture. Of direct clinical importance is the assessment of the degree of these disorders, which will reveal the subtle mechanisms of the onset and development of diseases. At present, various markers of ED have been identified, which can act as an indicator of both the severity of the disease and the effectiveness of the drug therapy, as well as methods for their assessment [21,22,25,45].

Vascular endothelium is a hormonally active tissue that regulates vascular tone by releasing vasodilating and vasoconstrictor factors and models the contractile activity of smooth muscle cells. Endothelial cells are the first to experience the effects of free oxygen radicals, oxidized low density lipoproteins, high cholesterol concentrations and hydrostatic pressure inside the vessels lined with them. With various vascular diseases and metabolic disorders, the ability of endothelial cells to release relaxing factors decreases, while the formation of vasoconstrictor factors persists or increases, which leads to ED [13].

ED is a complex process, based on, firstly, an imbalance between processes such as vasoconstriction and vasodilation, secondly, impaired production of factors of inflammation and vascular proliferation, and thirdly, damage to the thrombosis system. All this ultimately leads to remodeling of the vascular wall [17].

ED is considered as a systemic disorder characterized primarily by a decrease in the production of nitric oxide (NO). ED is a pathological condition that worsens vascular homeostasis and leads to the loss of protective properties of endothelial cells [19,31,39,40,60].

The leading role in the pathogenesis of ED is assigned to NO [17,19,60]. NO is synthesized in endothelial cells from L-arginine under the influence of the enzyme endothelial NO synthase (eNOS). Under the influence of various mediators, an increase in the concentration of intracellular calcium (Ca2 +) occurs, where it, by binding, forms the Ca2 + -calmodulin complex, which, acting as a cofactor, activates eNOS. The synthesis of NO proceeds with the participation of a number of other cofactors [39,40]. NO penetrates smooth muscle cells and causes relaxation by activating guanylate cyclase, thereby increasing the concentration of cyclic guanosine monophosphate, which, in turn, mediates the effects of NO. NO is a mediator of endothelium-dependent vasodilation (EDVD) due to the inhibitory effect on vasoconstrictors such as AT II and endothelin (ET). In addition, NO inhibits platelet aggregation, leukocyte adhesion, infiltration and proliferation of vascular smooth muscle cells. NO inhibits oxidative modification of LDL [31].

Specific inactivation of the eNOS gene is accompanied by an increase in mean blood pressure by approximately 15-20 mm Hg. Art. It is proved that patients with hypertension have a less vasodilating response to intraarterial administration of acetylcholine compared with the control normotensive group. There is also an inducible form of NO synthase (iNOS), which is produced in the vascular wall during inflammatory processes. iNOS produces an excess amount of NO, which leads to vasoconstriction and a decrease in endothelium-dependent vasodilation [19,39,40]. It is clear that the more iNOS is produced, the more severe the clinical manifestations.

In contrast to NO, as a vasodilator, the body produces a powerful vasoconstrictor - ET-1 or, in a number of literary sources, simply ET [21,25,54]. ET-1 belongs to the number of biologically active bicyclic polypeptides of a wide spectrum of action, consisting of a combination of 21 amino acids. Today it is one of the most significant regulators of the functional state of vascular endothelium.

It is known that endothelin-1 has a powerful vasoconstrictor effect, inhibits the formation of NO in the vessels, mediates the mitogenic effect, enhances the proliferation of cardiomyocytes and smooth muscle cells of the vascular wall, and stimulates the production of a number of cytokines and growth factors. In response to hypoxia, an increase in endothelial production of vasoconstrictor substances was noted along with a decrease in the formation of vasodilating substances. Endothelin-1 is considered as a marker of many vascular pathologies: coronary heart disease [55], myocardial infarction, atherosclerotic vascular damage, hypertension, preeclampsia and eclampsia, renal vascular pathology, ischemic brain damage, non-infectious pulmonary diseases. In patients with COPD with hypoxemia, the level of endothelin-1 in arterial blood is higher than in patients with COPD without hypoxemia [55].

