Журнал «Перспективи та інновації науки»
(Серія «Педагогіка», Серія «Психологія», Серія «Медицина»)
№ 5(51) 2025

UDC 616. 24 – 007. 272 – 072 : 661. 5

https://doi.org/10.52058/2786-4952-2025-5(51)-2622-2630

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CLINICAL SIGNIFICANCE OF CHANGES IN NITRIC OXIDE CONCENTRATION IN EXHAUSTED AIR IN PATIENTS WITH COPD

Abstract. The development of extrapulmonary effects of COPD is of important clinical and prognostic significance. Cardiovascular disorders are considered as one of the potential systemic manifestations of COPD, the earliest of which is endothelial dysfunction. In the last decade, the role of nitric oxide (NO) in the pathophysiology of respiratory diseases has been intensively studied, including as a marker of endothelial dysfunction. In COPD, there are enough factors that determine the development of endothelial dysfunction, such as hypoxia, increased levels of various biologically active substances, smoking, etc. In the modern literature, there are limited data on the study of the development of endothelial dysfunction and ventilation disorders in COPD patients who are not exposed to smoking and have an uncomplicated cardiovascular history. The aim of the study was to study the concentration of NO in exhaled air in non-smoking COPD patients without concomitant cardiovascular disease, depending on the severity of the disease in stable and exacerbations of COPD. 25 men with COPD (GOLD 1-4) in remission and exacerbation and 11 practically healthy men were examined. All of them had never smoked. The indicators of lung ventilation function and the concentration of NO in exhaled air were determined. It was found that both in the remission phase and in exacerbations of COPD, the concentration of NO in exhaled air exceeds the average values of the indicator in the control group ($p < 0.05$). During exacerbation of COPD in patients with a mild course of the disease (GOLD 1-2), the level of NO in exhaled air increases compared to remission ($p < 0.05$), but in patients with severe manifestations of COPD (GOLD 3-4) the increase in the indicator was not significant ($p > 0.05$). During exacerbation of severe COPD (GOLD 3-4), a correlation was established between the concentration of NO in exhaled air and the duration of the disease ($r = 0.67$, $p = 0.02$). No relationship was found between the level of NO in exhaled air and the age of patients, the frequency of exacerbations

per year, as well as indicators of lung ventilation function, regardless of the severity of the disease.

Keywords: COPD, endothelial dysfunction, nitric oxide, smoking, exacerbation, remission.

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КЛІНІЧНЕ ЗНАЧЕННЯ ЗМІНИ КОНЦЕНТРАЦІЇ ОКСИДА АЗОТА В ПОВІТРІ, ЩО ВИДИХАЄТЬСЯ У ХВОРИХ НА ХОЗЛ

Анотація. Розвиток позалегеневих ефектів ХОЗЛ має важливе клінічне та прогностичне значення. Як один з потенційних системних проявів ХОЗЛ розглядають кардіоваскулярні порушення, найбільш раннім з яких є ендотеліальна дисфункція. В останнє десятиліття інтенсивно досліджується роль оксиду азоту (NO) у патофізіології захворювань системи дихання, в тому числі як маркера ендотеліальної дисфункції. При ХОЗЛ існує достатньо факторів, що визначають розвиток ендотеліальної дисфункції, таких як гіпоксія, підвищення вмісту різних біологічно активних речовин, тютюнопаління та ін. У сучасній літературі обмежені данні, що до вивчення розвитку ендотеліальної дисфункції та вентиляційних порушень у хворих на ХОЗЛ, які не зазнають впливу тютюнопаління та мають не обтяжений серцево-судинний анамнез. Метою дослідження було вивчення концентрації NO в повітрі, що видихається у пацієнтів з ХОЗЛ, які не палять, без супутньої патології серцево-судинної системи, в залежності від тяжкості захворювання при стабільному перебігу та загострені ХОЗЛ. Обстежено 25 чоловіків, хворих на ХОЗЛ (GOLD 1-4) в ремісії й загострені та 11 практично здоровихчоловіків. Всі вони ніколи не палили. Визначалисьпоказники вентиляційної функції легень таконцентрація NO в повітрі, що видихається. Встановлено, що яку фазу ремісії так і при загострені ХОЗЛ концентрація NO в повітрі, що видихається перевищує середнізначення показника в групі контроля ($p < 0,05$). При загострені ХОЗЛ у хворих з нетяжким перебігом захворювання (GOLD 1-2) рівень NOв повітрі, що видихається підвищується в порівнянні з ремісією ($p <0,05$), алеу пацієнтів з тяжкими проявами ХОЗЛ (GOLD 3-4) зростання показника було недостовірне ($p > 0,05$). При загострені ХОЗЛ тяжкого перебігу (GOLD 3-4) встановлено кореляційний зв'зок між концентрацією NO в повітрі, що

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видихається та тривалістю захворювання (r = 0,67, p = 0,02). Не виявлено зв'зку між рівнем NO в повітрі, що видихається та віком пацієнтів, частотою загострень за рік, а також показниками вентиляційної функції легень, незалежно від тяжкості перебігу захворювання.

