# ENDOTHELIAL FUNCTION IN PATIENTS WITH COPD AND CARDIOVASCULAR DISEASE (REVIEW)

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**Abstract**

Cardiovascular pathology is one of the frequent comorbidities in patients with chronic obstructive pulmonary disease, due to both genetic predisposition and common risk factors (smoking, senile age, male gender, sedentary lifestyle, obesity). The article shows that development of endothelial dysfunction is one of the earliest phases of pathogenesis in this setting. Endothelial dysfunction mechanisms are defined and characterized, including imbalance of vasoconstricting and vasodilating agents with the emergence of "vicious circles" that violate hematovascular homeostasis. The role of nitric oxide, endothelin-1, intercellular adhesion molecule-1 (ICAM-1) in the development of endothelial dysfunction in COPD patients is discussed. The article defines the concept of oxidative stress, the most potent oxidants and mechanisms of their damaging effect are listed. A particular attention is paid to 8-isoprostane as a golden standard in assessment of oxidative stress in patients with COPD.

***Keywords:*** *chronic obstructive pulmonary disease, hypertension, coronary artery disease, heart failure, nitric oxide, endothelin-1, intercellular adhesion molecule-1, 8-isoprostane.*

## Background

Chronic obstructive pulmonary disease (COPD) is a medically, socially and economically relevant problem, both in Ukraine and worldwide, leading to limitation of exercise capacity and ranking third among causes of disability after coronary disease (CAD) and hypertension [1–3]. According to the World Health Organization (WHO), roughly every 10 seconds one person dies due to COPD. Currently, more than 210 million people suffer from this disease and by 2030, COPD trends to become the third leading cause of death in the world [2]. COPD is currently the 4th cause of death, which is primarily due to the high prevalence of smoking among both men and women. It is only surpassed by cardiovascular diseases, infectious diseases (including HIV infection/AIDS) and cancer [4].

According to the WHO estimates, about one third of the world's adult population are smokers. In our country, 58% of men and 14% of women consider themselves to be smokers. The prevalence of tobacco smoking among adolescents is impressive, reaching 50% by the age of 13–16 years. According to the British research company ERC, Ukraine ranks second in the world in terms of the number of cigarettes smoked per person per year. On average, a Ukrainian smokes 2,500 cigarettes a year, or seven a day [5]. More than 90% of COPD deaths occur in low- and middle-income countries.

The modern concept of COPD endorsed by the WHO experts emphasizes that severity and prognosis of COPD are often determined by extrapulmonary manifestations of concomitant diseases. This position was reflected in the Global Strategy for the Diagnosis, Treatment and Prevention of COPD (GOLD), 2011 [6].

Most patients with COPD have multiple concomitant diseases. A five-year follow-up of patients with COPD has shown that the risk of death increases not only in proportion to the severity of bronchial obstruction, but also with an increase in the number of concomitant diseases (from 1 to 3) [7].

COPD is accompanied by systemic manifestations, in particular, a significant increase in the incidence of cardiovascular diseases. In addition,

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it is cardiovascular complications that are the main cause of death in patients at the initial stages of COPD. The high frequency of the combination of COPD and cardiovascular pathology is due to genetic predisposition and common risk factors: smoking, senile age, male gender, sedentary lifestyle, obesity, obstructive sleep apnea/hypopnea, secondary hyperaldosteronism, as well as hypertensive effect of a number of drugs used for the treatment of patients with COPD (corticosteroids, beta-2 agonists, etc.) Hypertension, CAD (including myocardial infarction and angina pectoris), cardiac arrhythmias and heart failure (HF) are most common in patients with COPD [8].

The comorbidity of COPD and cardiovascular pathology is driven by a combination of complex multi-stage pathogenetic processes, among which it is difficult to single out the leading factor. Recent studies [9] emphasize the importance of the concept of comorbidity, which implies the formation of relationships and interactions between co-existing diseases, as well as presence of common pathogenetic mechanisms, such as chronic low grade inflammation, oxidative stress, and endothelial dysfunction.

The **purpose** of this review was to highlight the pathogenetic features of endothelial dysfunction in patients with comorbid course of chronic obstructive pulmonary disease and cardiovascular pathology.

Large epidemiological studies have demonstrated that the leading cause of mortality in patients with COPD and bronchial asthma (BA) is not respiratory failure, as it has been traditionally believed, but cardiovascular events. The severity of the course and prognosis in COPD and BA is determined by the involvement of heart and blood vessels in the pathological process [10], which can lead to development of concomitant cardiovascular pathology. At the annual ERS congress in 2009, J. Feary and N. Barnes from the UK presented the results of the Health Improvement Network, a computer database that unites more than 5 million case histories: – COPD patients are 5 times more likely to be diagnosed with cardiovascular diseases (CVD); – in the 35–45 years subgroup, patients with COPD have a 7.6 times higher risk of developing concomitant CVD; – in young patients with COPD, the risk of developing myocardial infarction increases 12-fold [11].