The production of ET-1 in the body is promoted by hypoxia, ischemia, hemodynamic overload, changes in acid-base balance, hyperglycemia, hypercholesterolemia, oxidative stress [25,30,40]. Inducers of ET synthesis are vasoconstrictors, growth factors, cytokines, thrombin, and adhesion molecules. In contrast, ET synthesis inhibitors are prostacyclin, estrogens, atrial natriuretic peptide, as well as the previously mentioned NO.

From the above it follows that endothelial dysfunction is considered as the main mechanism for the formation of increased pressure and its complications, and also serves as a quantitative marker of its progression [38].

Studies by S.I.Ovcharenko and co-authors on the determination of markers of systemic inflammation and endothelial dysfunction and their relationship with various parameters in patients with COPD in combination with hypertension revealed high levels of markers of inflammation and ED (highly sensitive C-reactive protein - hsCPB, a soluble form of the cell-cell adhesion molecule Type 1 - sICAM-1, endothelin-1 and sP-selectin). The study noted that as systolic blood pressure increases and bronchial obstruction worsens, the degree of violation of markers of inflammatory status and ED increases [10].

According to some authors, it was found that endothelium is involved in the pathological process at the earliest stages of increased pressure [48].

A number of clinical studies indicate that not only with increasing pressure, but also with other pathological conditions, an increase in ET-1 level is noted [38,40,57].

The concentration of ET-1 in blood plasma was highest in patients with hypertension, combined with atherosclerotic lesions of the arteries [60].

Particular importance should be given to the contribution of ED to the pathogenesis of chronic obstructive pulmonary disease (COPD). The systemic inflammation observed in COPD appears to be a key determinant of pulmonary and systemic ED [15.51.59]. However, a meta-analysis of an Italian group of scientists did not reveal a correlation between ED risk factors for COPD, but established a clear relationship between COPD and ED [16]. A number of studies have identified the relationship between airflow obstruction and endothelial status, assessed by determining the levels of C-reactive protein, interleukin-6, and malondialdehyde, as well as testing with endothelial-independent vasodilation [17].

The presence of high levels of ET-1 among patients with COPD contributes to a more malignant course of both pulmonary and cardiac pathology, leading to cardiovascular remodeling, which is manifested by dilatation of all heart chambers and the formation of chronic pulmonary heart [15,26,34,35,37,52] .

There are also two other ET isoforms - ET-2 and ET-3. Between themselves ET differ in the sequence of amino acids. The synthesis of all three ETs is encoded by

different genes [25,30]. ETs are identified in various organs and tissues. ET-1 is defined in endothelial cells, but unlike other ETs, it can also be synthesized in smooth muscle cells of blood vessels, neurons, hepatocytes, endometrium, mesagangliocytes, mammary endotheliocytes, and tissue basophils. Under pathophysiological conditions, a large number of nonendothelial cells in the heart, including cardiomyocytes, can also synthesize ET-1 in response to stretching of the myocardium, AT II, and norepinephrine [53].

Studies to determine the level of markers of inflammation, ED and their relationship with various parameters in patients with COPD in combination with hypertension revealed that the levels of ET-1 and s-Selectin exceeded normal values. An increased level of biochemical markers of ED can be a consequence of endothelial damage. The results showed an increase in the level of the studied markers (hsCRP, sICAM1, ET-1, sRselectin), which indicates the presence of active systemic inflammation and ED in patients with COPD + AH. It has been established that vascular wall lesions in patients with COPD + AH are characterized by a high level of soluble form of sICAM1, which confirms the presence of endothelial damaging factors [10].

The revealed statistically significant linear correlation between the level of hsCRP, ET-1 with FEV1 and SBP confirm the role of bronchial obstruction in the formation and progression of cardiovascular pathology, which indicates the presence of common pathogenetic processes in patients with COPD with hypertension. In the process of examining patients with COPD with hypertension, it was revealed that as the SBP increased and bronchial obstruction worsened, the degree of violation of the markers of inflammatory status and ED increased [10].