Ключові слова: ХОЗЛ, ендотеліальна дисфункція, оксид азоту, тютюнопаління, загострення, ремісія.

Statement of the problem. According to the data presented in the Global Strategy for Diagnosis, Treatment and Prevention of Chronic Obstructive Pulmonary Disease (COPD), along with lung damage, the disease is characterized by extrapulmonary effects, which allows defining COPD as a systemic pathology [5].

In recent years, extrapulmonary manifestations of the disease have been discussed increasingly [2,5]. It has been shown that the development of extrapulmonary effects of COPD has important clinical and prognostic significance [3]. Cardiovascular disorders are considered as one of the potential systemic manifestations of COPD, the most significant of which is endothelial dysfunction (ED) [4,5].

The endothelium is a highly specialized metabolically active monolayer of cells lining all vessels of the body. The endothelium produces vasorelaxing (endothelial relaxation factor - nitric oxide (NO), prostacyclin, endothelial hyperpolarizing factor) and vasoconstrictor (endothelin-1, thromboxane A2) substances [1].

In the last decade, the role of NO in the pathogenesis of various pathologies of the lungs and cardiovascular system has been intensively studied. At rest, the endothelium constantly secretes NO, maintaining normal arterial tone. NO is synthesized from L-arginine under the influence of NO synthases (NOS). There are 3 known forms of NOS: endothelial, macrophage and neuronal, which lead to local synthesis of NO and determine its effect on the respiratory system. NO secreted by endothelial cells has a vasodilatory effect at the level of small arteries and arterioles, regulating vascular resistance [4, 6]. It has been established that hypoxia reduces NO synthesis. Under normal conditions, NO synthase activity in the lungs is found in the endothelium of large and medium-sized vessels. Hypoxia stimulates the synthesis of macrophage NOS in smooth muscle cells of small vessels, where macrophage NOS is not normally detected. Under hypoxia, the content of endothelial NOS in the pulmonary vessels decreases, a deficiency of endothelial NO occurs, which leads to vasoconstriction and the development of pulmonary hypertension and, at the same time, hyperproduction of NO in the smooth muscle, causing vascular damage [3, 7].

Under physiological conditions, there is a balance between endothelium-dependent vasodilators and vasoconstrictors, the disruption of which leads to local spasm and increased vascular tone. Receptors located in the endothelium, converting mechanical signals, induce NO synthase, which leads to the accumulation of NO and

vasodilation [6, 9]. Macrophage NO is involved in anti-infective protection by enhancing the intracellular destruction of microorganisms. The ability of alveolar macrophages to produce NO plays an important role in maintaining local immune homeostasis in the respiratory tract [4].

NO accumulation causes relaxation of vascular smooth muscle cells by reducing the concentration of Ca2+ in the cytoplasm, and also neutralizes the bronchoconstrictor effect of acetylcholine. Data allowing us to consider NO as a mediator preventing bronchoconstriction were obtained in experiments on models of isolated trachea and bronchi [7].

According to modern concepts, the normal concentration of NO in the bronchi is on average 7 (from 3 to 11) ppb (part per billion – molecules per 1 billion water molecules) [2, 5]. There are data indicating higher NO levels in the bronchi – from 5 to 25 ppb [9]. In our work, we focused on the average concentration of NO in exhaled air in healthy people in the control group, which was 12.1 ppb.

Also, an increase in the level of NO in exhaled air depends on the presence of inflammatory changes in the bronchi, which affect the activity of NOS [6, 9]. Bradykinin, acetylcholine, histamine, thrombin and physical factors (blood flow, pulse pressure), as well as antidiuretic hormone stimulate the secretion of NO [4].

A number of studies have shown that in diseases accompanied by inflammation of the respiratory tract, the content of NO in exhaled air increases. Currently, NO is recognized as an important marker of inflammation activity in bronchial asthma [6]. Thus, NO plays an important role in the regulation of lung function and in the pathophysiology of diseases of the respiratory system [9].

