ENGLISH VERSION: COPD: THE IMPACT OF COMORBID CARDIOVASCULAR DISEASE ON THE LEVEL OF FRACTIONAL EXHALED NITRIC OXIDE*

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At present, comorbid cardiovascular disease, especially coronary heart disease (CHD), becomes increasingly common in patients with chronic obstructive pulmonary disease (COPD). These nosologies are characterized by some similar symptoms, therefore, if patient has both diseases it is not always possible to determine the cause of health deterioration. Thus, it is relevant for physicians to search for a specific marker that would allow the differentiation of the condition's data. In this context, determining the level of fractional exhaled nitric oxide (FeNO) is quite promising. The aim of our study was to investigate the effect of CVD on FeNO levels and the possibility of using this indicator as a specific marker of COPD exacerbation. During the study, patients were divided into groups depending on the phase of COPD, as well as the presence of cardiovascular disease (CVD). Spirometry was performed in all patients, as well as the determination of FeNO level in exhaled air. It has been found that the presence of cardiovascular diseases does not affect FeNO level in exhaled air in patients without bronchial obstruction, as well as in patients with COPD, regardless of phase. FeNO level in exhaled air was significantly higher in patients with COPD in exacerbation phase, regardless of the presence or absence of concomitant CVD as compared to COPD in remission, patients with cardiac disorders, and healthy people.

Key words: chronic obstructive pulmonary disease, coronary heart disease, fractional exhaled nitric oxide.

Relevance of the research.

Chronic obstructive pulmonary disease (COPD), as well as coronary heart disease (CHD), constitutes a relevant medical and social problem due to the high levels of morbidity, disability and mortality worldwide [1,2]. Epidemiological studies, conducted in 2006-2007 by D. M. Mannino and co-authors have shown that most patients with COPD die due to cardiovascular causes (25% of cases) [8].

Epidemiological and clinical studies of the last decade have observed an increase in the number of COPD combined with coronary artery disease [6,7]. The combination of cardiac and pulmonary disease is considered to be prognostically unfavorable due to mutually exacerbating course of the disease [1,10].

Moreover, analysis of the causes of hospital admissions of patients with COPD, conducted on the basis of the results from major research Lung Health Study has shown that in 42% of cases the basic admission causes in COPD are cardiovascular events while the respiratory complications account for only 14% [7].

Taking into account the presence of some common risk factors in patients with CHD and COPD (smoking, atherosclerosis of the arteries due to immune inflammation, possibly induced by bacteria, viruses and pollutants) [1,9], one can assume that these diseases have mutually potentiating impact on microvascular endothelium, causing changes in its reactivity. Nitrogen oxide (NO) is one of the indicators in favour of endothelial dysfunction.

On the one hand, NO in exhaled air (FeNO) serves as a marker of local inflammation of airway and can be used for early detection of COPD exacerbation. On the other hand, it is an accepted fact that NO increases in plasma due to endothelial dysfunction intrinsic to cardiac disease [3,4].

COPD and CHD are characterized by some similar symptoms (shortness of breath, decreased exercise tolerance), so if a patient has both diseases it is not always possible to determine the cause of health deterioration. Therefore, it is relevant for physicians to search for a specific marker that would allow the differentiation of the condition's data. In this context, determining the level of nitric oxide in exhaled air (FeNO – fractional exhaled nitric oxide) is quite promising. However, the question of whether this is merely a marker indicative of the presence of pulmonary disease, or whether it changes under the influence of concomitant cardiovascular disease (CVD) remains debated.

Materials and methods of the research:

The study involved 60 patients with verified diagnosis of COPD. Group 1 consisted of 37 patients in remission, group 2 included 23 people in exacerbation stage. The presence, severity of obstruction and group of COPD, as well as the phase of the pathological process, was established in accordance with the criteria of the order of the Ministry of Public Health of Ukraine No 555 as of 27.06.2013 [2]. All patients received standard treatment depending on the stage of the disease and the group.

11 healthy volunteers, never-smokers, with normal respiratory function (NRF) were included in the control group 3. Comparison group 4 consisted of 7 patients with confirmed cardiovascular disease, not suffering from COPD.

In the course of research, the patients were divided into subgroups based on the presence of cardiovascular disease: subgroup 1A consisted of COPD patients in remission without CVD; subgroup 1B included patients with COPD who suffer from cardiac pathology; subgroup 2A – patients with COPD in exacerbation who do not have the history of cardiovascular disease; subgroup 2B – patients with COPD in exacerbation, with cardiovascular diseases.

In order to verify the diagnosis of COPD, in all patients the respiratory function (RF) was determined using spirograph "Masterlab" (Jaeger, Germany): the levels of forced expiratory volume in the first second (FEV1), forced vital capacity (FVC), ratio of FEV1 / FVC were analyzed; test for reversibility of airflow obstruction with short-acting β2-agonist (salbutamol) was conducted. Assessment of the degree of obstruction was performed by

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post-bronchodilatatory test (as recommended by GOLD, 2013).

With regard to CVD, the study included patients with previously verified chronic ischemic heart disease and / or hypertensive disease.

FeNO concentration was determined using "Niox Mino" device (Aerocrine, Sweden).

All patients were surveyed by mMRC scale for dyspnea assessment.

"Statistics 6.1" was used for statistical processing of the results. For adequately distributed variables, methods of parametric statistics with calculation of the mean values, standard deviation (M ± m) and Student's t test were used. For inadequately distributed variables, methods of nonparametric statistics with the definition of the median and quartiles Med [25%-75%], Mann-Whitney or Kruskal-Wallis test for the significance of differences were used. Reliably significant results were considered at $p<0.05$. The significance of differences in quality and binary parameters was assessed using the chi-square ($\chi 2$) for $n<5$ – using the Fisher's exact test for frequencies. Besides, the correlation analysis of FeNO levels and indicators of FVD using Spearman's test (R) was conducted.