A prospective study [55] showed the relationship between endothelial dysfunction and the development of adverse cardiovascular complications in patients with coronary heart disease, hypertension, and peripheral atherosclerosis.That is why the concept of endothelium as a target organ in the prevention and treatment of CVD is currently formulated.

This position was also confirmed in the studies of S.I.Ovcharenko, Z.N. Nersenyan, in which, in order to determine prognostic significant markers of inflammatory status and endothelial dysfunction in patients with COPD in combination with hypertension. Thus, it was shown in the work that, as bronchial obstruction worsens, the intensity of markers of inflammation and endothelial dysfunction increases [10].

A local inflammatory response in the lungs is accompanied by activation of systemic inflammation, increased oxidative stress, which also leads to impaired vascular endothelial function [27]. These processes are caused by the action of various acute-phase parameters (C-reactive protein - CRP) and pro-inflammatory cytokines (interferon?, interleukins-IL, tumor necrosis factor ?-TNF?), the level and activity of which increase significantly in many chronic diseases of internal organs, including with COPD [9]. The literature data indicate that the development of ED is currently one of the main factors in the pathogenesis of PAH in COPD.

Recently, the role of NO has been actively studied in the pathogenesis of lung diseases. It has been shown that ED in COPD is manifested by a decrease in vasodilation, which may be due to both a decrease in the release of the endothelial relaxing factor and a decrease in the susceptibility of vascular smooth muscles to this substance [11]. With prolonged hypoxia, endothelial relaxation functions decrease, which causes a narrowing of the vessels of the lungs and the occurrence of PAH. NO in COPD determines a particularly high oxidative activity in the lower respiratory tract, as inducible NO synthase is expressed mainly during their inflammation. E.G. Zarubina et al. [4] a study

was conducted of endothelial regulation of vascular tone using ultrasound in patients with COPD in the acute stage and coronary heart disease. It was established that the increase in NO in patients with combined pathology was less in comparison with the group with only COPD and the group with coronary heart disease.

Some studies presented data on an increase in selectin levels in patients with COPD and PAH, indicating the development of ED [58].

As mentioned above, endothelin-1, a polypeptide that is synthesized in bronchial epithelium, endothelium, and macrophages, plays an important role in the pathogenesis of ED. An increase in its concentration is recorded in patients with COPD and PAH, provoking the development of vasoconstriction and the progression of ED [28]. So, when examining patients with COPD in combination with coronary heart disease and hypertension (GB), ED was revealed, manifested by overproduction of endothelin-1 and natriuretic peptide C [2]. At the same time, it is indicated that CNP is a more sensitive indirect marker of ED. This indicates an exacerbation of NO deficiency in the combination of COPD with AH compared with mononosology. Similar results were obtained in the work of S. A. Pribylov [12], where patients with COPD and chronic heart failure (CHF) of ischemic origin showed a higher plasma content of endothelin-1 in combination with ED and an increase in pulmonary pressure, accompanied by diastolic myocardial dysfunction.

According to the research of A.Kh. Akhmineva [2], the study of markers of endothelial dysfunction in chronic obstructive pulmonary disease in a combined pathology in patients with COPD in combination with hypertension and coronary heart disease revealed endothelial dysfunction, manifested by hyper-production of ET-1 and NPS. There was a statistically significant increase in the level of NSAIDs in the group of patients with COPD + AH compared with those in the groups AH and COPD, while the level of ET-1 with a combination of COPD + AH remained comparable to the levels in the groups of patients with COPD and AH. This indicates that CNP is a more sensitive indirect indicator of endothelial dysfunction and indicates an aggravation of nitric oxide deficiency in the combination of COPD + AH compared with mononosology.

It is believed that circulating endothelial progenitor cells (CEPCs) play an important role in maintaining the integrity of the endothelium [32]. There is evidence that a decrease in the level of CEPCs disrupts the systemic function of the vascular wall, which in turn increases the cardiovascular risk.