Based on the above, in COPD there are enough factors that determine the development of ED, such as hypoxia, an increase in the content of various biologically active substances, etc. [3]. On the other hand, the prevalence of cardiovascular pathology accompanied by endothelial damage among patients with COPD is higher than in the general population [2, 9]. Therefore, the question of cause-and-effect relationships in the development of ED in patients with COPD remains unresolved. Tobacco smoking is also a proven factor determining the development of ED and masking the tendency to increase NO levels during exacerbation of COPD. The effect of tobacco smoke and inflammation of the bronchial wall are considered potential mechanisms of ED, including in the early stages of the disease [6, 8].

At the same time, there is limited data in the current literature on the study of the development of ED and ventilation disorders in COPD patients who are not exposed to tobacco smoke and have a non-complicated cardiovascular history.

Purpose of the study. To study the concentration of NO in exhaled air in non-smoking patients with COPD without concomitant cardiovascular pathology in remission and exacerbation, depending on the severity of the disease.

Materials and research methods. A total of 25 men (mean age 61.13 ± 2.10 years, mean disease duration 11.97 ± 0.63 years) suffering from COPD of varying

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severity (GOLD 1-4) were examined. All of them had either never smoked or abstained from smoking for more than five years. The diagnosis of COPD was established in accordance with the criteria set out in the Order of the Ministry of Health of Ukraine No. 1610 dated September 20, 2024 [1]. All patients received standard therapy depending on the severity of the disease.

The patients were divided into 2 groups depending on the severity of COPD: group 1 consisted of 13 patients with mild COPD (GOLD 1-2), group 2 - 12 patients with severe manifestations of the disease (GOLD 3-4). All patients were examined both in exacerbation and remission. The control group 3 included 11 practically healthy volunteers who had never smoked, with normal indices of the pulmonary ventilation function.

To verify the diagnosis of COPD, the indices of the pulmonary ventilation function were determined using the MasterLab spirograph (Jaeger, Germany): the levels of forced expiratory volume in the first second (FEV1), forced vital capacity (FVC), and the FEV1/FVC1 ratio were analyzed; a test for the reversibility of bronchial obstruction with a short-acting β2-agonist (salbutamol) was performed. The concentration of NO in exhaled air was determined using the Niox Mino device (Aerocrine, Sweden) in the stable course of COPD and during exacerbations.

The studies were conducted from 8 to 10 am, on an empty stomach, before taking medications.

The number of exacerbations per year was studied prospectively. The observation period was 12 months. For statistical processing of the obtained results, the program "Statistics 6" was used with the definition of the arithmetic mean, the criterion of reliability of differences, the level of significance of differences. A correlation analysis was also carried out between the indicators of the NO level in exhaled air and the indicators of the ventilation function of the lungs, the age of patients, the duration of COPD and the frequency of exacerbations of the disease per year.

Results anddiscussion. Both groups of patients and the control group were comparable in age, but the groups of patients had different degrees of airway obstruction severity and disease duration. Patients in group 2 demonstrated a significantly longer disease duration and a greater number of exacerbations per year (Table 1).

Table 1

Characteristics of the examined patients

Indicators	Groups		
	1 (n = 13)	2 (n = 12)	3 (n = 11)
GOLD	1-2	3-4	-
Age (M ± m, years)	59,05 ± 1,82	63,20 ± 2,38	57,72 ± 2,87
Duration of disease (M ± m, years)	8,11 ± 0,49	15,83 ± 0,76	-
Number of exacerbations per year (M ± m)	1,02 ± 0,18	2,11 ± 0,26	-

Note: p> 0.05 for the “age” indicator in all patient groups, p< 0.05 for the indicators of disease duration and the number of exacerbations per year in patient groups 1 and 2.

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The average values of the lung ventilation function indicators in the groups are presented in Table 2.