Results and their discussion

Patients of the control group, as well as the comparison group were matched for age, sex, weight, BMI ($p>0.05$). Groups of patients with COPD also did not differ significantly in the number of smokers, the index of pack / years duration of the disease ($p> 0.05$) (Table 1).

Table 1
Characteristics of the comparison groups

Index, units	Group 1		Group 2		Group 3, n=7	Group 4, n=11
	1A, n=16	1B, n=21	2A, n=13	2B, n=10		
Sex, n (%)	m=13; (81.3) f =3; (18.7)	m=18; (85.7) f =3; (14.3)	m =11; (84.6) f =2; (15.4)	m =10; (100) f =0;	m =6; (85.7) f =1; (14.3)	m =10; (90.9) f=1; (9.1)
Age Med [25%-75%], years	62.0 [54.5-70.0]	65.0 [55.0-78.0]	62.0 [56.0-66.0]	73.0 [66.0-74.0]	64.0- [62.0-70.0]	59.0 [57.0-64.0]
Weight Med [25%-75%], kg	74.0 [68.5-85.5]	82.0 [74.0-90.0]	72.0 [60.0-80.0]	88.0 [72.0-95.0]	86.0 [79.0-92.0]	79.0 [75.0-84.0]
BMI Med [25%-75%], kg/m^2	27.0 [22.0-30,0]	28,0 [24,0-31,0]	24,0[21,0-26,0]	28,0 [23,0-33,0]	28,5 [25,0-33,5]	26,5[22,5-28,0]
Number of smokers, n (%)	n=7 (43)	n=8 (38)	n=5 (38)	n=3 (30)	n=5 (45)	n=0
Pack / years index	29.5 [23.0-35.0]	40.5 [15.0-70.0]	38.0 [30.0-41.0]	26.0 [15.0-45.0]	23.5 [12.5-38.0]	25.0 [15.0-45.5]
Duration of the disease Med [25%-75%], years	5.0 [3.5-9.0]	5.0 [3.0-10.0]	6.0 [3.0-10.0]	3.5 [3.0-10.0]		
Forced expiratory volume Med [25-75%] %	59.7 [43.4-74.2]	48.9 [36.3-53.7]	43.0 [32.0-47.0]	40.0 [33.0-58.0]	89.9 [88.7-102.5]	97.0 [90.0-100.0]

At the next stage, all patients underwent measurement of FeNO in exhaled air. Analyzing the data, we found that in patients with non-acute chronic obstructive pulmonary disease, regardless of the presence of cardiovascular disease (1A and 1B group) results were not significantly different from patients without lung disease, but with cardiovascular disease (Group 3) and from healthy volunteers (group 4). Meanwhile, in patients with COPD in exacerbation (2A and 2B group) NO indicators in exhaled air were significantly higher as compared to healthy patients suffering from cardiovascular disease, as well as with patients with chronic obstructive pulmonary disease in remission (Fig. 1, Table 2).

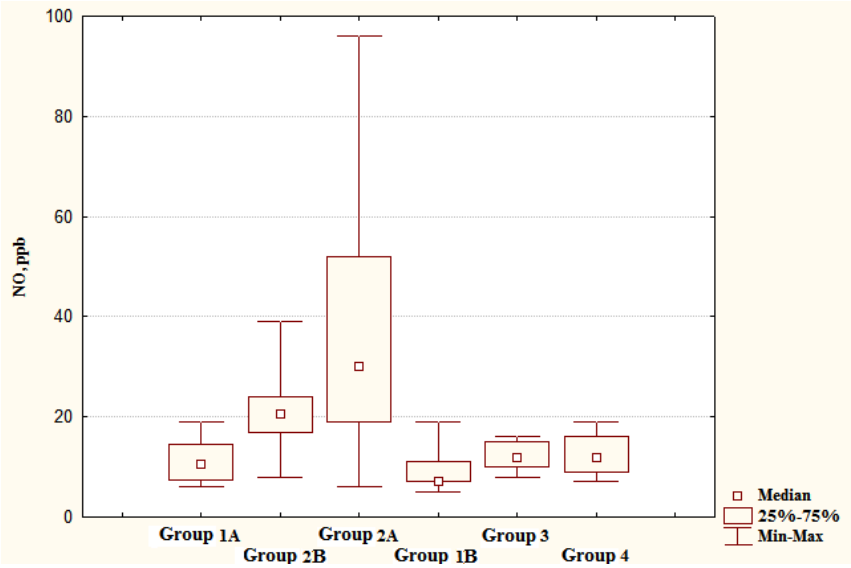

Fig. 1. NO level in the exhaled air in groups

Table 2

The confidence level of p differences between groups and subgroups in the measurement of FeNO

P_{1A-1B}=0.114	P_{1A-4}=0.400	P_{1B-4} =0.070	P_{2B-3}=0.006
P_{1A-2B} =0.001	P_{1B-2A} =0.000	P_{2A-2B}=0.090	P_{2B-4}=0.028
P_{1A-2B} =0.001	P_{1B-2B} =0.000	P_{2A-3}=0.002	P_{3-4}=0.750
P_{1A-3}=0.460	P_{1B-3} =0.050	P_{2A-4}=0.010	

Conclusions:

1. Cardiovascular pathology does not affect FeNO level in exhaled air in patients without bronchial obstruction, as well as in patients with COPD, regardless of phase.

2. During exacerbation of COPD, regardless of the presence or absence of concomitant diseases of the cardiovascular system, NO level in exhaled air was significantly higher as compared to healthy people and patients with chronic obstructive pulmonary disease in remission, as well as patients with cardiac disease.

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