In the work of S. Pizarro et al. [47] in patients with COPD, a decrease in the number of CEPCs that perform a reparative function in response to damage to the vascular wall and / or tissue ischemia was found, which in turn led to the progression of atherosclerosis and the development of CVD. A study in patients with COPD [36] combined with PAH showed a decrease in CEPCs. Moreover, the number and functional abilities of CEPCs had a negative correlation with the level of pressure in the pulmonary artery. It is suggested that a violation of epigenetic regulation plays a role in the dysfunction of CEPCs, which may contribute to the development of cardiovascular events in patients with COPD [46].

There is evidence of the involvement of Rhokinase in vascular endothelial damage. To date, 2 of its isoforms are known: Rho-kinase1 and Rho-kinase2. The latter is expressed in vascular smooth muscle cells and endothelial cells. Activation of Rho kinase 2 of active GTP-bound Rho-A leads to sensitization of calcium in smooth muscle cells through phosphorylation-mediated inhibition of myosin light chain phosphatase activity and thereby enhances the activity of the regulatory myosin light

chain. It is known that Rho-kinase is involved in many pathophysiological processes, among which the following can be distinguished: narrowing of blood vessels, including the development of myogenic tone and excessive contractile ability of smooth muscles, reduction of smooth muscles of the bronchi in COPD, PAH, ED. These data are confirmed by a number of studies. So, in the work of Y.Bei et al. [18] showed that activation of RhoA / Rhokinase plays an important role in the development of ED in patients with COPD. A significant decrease in endothelium-dependent relaxation and NO levels was found, while the activity of RhoA / Rhokinase was increased in the pulmonary arteries of patients with COPD compared with the control group. Thus, the researchers associated the development of ED in patients with COPD with a suppression of the activity of endothelial NO synthase and activation of RhoA / Rhokinase.

According to N.A. Caroli, A.P. Rebrova during exacerbation in patients with COPD with hypertension, the rates of EDVD were significantly lower than in patients without hypertension [5]. A decrease in EDVD of less than 10% in patients with COPD in the presence of hypertension is detected 2 times more often than without it (59.1% versus 25%) and almost 6 times more often than in healthy individuals (59.1% versus 10%). The data obtained indicate a more pronounced violation of the endothelium-dependent function of the vascular wall in patients with COPD in the presence of hypertension. An increase in the number of circulating endothelial cells (CEC) and their conglomerates in patients with COPD during an exacerbation of the disease, regardless of the presence of hypertension, was also found. Thus, this work has demonstrated that patients with COPD without hypertension already have damage to the vascular wall and impaired antithrombogenic and vasoregulatory function of the endothelium. Moreover, these disorders exist both in the period of exacerbation and in the period of a stable state of patients, and are more pronounced in patients with severe COPD. The identified violations are based on a whole range of pathogenetic factors. The data obtained confirm that the presence of hypertension in patients with COPD leads to more pronounced damage to the vascular wall and a violation of its vasoregulatory function than in patients without hypertension. These differences are most pronounced during an exacerbation of COPD, which may be due to the depletion of compensatory mechanisms in patients with hypertension. Moreover, in the period of stable course of COPD in patients with hypertension, damage to the vascular wall is more pronounced, and in the period of exacerbation, a violation of EDVD is more pronounced than in patients with COPD without hypertension.

Conclusion. Thus, the combination of hypertension and COPD has a negative effect on the state of the vascular wall. In comorbid conditions, endothelial damage and endothelial dysfunction are more pronounced than in the presence of a single disease.

Endothelial dysfunction and chronic persistent inflammation are interrelated processes that play a key role in the development and progression of both COPD and hypertension. These mechanisms constantly potentiate each other, creating a vicious cycle, and contribute to the formation and progression of hypertension in COPD. The appearance of cardiorespiratory comorbidity, accompanied by a syndrome of mutual burdening, forms the features of the clinical picture and diagnosis, which causes certain difficulties in the management of such patients.

