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THE CONNECTION BETWEEN CLINICAL AND ANAMNESTIC PARAMETERS AND MARKERS OF ENDOTHELIAL DYSFUNCTION IN PATIENTS WITH COPD

Abstract. Currently, chronic obstructive pulmonary disease (COPD) is considered a systemic pathology. Among the extrapulmonary manifestations, cardiovascular disorders are distinguished, the earliest manifestations of which are endothelial dysfunction. It has been proven that one of the most important factors in the pathogenesis of endothelial dysfunction is nitric oxide (NO). However, the literature notes inconsistency in the data demonstrating the influence of anamnestic or clinical parameters of COPD on the formation and progression of endothelial dysfunction.

The aim of the study was to investigate the relationship between the concentration of NO in exhaled air in patients with COPD and certain clinical and anamnestic parameters of the disease depending on the severity of the pathological process.

Twenty-five men with COPD, GOLD stages 1–4, were examined. The control group consisted of 11 practically healthy individuals. A correlation was established between the concentration of NO in exhaled air and the duration of the disease ($r = -0.67$, $p = 0.02$) in patients with COPD, GOLD 3–4 during exacerbation, which may indicate the formation and progression of endothelial dysfunction with increasing disease duration.

In the stable course of the disease in this group, the concentration of NO in exhaled air did not depend on the studied parameter. In patients with COPD, regardless of the severity and phase of the pathological process, age, the frequency of exacerbations per year, and indicators of external respiratory function did not affect the concentration of NO in exhaled air and, accordingly, were not significant parameters determining the level of the studied marker in this population.

Keywords: COPD, endothelial dysfunction, nitric oxide in exhaled air.

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ВЗАИМОСВЯЗЬ МЕЖДУ КЛИНИКО-АНАМНЕСТИЧЕСКИМИ ПАРАМЕТРАМИ И МАРКЕРОМ ЭНДОТЕЛИАЛЬНОЙ ДИСФУНКЦИИ У БОЛЬНЫХ ХОЗЛ

Анотація. В даний час ХОЗЛ розглядається як системна патологія. Серед позалегеневих проявів виділяють кардіоваскулярні порушення, найбільш ранніми проявами яких є ендотеліальна дисфункція. Доказано, что в патогенезе ЭД одним из важнейших факторов является NO. Однак, в літературі відзначена неоднозначність даних, які доводять вплив анамнестичних або клінічних параметрів ХОЗЛ на формування та прогресування ендотеліальної дисфункції. Метою дослідження було вивчення взаємозв'язку між концентрацією NO в повітрі, що видихається у хворих на ХОЗЛ і деякими клініко-анамнестичними параметрами захворювання в залежності від тяжкості патологічного процесу. Обстежено 25 чоловіків хворих на ХОЗЛ, GOLD 1-4. в групу контролю увійшли 11 практично здорових осіб. Встановлено кореляційний зв'язок між концентрацією NO в повітрі, що видихається і тривалістю захворювання ($r = -0,67$, $p = 0,02$) у хворих на ХОЗЛ, GOLD 3-4 при загостренні, що може свідчити про формування та прогресування ендотеліальної дисфункції зі збільшенням тривалості захворювання. При стабільному перебігу у данного контингенту концентрація NO в повітрі, що видихається не залежала від досліджуваного параметра. У хворих на ХОЗЛ, незалежно від тяжкості та фази патологічного процесу, вік, частота загострень на рік, показники функції зовнішнього дихання не впливають на концентрацію NO в повітрі, що видихається і, відповідно, не є істотними параметрами, що визначають рівень досліджуваного маркера у представленого контингенту.

Ключові слова: ХОЗЛ, ендотеліальна дисфункція, оксид азоту у повітрі, що видихається.

Problem Statement. Currently, chronic obstructive pulmonary disease (COPD) is considered a systemic pathology characterized by extrapulmonary manifestations [2,3], among which cardiovascular disorders deserve special attention, the earliest manifestation of which is endothelial dysfunction (ED) [1,4]. Vascular endothelium is represented by a highly specialized, metabolically active monolayer of cells capable of producing vasorelaxing substances (nitric oxide (NO), prostacyclin, endothelial hyperpolarizing factor, etc.) and vasoconstrictor substances (endothelin-1, thromboxane A_2, etc.), between which a balance is maintained under physiological conditions. It has been proven that one of the most important factors in the pathogenesis of ED is nitric oxide (NO). Receptors located in the endothelium transform mechanical signals and induce NO synthase, which leads to the accumulation of NO and vasodilation due to a decrease in Ca^{2+} concentration in the cytoplasm [1,3]. In this regard, a large number of studies in COPD patients are currently devoted to the investigation of vascular endothelial function and the development of ED [1,2,3]. At the same time, the literature

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reports inconsistency in data demonstrating the influence of anamnestic parameters and clinical manifestations of COPD on the formation and progression of ED. This determined **the aim of our study** — to investigate the relationship between the concentration of NO in exhaled air in COPD patients and certain anamnestic data as well as clinical parameters of the disease.

Materials and Methods. Twenty-five men were examined (mean age – 61.13 ± 2.10 years; mean disease duration – 11.97 ± 0.63 years) suffering from COPD, GOLD stages 1–4. All of them had either never smoked or had abstained from smoking for more than five years. The diagnosis was established in accordance with the Order of the Ministry of Health No. 1610 dated September 20, 2024. All patients received standard therapy depending on the severity of the disease. Exclusion criteria included concomitant cardiovascular pathology (according to medical history, objective examination, blood pressure measurement, ECG, echocardiography, and blood lipid profile indicators).