Endothelial dysfunction is a vascular complication of BA and COPD, which, in turn, aggravates the growing respiratory failure, hypoxemia and tissue hypoxia [12]. In this regard, the functional state of the endothelium at different periods of the disease is the subject of active study.

To date, more and more data are accumulating that not only local inflammation in the bronchi, but also persistent systemic inflammation, typical for patients with COPD, makes a significant contribution to the development and progression of endothelial dysfunction, atherosclerosis and CVD in patients with broncho-obstructive pathology, determining the interest to this problem.

**8-isoprostane as the gold standard for assessing oxidative stress in patients with COPD**

The main role in the mechanisms of development of endothelial dysfunction is played by oxidative stress developing against a background of hypoxia [13], which leads to an increase in the production of powerful vasoconstrictors, cytokines and tumor necrosis factor-α (TNF-α). For today, the term "oxidative stress" (OS) is understood as a state in which the amount of free radicals generated in the body significantly exceeds the capacity of endogenous antioxidant systems that ensure their elimination [14]. OS is a common pathway leading to damaging of the vascular endothelium. The disturbance of the equilibrium between synthesis and elimination of reactive oxygen species (ROS) such as (O2-) and (H2O2) affects the homeostasis of cellular oxidative stress, playing an important role in the development of cardiovascular disease [14]. Uncontrolled generation of ROS and their derivatives causes damage to proteins, nucleic acids, enzymes and biological membranes, which may lead to cellular death. OS might also lead to the appearance of cellular mutations and malignant transformation [15]. Toxic components of cigarette smoke can also induce OS, leading to disruption of the functional activity of the endothelium.

8-iso-PgF2α (8-isoprostane) is considered to be one of the most specific biological markers that allows estimation of the level of free radicals production with a sufficient degree of accuracy, reliability, and reproducibility. 8-isoprostane is a metabolic product in the reactions of peroxidation of arachidonic acid, isomeric prostaglandin F2, and its amount is directly proportional to the level of free radicals formed. Determination of the level of 8-isoprostane serves as the gold standard for in vivo oxidative stress evaluation [16].

8-isoprostane reflects the cellular effects of OS and, therefore, the inflammatory process in the airways. In recent years, there has been an increasing interest in the study of the lungs by means of non-invasive methods, including measurement of biomarkers in exhaled air and

exhaled breath condensate (EBC) [17]. These methods are safe, do not affect lung function and the level of exhaled mediators [18], which allows their use as epidemiological methods for studying pathological processes (OS and inflammation) in respiratory diseases.

The concentration of 8-isoprostane in the EBC was increased in patients with remission of COPD compared with healthy non-smokers [19, 20]. Also, the level of 8-isoprostane in EBC was increased in healthy smokers [20] and patients with exacerbation of COPD [19, 21, 22]. Montuschi P. et al. showed that the levels of 8-isoprostane in patients with COPD, both smokers and non-smokers, were 1.8 times higher than in healthy smokers. In healthy non-smokers, its concentration was 2.2 times lower than in healthy smokers. There were no correlations between the level of 8-isoprostane and forced expiratory volume in 1 second (FEV1), smoking experience, cellular composition of sputum or severity of dyspnea in patients with COPD [19, 20]. However, a 2-fold increase in 8-isoprostane level in EBC compared to healthy people was reported in patients with mild course of bronchial asthma, and in severe course, its level was 3 times higher than in patients with mild bronchial asthma, regardless of inhalation treatment received. After treatment, its concentration decreased [23, 24].

**Pathogenetic features of endothelial dysfunction in patients with chronic obstructive pulmonary disease and cardiovascular pathology**