It is important to note that the task of modern researchers is to find ways of early detection and correction of changes in the functioning of the endothelium. Only a comprehensive assessment of endothelial function can act as the severity of the prognosis of ED in patients with COPD, as well as an indicator of the effectiveness of drug

therapy. To improve the duration and quality of life of patients, reduce the risk, the frequency of complications and mortality rates, it is necessary to study the function of the endothelium in more detail and look for ways of drug correction taking into account the pathogenetic mechanisms of its formation.

References:

1.Arterial hypertension and COPD - a rational choice of therapy // T.V. Adasheva, V.S. Zadionchenko, M.V. Matsievich [et al.] // Rus. honey. journal -2006. -T. 14, No. 10. - pp.795-800.

2.Akhmineeva A.Kh. Biochemical markers of endothelial dysfunction in chronic obstructive pulmonary disease in combination with hypertension, coronary heart disease Therapeutic archive, 2014, Volume: 4s. 2014.-N 3.-pp.20-23.

3.Zadionchenko V.S. Arterial hypertension and chronic obstructive pulmonary disease are clinical and pathogenetic parallels and treatment options. Grew up. cardiol. journal 2009; 6: 62-9./ Zadionchenko V.S.Arterial'naiagi pertoniiai khronicheskaiaobstruktivnaia bolezn 'legkikh - kliniko-patogeneticheskie paralleli i vozmozhnosti terapii. Ros. kardiol. zhurn. 2009; 6: 62-9. [in Russian].

4.Zarubina E.G., Mishina E.A., Osadchuk M.A. The role of endothelial dysfunction in the pathogenesis of combined cardiopulmonary diseases. Clinical medicine. 2006; 5: 31-34.

5.Karoli N.A., Rebrov A.P. Chronic obstructive pulmonary disease and arterial hypertension: the vascular wall as a target organ in comorbid patients. Rational Pharmacotherapy in Cardiology 2017; 13 (4) / Rational Pharmacotherapy in Cardiology 2017; 13 (4), 513-518.

6.Clinical Dopplerography of occlusive lesions of the arteries of the brain and limbs: textbook. Method. leadership / E.B. Cooperberg, A.E. Gaidashev, A.V. Lavrentyev [et al.] .- M.: Publishing House of the SCSSH RAMS them. Bakuleva, 2007. - 256 p.

7.Kubazhi Khalil. Peculiarities of the course and prognosis in patients with chronic obstructive pulmonary disease in combination with coronary heart disease and arterial hypertension: Diss. ... cand. honey. sciences. Ryazan; 2013.

8.Kutsenko M.A., Chuchalin A.G. The paradigm of comorbidity: syntropy of COPD and IHD. Russian medical journal. 2014; 5: 389-393.

9.Mamaeva M.G., Demko I.V., Verigo Y.I. et al. Markers of systemic inflammation and endothelial dysfunction in patients with chronic obstructive pulmonary disease. Siberian Medical Review. 2014; 1 (85): 12-19.

10.Ovcharenko S.I., Nersesyan Z.N., Morozova T.E. Chronic obstructive pulmonary disease in combination with arterial hypertension: an assessment of systemic inflammation and endothelial dysfunction. Pulmonology. 2015; 25 (5): 561-565.

11.Poplavskaya E.E., Lis M.A. The state of endothelial function and phagocytosis activity in chronic obstructive pulmonary disease and coronary heart disease. Journal of Grodno State Medical University. 2010; 1 (29): 29-31.

12.Pribylov S.A. Pulmonary hypertension, endothelial dysfunction and their correction with lisinopril in patients with heart failure with a combination of coronary heart disease and chronic obstructive pulmonary disease. Cardiology. 2006; 46 (9): 36-40.

13.Yarmysh N.V., Terrible L.N. Endothelial dysfunction and its regulatory factors. Bulletin of problems of biology and medicine. 2014; 2 (111): 37-43.