Table 2

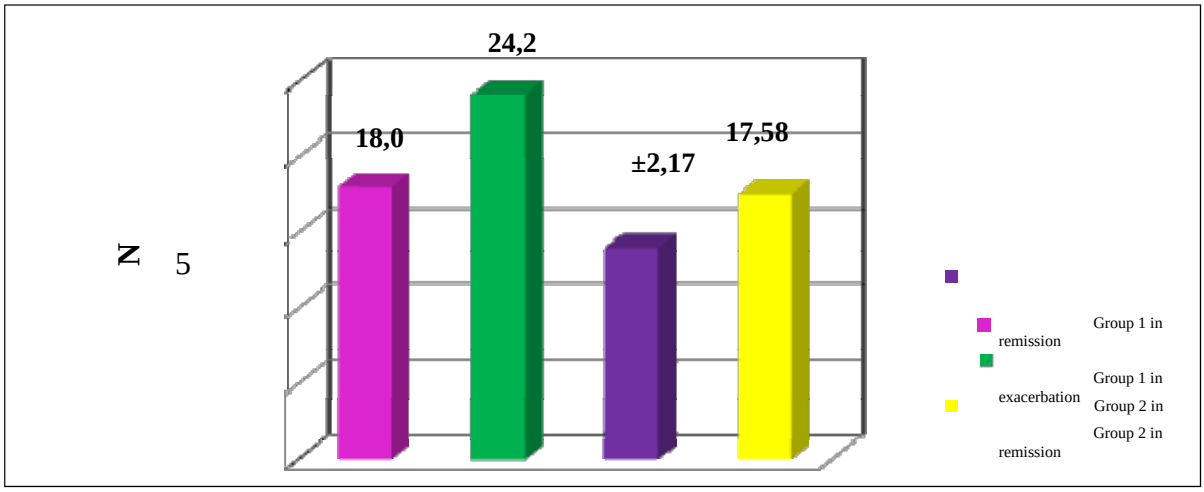
Indicators of ventilation function of the lungs in groups

Indicators	Groups				
	1 (n = 13)		2 (n = 12)		3 (n = 11)
	remission	exacerbation	remission	exacerbation	control
FEV1 (M ± m,% of expected)	78,32 ± 3,67	67,95 ± 3,01	41,22 ± 2,38	37,25 ± 2,51	98,32 ± 4,21
FVC (M ± m, % of expected)	98,02 ± 3,81	86,70 ± 3,50	69,68 ± 2,49	68,72 ± 3,85	111,83 ± 3,98
FEV1/FVC	68,56 ± 2,1	61,65 ± 1,78	44,68 ± 2,25	40, 67 ± 2,72	89,52 ± 1,46

Note: $p < 0.05$ for FEV1 and FVC levels during exacerbation in group 1.

As can be seen from Table 2, the FEV1 and FVC levels significantly decreased only in Group 1 with a mild course of the disease in the exacerbation phase ($p < 0.05$). Chronic inflammation in mild COPD (GOLD 1-2) in the exacerbation phase is most likely accompanied by more pronounced bronchial mucosal edema, mucus hypersecretion and smooth muscle bronchospasm. The ventilation function of the lungs in the control group was not reduced.

The NO level in exhaled air in the control group was 12.10 ± 1.4 ppb. The results of measuring the NO level in exhaled air in patients depending on the stage and phase of COPD are presented in Drawing 1.



Drawing. 1. NO levels in exhaled air in patients in comparison and control groups

As can be seen from the presented drawing, in non-smoking patients with COPD in the exacerbation phase and even in the remission phase, the concentration of NO in the exhaled air significantly exceeded the average values of the control

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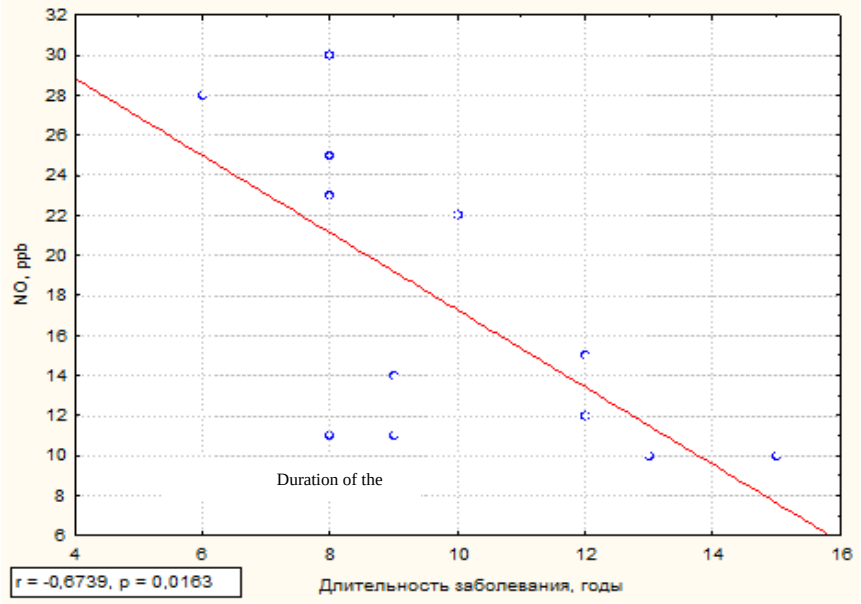
group ($p < 0.05$), which is most likely due to the persistence of inflammation in the respiratory system of patients regardless of the phase of the disease. At the same time, the indicators in group 1 were insignificantly higher than in group 2 ($p > 0.05$). Most likely, in patients with COPD, in the absence of exposure to tobacco smoke as a powerful factor of oxidative stress, endothelial dysfunction is expressed insignificantly.