Currently, the prominent role of endothelium and nitric oxide in the genesis of cardiovascular complications of COPD has been proven. The unique position of endothelial cells at the border between circulating blood and tissues, and in the case of the lungs, the air environment of the alveolar space and blood, makes them not only the most important, but also the most vulnerable to various pathogenic influences that can cause damage to endothelial cells, thereby contributing to the development of endothelial dysfunction (ED) [25]. ED is based on structural (apoptosis and desquamation of endothelial cells) and functional (imbalance between biologically active substances produced in the endothelium) changes. Endothelium forms a thin semi-permeable membrane lining the heart and blood vessels from the inside, continuously producing a huge amount of biologically active substances (BAS). Hence, the complex of endothelial cells may be considered a giant paracrine organ distributed throughout the human body [26]. Endothelial cells produce BAS that take part in the regulation of vascular tone, synthesis of growth factors and mediators of nonspecific inflammation. In healthy individuals, the effect of endothelial BAS is in dynamic equilibrium. The main role of the endothelium is associated with dilatation of the vascular bed, which provides the peripheral muscles and internal organs with adequate blood supply [27]. Under physiological conditions, secretion of vasodilating substances predominates. Nitric oxide (NO), which controls the basal tone of arterioles and, as a consequence, participates in blood pressure (BP) control, is the main endothelium-derived vasodilating factor. If the ability of endothelial cells to produce vasodilating substances decreases, and the formation of vasoconstrictors persists or increases, the so-called ED is formed – a disturbance of the equilibrium of oppositely acting BAS that violates hematovascular homeostasis. Endothelium is a dynamic system that maintains the normal properties of circulating blood by inhibiting hypercoagulation and preventing leukocyte adhesion [28].

In the pathogenesis of COPD, the main factor in the development of ED is a decrease in NO synthesis with preserved or increased secretion of vasoconstrictors (endothelin-1, thromboxane, angiotensin II), as well as cytokines and tumor necrosis factor-α (TNF-α) that further suppress nitric oxide production [28], which impairs endothelium-dependent vasorelaxation and leads to degradation and adverse changes in vascular cytoarchitectonics.

Many studies have assessed the diagnostic value of plasma ED biomarkers, since this is a simple and objective method that provides information both on normal physiological processes and in pathology. Taking into account the fact that the levels of circulating plasma BAS depend not only on the severity of ED but also on other factors (concomitant pathology, immune diseases, chronic infections), the results being significant in a separate study may not necessarily reflect the picture at the populational level. Therefore, an ED biomarker should optimally have a predictive role in relation to the cardiovascular risk. The results of earlier studies [29] showed that E- and P-selectins, endothelin-1, von Willebrand factor, cell adhesion molecules, and thrombomodulin have a significant prognostic value in this context.

A significant increase in the blood endothelin-1 (ET-1) level has been reported in patients with uncomplicated hypertension. In patients with stage 2 and 3 hypertension, the level of ET-1 and its precursor increases 10-fold [30]. ET-1 is a

large bicyclic polypeptide synthesized in the vascular endothelium, bronchial epithelium and in alveolar macrophages. Its main function is to activate vasoconstriction, particularly in small vessels. Another function of ET-1 is the ability to influence platelet adhesion, which contributes to formation of microthrombosis [31]. In hypoxia, the level of ET-1 in the blood increases. Especially high plasma levels are detected in COPD exacerbation. In patients with COPD with hypoxemia, the level of ET-1 in the arterial blood is higher compared to those without hypoxemia [32]. High levels of ET-1 contribute to the further progression of ED, thereby aggravating the course of the disease [33]. A significant association has been shown between the level of ET-1 and hemodynamic parameters of pulmonary circulation. Shao D. et al. have shown the correlation between ET-1 levels with pulmonary artery pressures and pulmonary vascular resistance [34]. Presence of high ET-1 levels in patients with COPD contributes to adverse cardiovascular and pulmonary remodeling with dilation of the cardiac chambers and formation of a chronic cor pulmonale [35–37]. ET-1 induces prolonged vasoconstriction, hypertrophy of the smooth myocytes and endothelial remodeling affecting arterial elasticity [38]. Thus, it can be assumed that impaired endothelial function triggers the process of structural and anatomical changes in the vascular wall and increases the arterial stiffness [39].