Study design: patients were divided into two groups depending on the severity of the disease. Group 1 included 13 patients with COPD GOLD 1–2, and group 2 included 12 patients with COPD GOLD 3–4. All examinations were performed twice — during exacerbation and remission of COPD. The control group (group 3) included 11 practically healthy volunteers who had never smoked and had normal indicators of external respiratory function (ERF).

To verify the diagnosis of COPD, ERF parameters were determined using a MasterLab spirometer (Jaeger, Germany). The following parameters were analyzed: forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC), and the FEV_1/FVC ratio. A bronchodilator reversibility test was performed using a short-acting β_2-agonist (salbutamol 400 μg). In addition, the concentration of NO in exhaled air was assessed using the Niox Mino device (Aerocrine).

Measurements of ERF parameters and NO concentration in exhaled air were carried out from 8:00 to 10:00 a.m., on an empty stomach, before taking medications. Statistical analysis of the results was performed using the Statistica 7 software with the calculation of the arithmetic mean, significance of differences, and correlation analysis.

Results and Discussion. The characteristics of all examined patients according to age, stage and duration of the disease, as well as the number of COPD exacerbations per year, are presented in Table 1. According to the presented data, patients in all groups were comparable in age, which indicates the representativeness and comparability of this sample.

Table 1

Characteristics of the examined patients

Indicators	**Groups**		
	1 (n = 13)	**2 (n = 12)**	**3 (n = 11)**
Severity of the disease	GOLD 1-2	GOLD 3-4	Practically healthy

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

Note. *p < 0,05 for indicators in groups 1 and 2.

In Group 2, disease duration and the number of exacerbations per year (Table 1) were significantly higher, which is explained by the more severe course of COPD in this cohort of patients.

FVD indicators in the groups, depending on the disease phase and in comparison with the control group (healthy individuals), are presented in Table 2.

Table 2

FVD indicators in groups depending on the phase of the disease

Indicators	Groups				
	1 (n = 13)		2 (n = 12)		3 (n = 11)
	remission	exacerbation	remission	exacerbation	control
FEV1 (M ± m, % of predicted)	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 indicators in group 1.

According to the obtained data, the levels of FEV1 (p=0.037), FVC (p=0.039) and the FEV1/FVC ratio (p=0.015) significantly decreased during exacerbation only in group 1, which may indicate a significant impairment of FEV1 in these patients. According to Table 2, FEV1 indices were significantly lower in patients of the second observation group with COPD, which is explained by the higher severity class of the underlying disease (GOLD 3-4). It should also be noted that in practically healthy individuals, all FEV1 indices were significantly higher (by 1.2 - 2.7 times) than in patients with COPD, regardless of the stage or period of the disease - remission or exacerbation (p < 0.05).

A correlation analysis of examination results in patients with COPD revealed a significant negative correlation (r = -0.67, p = 0.02) between NO concentration in exhaled air and disease duration in Group 2 during the exacerbation period. However,

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no correlation was found between the studied parameters in the presented cohort during remission (r = 0.12, p = 0.71). Most likely, in patients with severe COPD during exacerbations, NO production decreases with disease duration, which may serve as an early sign of the development and progression of ED and negatively impact the prognosis of the disease. Moreover, in patients in remission with severe COPD, NO levels did not depend on disease duration, possibly indicating a stable course of vascular endothelial dysfunction outside the exacerbation period.

In patients with a mild course of the disease, regardless of the phase of the pathological process, a reliable correlation between the level of NO and the duration of the disease was not registered (in remission - r = - 0.15, p = 0.63, in exacerbation - r = 0.47, p = 0.10), which may confirm a less significant relationship between the level of the studied ED marker and the duration of the disease in the presented contingent of patients.

Also, no reliable correlation was recorded 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).

Thus, patient age, regardless of the severity and phase of the pathological process, was not a significant predictor of exhaled NO levels in the study groups. It is likely that measuring exhaled NO levels in combination with other markers of ED is necessary to study the influence of patient age on vascular endothelial function.

In addition, an insignificant correlation was recorded between the level of NO in exhaled air and the frequency of exacerbations per year of COPD 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). Also, no relationship was found between the main indicators characterizing FEV1 and the level of NO in exhaled air. Thus, the correlation with the FEV1 indicator 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.

Thus, regardless of the severity and phase of COPD, the number of exacerbations per year of the disease and the FVD indicators are not associated with changes in the level of NO in exhaled air in the studied cohort of patients, being, most likely, less significant markers indicating the progression of ED.

Conclusions:

1) In non-smoking patients with COPD (GOLD 3-4), NO concentration in exhaled air decreases with increasing disease duration during exacerbations, which most likely indicates the development and progression of endothelial dysfunction.

2) In non-smoking patients with COPD (GOLD 3-4), during stable disease, NO concentration in exhaled air does not depend on disease duration, which may be associated with a stable vascular endothelium.

3) In non-smoking patients with COPD, regardless of the severity and phase of the pathological process, age, frequency of exacerbations per year, and pulmonary

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function indicators do not affect NO concentration in exhaled air and, accordingly, are not significant parameters influencing the level of the studied marker.

Prospects for further research. In further studies of the influence of anamnestic and clinical parameters of COPD on the development and formation of ED, it is advisable to take into account the level of NO in exhaled air in combination with laboratory (endothelin-1, alveolar macrophages, etc.) and instrumental (occlusion test, test with nitroglycerin) indicators of vascular endothelial dysfunction.

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