14.Agusti A., Calverley P.M., Celli B. Characterisation of COPD heterogeneity in the ECLIPSE cohort. Respir. Res.2010; 11: 122.

15.Almagro P, Cabrera FJ, Diez J, Boixeda R, Alonso Ortiz MB, Murio C et al. Comorbidities and Short-term Prognosis in Patients Hospitalized for Acute Exacerbation of COPD. Chest. 2012;142(5):1126-33. DOI: 10.1378/chest.11-2413.

16.Ambrosino P, Lupoli R, Iervolino S, De Felice A, Pappone N, Storino A et al. Clinical assessment of endothelial function in patients with chronic obstructive pulmonary disease: a systematic review with meta-analysis. Internal and Emergency Medicine.2017;12(6):877-85.DOI: 10.1007/s11739-017-1690-0.

17.Babushkina I. V., Sergeeva A. S., Pivovarov Yu. I., Kurilskaya T. E., Koryakina L. B. Structural and Functional Properties of Vascular Endothelium. Kardiologiia. 2015;55(2):82-6

18.Bei Y., DuongQuy S., HuaHuy T. Et al. Activation of RhoA/Rhokinase pathway accounts for pulmonary endothelial dysfunction in patients withchronic obstructive pulmonary disease. Physiol. Rep. 2013; 1 (5): e00105.

19.Bulaeva N. A., Golukhova E. Z. Endothelial dysfunction and oxidative stress: role in the development of cardiovascular disease. Creative cardiology. 2013;1:14-22.

20.Campo G., Pavasini R., Malag?M. et al. Chronic obstructive pulmonary disease and ischemic heart disease como bidity: overview of mechanisms and clinical management. Cardiovasc. Drugs Ther. 2015;29 (2): 147-157.

21.Capone C, Faraco G, Coleman C, Young CN, Pickel VM, Anrather J et al. Endothelin1-Dependent Neurovascular Dysfunction in Chronic Intermittent Hypoxia. Hypertension. 2012;60 (1):106-13. DOI: 10.1161/ HYPERTENSIONAHA.112.193672.

22.Cavailles A, Brinchault-Rabin G, Dixmier A, Goupil F, GutGo bert C, Marchand-Adam S et al. Comorbidities of COPD. Euro pean Respiratory Review. 2013;22(130):454-75. DOI: 10.1183/ 09059180.00008612.

23.Chandra D., Gupta A., Strollo P.J. Jr, et al. Airflow Limitation and Endothelial Dysfunction. Unrelated and Independent Predictors of Atherosclerosis. Am J Respir Crit Care Med. 2016;194(1):38-47.

24.Chandy D., Aronow W.S., Banach M. Current perspectives on treatment of hypertensive patients with chronic obstructive pulmonary disease. Integr Blood Press Control. 2013; 6:101-9.

25.Davenport AP, Hyndman KA, Dhaun N, Southan C, Kohan DE, Pollock JS et al. Endothelin. Pharmacological Reviews. 2016; 68(2):357-418. DOI: 10.1124/ pr.115.011833.

26.Ives SJ, Harris RA, Witman MAH, Fjeldstad AS, Garten RS, McDaniel Jet al. Vascular Dysfunction and Chronic Obstructive Pulmonary Disease: The Role of Redox Balance.Hypertension.2014;63(3):459-67.DOI:10.1161/ HYPERTENSIONAHA.113.02255.

27.Fabbri L.M., Rabe K.F., Ukena C. et al. From COPD to chronic systemic inflammatory syndrome? Lancet. 2007; 370: 797-799.

28.Feng E.Z., Yang S.Y., Huang N.X. et al. Plasma endothelin-1 and nitric oxide correlate with ligustrazine alleviation of pulmonary artery hypertension in patients of chronic cor pulmonale from high altitude plateau during acute exacerbation.Zhongguo Ying Yong Sheng Li Xue Za Zhi. 2014; 30 (6): 532-537.