The interaction of leukocytes with the endothelium occurs through special adhesive molecules, which are present on both endothelial cells and leukocytes. Selectins (P, E, L) present a class of adhesion molecules. P- and E-selectins are expressed by the endothelium. An increase in the endothelial adhesiveness plays an important role in the pathogenesis of ED in inflammation, atherosclerosis, septic shock, and other pathological processes. P-selectin is accumulated in the endothelium and released from it during stimulation. Adhesion molecules may be getting into the bloodstream not only with stimulation of the endothelium, but also in its activation and damage, as evidenced by data provided by E. Oelsner et al. (2013), showing high levels of endothelial dysfunction biomarkers (endothelin-1 and adhesive molecules (P-selectin and ICAM-1)) in COPD patients with their level correlating to the severity of bronchial obstruction [40]. This data is also confirmed by the results of the Framingham study, in which patients with COPD had high levels of inflammation markers: CRP, ICAM-1 and P-selectin, the activity of which had an inverse relationship with the value of forced expiratory volume in 1 second (FEV 1) [41]. A study by J. Zhonghua et al. has also shown an increase of P-selectin levels in patients with COPD, which was more prominent during exacerbations [42]. As for the previously mentioned intercellular adhesion molecule-1 (ICAM-1), it belongs to the family of immunoglobulins and serves as a functional ligand for the leukocyte integrin LFA-1 (Lymphocyte Function-Associated Antigen-1). Adhesion of monocytes to activated endothelial cells due to overexpression of ICAM-1 on their surface is considered the earliest stage of endothelial damage. Inhibition of adhesion molecules expression, in particular ICAM-1, prevents the accumulation of inflammatory agents in the vascular wall, which reduces their ability to cause endothelial damage that is characteristic of COPD [43] and cardiovascular pathology [44].

The leading role in reduction of the endothelium-dependent vasodilation (EDVD) in patients with COPD is played by intracellular OS, and smoking is the most significant exogenous factor in its formation. Free radical oxidation significantly reduces NO production by endothelial cells [45], which is manifested by suppression of NO synthase expression by endothelial cells and stimulation of adhesion molecules expression, followed by increased adhesion of leukocytes to the luminal surface of the vascular wall [46]. It has been shown that cigarette smoking leads to impaired vascular reactivity, namely, weakening of endothelium-dependent vasodilation [47]. It was found that an increase in smoking intensity was characterized by a progressive decrease in EDVD, as well as development of not only endothelial damage, but an adverse remodeling of deeper layers of vascular wall in smoking COPD [48].

To date, the features of the formation and clinical significance of increased arterial stiffness in patients with CVD (atherosclerosis, hypertension, ischemic heart disease) are most fully studied [49]. Perhaps, it is the increased arterial stiffness and endothelial dysfunction that is the link between COPD and CVD.

**Features of the course of hypertension, coronary artery disease, heart failure in COPD**

Previous studies have shown that the patients with a comorbid course of COPD and CVD have distinct clinical features compared to isolated course of these diseases.

The patients with hypertension and COPD are characterized by a higher resting heart rate (HR) [50]; more frequent target organs damage, including renal failure, and a higher risk of

cardiovascular complications when compared with hypertensive patients without COPD at the same blood pressure (BP); hypertension in patients with COPD is characterized by earlier manifestation and higher BP values [51]. In patients with COPD, significant changes in the course of hypertension are related mainly to the night period: disturbance of the circadian rhythm of blood pressure with insufficient night dip; a more significant increase in DBP and an increase in the morning surge. All patients showed an increase in blood pressure variability [52]. It follows that such patients need to optimize BP control in the evening and night hours.

In a Spanish study evaluating airflow restriction using spirometry in patients with/without CVD in general population and among hospitalized CAD patients, airflow restriction was found in 19.2%, 17.5% and 33.6%, respectively [53]. The highest prevalence of COPD was observed among patients with CAD. Therefore, it would be beneficial for all CVD patients to undergo spirometry [54]. The patients with established CAD and COPD had more severe atherosclerosis vs those without COPD [55]. Another study showed that patients with COPD had more atherosclerotic lesions found in PCI compared with patients without COPD, and these patients had a higher mortality rate [56, 57].

The PREMIER study, which evaluated the course of myocardial infarction, showed that in patients with COPD, the risk of mortality and readmission was twice as high and the quality of life was lower [58,59]. A large retrospective observational study of Swedish COPD patients in primary care has shown that coexisting heart failure, stroke and myocardial infarction were the strongest predictors of death, highlighting the importance of early detection and treatment of comorbidities. A reduced risk of death was also found to be associated with the use of inhaled corticosteroids, beta-blockers and aspirin, and an increased risk associated with the use of long-acting muscarinic antagonists and N-acetyl-cysteine [60].

**Conclusions**

The development of cardiovascular diseases against a background of chronic obstructive pulmonary disease may be considered to some extent natural. The evidence shows that endothelial dysfunction is one of the main components in the pathogenesis of comorbid course of chronic obstructive pulmonary disease with hypertension, coronary heart disease. Assessment of the endothelial function may be of importance for expanding understanding of pathogenesis in many conditions and clinically for predicting the development of complications. This will make it possible to use drug therapy in the treatment of such patients, including the drugs that have a positive effect on the state of the endothelium.

**Declarations**

**Statement of Ethics**

The authors have no ethical conflicts to disclosure.

**Consent for publication**

All authors give their consent to publication.

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