The use of inhaled glucocorticosteroids in the treatment of patients with severe and very severe COPD can explain the relative decrease in NO production in the 2nd group of patients [2].

During exacerbation in patients with mild COPD (GOLD 1-2), the level of NO in exhaled air statistically significantly increased compared to remission ($p < 0.05$). Such an increase could be due to an increase in macrophage NOS (in response to the effects of infectious agents) and the stimulating effect of inflammatory mediators with a preserved level of endothelial NOS. Therefore, these changes can rather be interpreted as a compensatory reaction in response to acute inflammation of the respiratory tract.

A significantly less pronounced increase in the level of NO in exhaled air during an exacerbation in severe COPD (GOLD 3-4) most likely indicates the exhaustion of compensatory mechanisms and the loss of the ability of the vascular endothelium to adequately respond to impaired pulmonary ventilation function and hypoxia. When studying the relationship between the concentration of NO in exhaled air and the duration of the disease in different groups during exacerbation and remission, it was noted that only during exacerbation in patients of group 2 did the levels of these indicators significantly correlate ($r = 0.67$, $p = 0.02$) (Fig. 2), while in the other groups no correlation was recorded between the parameters studied.



Drawing. 2. The relationship between the level of exhaled NO and the duration of the disease in group 2 during an exacerbation.

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With increasing duration of the disease during exacerbation, NO production decreases, which most likely may indicate depletion of compensation mechanisms and early manifestation of endothelial dysfunction.

We did not find a reliable correlation between the level of NO in exhaled air and the age of patients in group 1 (in remission - r = 0.23, p = 0.47, in exacerbation - r = 0.14, p = 0.28) and in group 2 (in remission - r = - 0.11, p = 0.37, in exacerbation - r = 0.20, p = 0.25).

An insignificant correlation was found between the level of NO in exhaled air and the frequency of exacerbations per year both in group 1 (in remission – r = - 0.06, p = 0.84, in exacerbation – r = - 0.17, p = 0.57) and in group 2 (in remission – r = - 0.16, p = 0.61, in exacerbation – r = 0.23, p = 0.47).

We did not find a relationship between the main indicators characterizing the ventilation function of the lungs and the level of NO in exhaled air. Thus, the correlation with the FEV1 index in group 1 was r = - 0.18, p = 0.57 in remission and r = - 0.21, p = 0.48 in exacerbation, in group 2 - r = 0.28, p = 0.53 in remission and r = 0.19, p = 0.35 in exacerbation.

Most likely, chronic inflammation of the respiratory tract can mask ED in patients with COPD. For a more complete understanding of the pathogenetic links in the development and formation of vascular endothelial dysfunction in this category of patients, it is necessary to take into account changes in other indicators (both laboratory - endothelin-1, alveolar macrophages, etc., and instrumental - occlusion test, nitroglycerin test) in combination with a change in the level of NO in the exhaled air.

Conclusions

1) in non-smoking patients with COPD, the concentration of NO in the exhaled air is significantly higher compared to the control group, regardless of the severity of the disease and the phase of the pathological process;

2) during an exacerbation in non-smoking patients with COPD, the concentration of NO in the exhaled air significantly increases compared to remission only in patients with a mild course of the disease (GOLD 1-2);

3) during an exacerbation of COPD in patients with a mild course of the disease (GOLD 1-2), the concentration of NO in the exhaled air is significantly higher than in patients with a severe course (GOLD 3-4), which most likely reflects the degree of vascular damage and the severity of compensatory reactions in response to increased inflammation;

4) in patients with severe COPD (GOLD 3-4), during an exacerbation, with an increase in the duration of the disease, the concentration of NO in the exhaled air decreases, possibly foreshadowing the development of pulmonary hypertension;

5) the level of NO in exhaled air in non-smoking patients with COPD (GOLD 1-4) does not depend on the age of the patients, respiratory function indices, and the frequency of exacerbations of the disease per year.

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