29.Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. (Global Initiative for Chronic Obstructive lung Disease (GOLD). The updated 2015 report is available on 3. www.goldcopd.com).

30.Golukhova E. Z., Aliyeva A. M., Kakuchaya T. T., Arakelyan G. G., Bulae va N. I.

Endothelin - modern biomarker of cardiovascular diseases. Creative cardiology. 2011;2:97-103.

31.Gungor ZB, Sipahioglu N, Sonmez H, Ekmekci H, Toprak S, Ayaz G et al. Endothelial Dysfunction Markers in Low Cardiovascular Risk Individuals: Comparison of Males and Females. Journal of Medical Biochemistry. 2017;36(1):62-72. DOI: 10.1515/jomb-2016-0030.

32.Janssen W.J., Yunt Z.X., Muldrow A. et al. Circulating hematopoietic progenitor cells are decreased in COPD. COPD. 2014; 11 (3): 277-289.

33.Karoli N.A., Rebrov A.P. Arterial hypertension in patients with bronchial asthma and chronic obstructive pulmonary disease. Klinitsist. 2011;2:20-30.

34.Kirkham PA, Barnes PJ. Oxidative Stress in COPD. Chest. 2013;144(1):266-73. DOI: 10.1378/chest.12-2664.

35.Kushnarenko N. N., Govorin A. V. Clinical significance of endothelial dysfunction and insulin resistance syndrome in patients with gout with hypertension. Rational Pharmacotherapy in Cardiology. 2013;9(5):482-7.9 ISSN 0022-9040.

36.Liu P., Zhang H., Liu J. et al. Changes of number and function of late endothelial progenitor cells in peripheral blood of COPD patients combined with pulmonary hypertension. Thorac. Cardiovasc. Surg. 2014 Sep. 16. [Epub ahead of print].

37.Mannino DM, Sanderson WT. Using Big Data to Reveal Chronic Respiratory Disease Mortality Patterns and Identify Potential Public Health Interventions. JAMA. 2017;318(12):1112-4. DOI: 10.1001/jama.2017.11746.

38.Mel'nikova Yu.S., Makarova T.P. Endothelial dysfunction as a central link chronic diseases pathogenesis. Kazan medical journal. 2015;96(4):659-65.

39.Mordi I, Mordi N, Delles C, Tzemos N. Endothelial dysfunction in human essential hypertension: Journal of Hypertension.2016;34(8):1464-72.

40.Mnzel T, Camici GG, Maack C, Bonetti NR, Fuster V, Kovacic JC. Impact of Oxidative Stress on the Heart and Vasculature. Journal of the American College of Cardiology.2017;70(2):212-29.DOI: 10.1016/j.jacc.2017. 05.035.

41.Mnzel T, Gori T, Keaney JF, Maack C, Daiber A. Pathophysiological role of oxidative stress in systolic and diastolic heart failure and its the rapeutic implications. European Heart Journal. 2015;36(38):2555-64. DOI: 10.1093/eurheartj/ehv305.

42.Murray C.J., Lopez A.D. Measuring the global burden of disease. N. Engl. J. Med. 2013; 369: 448-457.

43.Nosratola D., Bernardo R. Mechanisms of disease: oxidative stress and inflammation in the pathogenesis of hypertension. Nat. Clin. Pract. Nephrol. 2006; 2 (10): 582-593.

44.Pan J., Xu L. Cai S.X. et al. The association of pulmonary function with carotid atherosclerosis in older Chinese: Guangzhou Biobank Cohort StudyCVD Subcohort. Atherosclerosis. 2015; 243 (2): 469-476.

45.Park KH, Park WJ. Endothelial Dysfunction: Clinical Implications in Cardiovascular Disease and Therapeutic Approaches. Journal of Kore an Medical Science. 2015;30(9):1213-25. DOI: 10.3346/jkms.2015.30.9.1213.

46.Paschalaki K.E., Starke R.D., Hu Y. et al. Dysfunction of endothelial progenitor cells from smokers and chronic obstructive pulmonary disease patients due to increased DNA damage and senescence. Stem. Cells.2013; 31 (12): 2813-2826.

47.Pizarro S., GarcaLucio J., Peinado V.I. et al. Circulating progenitor cells and vascular dysfunction in chronic obstructive pulmonary disease. PLoS One.2014; 9 (8): e106163.

48.Popova M. A., Terentyeva N. N., Dolgopolova D. A., Marenina T. V. Endothelial dysfunction with stable angina and myocardial infarction in combination with chronic obstructive pulmonary disease. Bulletin of Siberian medicine. 2015;14(6):68-74.

49.RodriguezMiguelez P., Seigler N., Bass L. et al. Assessments of endothelial function and arterial stiffness are reproducible in patients with COPD. Int. J. Chron. Obstruct. Pulm. Dis.2015; 10: 1977-1986.; 11. Campo G., Pavasini R., Malag?M. et al. Chronic obstructive pulmonary disease and ischemic heart disease como bidity: overview of mechanisms and clinical management. Cardiovasc. Drugs Ther. 2015;29 (2): 147-157.

50.Schneider K.M., O'Donnell B.E., Dean D. Prevalence of multiple chronic conditions in the United States' Medicare population. Health Qual. Life Outcomes.2009; 7: 82.

51.Selikhova M. A., Kuvaev V. S. Up-to-date state of the problem concerning endothelial dysfunction correction in COPD. Aspirantskiy Vestnik Povolzhiya. 2012;5-6:66-8

52.Shpagin I. S., Kotova O. S., Pospelova T. I., Gerasimenko O. N., Shpagina L. A., Ermakova M. A. Chronic obstructive pulmonary disease in combination with essential arterial hypertension: clinical, functional and molecular genetic features. Bulletin of mo dern clinical medicine. 2016;9(4):56-65..

53.Smiljic S. The clinical significance of endocardial endothelial dysfunction. Medicina. 2017;53(5):295-302. DOI: 10.1016/j.medici.2017.08.003.

54.Strisciuglio T, De Luca S, Capuano E, Luciano R, Niglio T, Trimarco B et al. Endothelial Dysfunction: Its Clinical Value and Methods of Assessment. Current Atherosclerosis Reports. 2014;16(6). DOI: 10.1007/s11883-014-0417-1.

55.Suylen R.I., Smits J.F., Daemen M.J. Pulmonary artery remodeling difference in hypoxia and monocrotaline induced pulmonary hypertension. Am. J. Respir. Erit. Care Med. 2008; 157: 1423-1428.

56.Takahashi T., Kubo H. The role of microparticles in chronic obstructive pulmonary disease. Int. J. Chron. Obstruct.Pulm. Dis. 2014; 9: 303-314.

57.Talavera-Adame D. Endothelium-derived essential signals involved in pancreas organogenesis. World Journal of Experimental Medicine. 2015;5(2):40. DOI: 10.5493/ wjem.v5.i2.40.

58.Tanaseanu C., Tudor S., Tamsulea I. et al. Vascular endothelial growth factor, lipoporotein-associated phopholipase A2, sPselectin and antiphospholipid antibodies, biological markers with prognostic value in pulmonary hypertension associated with chronic obstructive pulmonary disease and systemic lupus erithematosus. Eur. J. Med. Res. 2007; 12 (4): 145-151.

59.Vignon-Zellweger N, Heiden S, Miyauchi T, Emoto N. Endothelin and endothelin receptors in the renal and cardiovascular systems. Life Sciences. 2012;91(13-14):490-500. DOI: 10.1016/j.lfs.2012.03.026.

60.Vorobeva E. N., Vorobyev R. I., Sharlaeva E. A., Fomicheva M. L., Sokolova G. G., Kazyzaeva A. S. et al. Endothelial dysfunction in cardiovascular diseases: risk factors, methods of diagnosis and correction. Acta Biologica Sibirica. 2016;2(1):21-40.