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Features of the Functional Status and Cytokine Profile of Patients with Chronic Heart Failure in Combination with Chronic Obstructive Pulmonary Disease

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Abstract

The purpose of this research was to study the effect of COPD on the functional status and cytokine profile of patients with chronic heart failure (CHF) with different ejection fraction (EF).

Methods and Results: The study involved 240 patients diagnosed with CHF (mean age of 72.4±8.7 years). Among them, 80 patients were diagnosed with CHF and COPD. Depending on the presence of COPD, the patients were divided into two groups: Group 1 included 160 patients with CHF without COPD; Group 2 included CHF 80 patients with COPD. According to the value of LVEF, each of the two groups was divided into two more subgroups: In Group 1, CHFpEF (EF≥50%) was recorded in 69 patients (Subgroup 1) and CHFrFV (EF<50%) in 91 patients (Subgroup 2). In Group 2, CHFpEF was observed in 36 patients (Subgroup 3) and CHFrEF in 44 patients (Subgroup 4). The 6-minute walk distance (6MWD) was measured in meters and compared with the proper 6MWD(i). All patients included in the study underwent the Borg test to assess dyspnea after 6MWT. The serum levels of NT-proBNP, hs-CRP, IL-1β, IL-6, and TNF-α were determined using an automatic analyzer IMMULITE 2000 (Siemens Diagnostics, USA) and quantitative ELISA kits. The patients with CHFpEF had higher levels of hs-CRP, pro-inflammatory cytokines than patients with CHFrEF. The combination of COPD and CHF amplifies systemic inflammation (hs-CRP, proinflammatory cytokines) and myocardial remodeling processes (NT-proBNP) in comparison with the isolated course of CHF. COPD negatively affects the functional status of patients with CHF with different EF by lower values of 6MWD, 6MWD/6MWD(i) ratio, and higher results on the Borg dyspnea test. **International Journal of Biomedicine. 2021;11(1):9-13.**)

Key Words: chronic heart failure • ejection fraction • COPD • cytokines

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Abbreviations

6MWT, the 6-minute walking test; **6MWD**, the 6-minute walk distance; **CHF**, chronic heart failure; **COPD**, chronic obstructive pulmonary disease; **CHFrEF**, CHF with reduced EF, **CHFpEF**, CHF with preserved EF; **EF**, ejection fraction; **hs-CRP**, high-sensitivity C-reactive protein; **HR**, heart rate; **IL**, interleukin; **LVEF**, left ventricular EF; **NT-proBNP**, N-terminal pro-brain natriuretic peptide.

Introduction

With the increase in life expectancy (both of patients with cardiovascular disease and people in general), chronic heart failure (CHF) is becoming more widespread. CHF decompensation plays a dominant role among the reasons for hospitalization in cardiology departments, especially among patients over 65 years of age.[1] In the USA and European countries, more than 1 million patients are hospitalized annually for CHF. The annual mortality rate of outpatients

with CHF is 7%, and of those hospitalized - 17%.[2] The prognosis for such patients is significantly worsened when CHF is combined with other diseases.[3,4]

Difficulties in diagnosing CHF in patients with COPD, and the choice of tactics and methods of therapy in recent years, determine the increased scientific interest in the study of the cardiorespiratory continuum. It is believed that COPD affects from 25% to 42% of CHF patients.[5-7] The comorbid course of these pathologies is associated with an increased risk of readmission and death.

Respiratory failure is traditionally considered the leading cause of death in COPD patients, but this judgment is valid only for the severe course of the disease. In patients with mild and moderate forms of COPD, patients with cardiovascular disease come first in the structure of mortality. The risk of cardiovascular death in COPD patients is 2-3 times higher than in the population. Thus, Sin et al.[8] found that for every 10% decrease in FEV_1, the risk of developing a non-fatal coronary event increases by almost 20%, overall mortality by 14%, and cardiovascular mortality by 28%. According to the TORCH study, the causes of death of COPD patients can be represented as follows: 27% of deaths are due to cardiovascular complications, 35% to respiratory causes, 21% are associated with malignant neoplasms, and 10% for a number of other reasons.[9] In the remaining 7% of cases, the cause of death was not established.

The relationship between the mechanisms of the development of COPD and patients with cardiovascular disease is studied from every angle. The general mechanisms of etiopathogenesis include systemic inflammation, oxidative stress, and endothelial dysfunction.[10-12] The development of systemic inflammation is associated with the release of pro-inflammatory cytokines into the bloodstream, products of lipid peroxidation that induce overproduction of a number of other mediators. Thus, in the development of CHFpEF, a special role is assigned to excessive activation of the sympathetic-adrenal system and the subsequent increase in the synthesis of pro-inflammatory cytokines (TNF-α, IL-1). This, in turn, leads to an increase in the activity of nitric oxide synthases and production of NO in tissues, which has negative effects on the cardiovascular system (apoptosis and fibrosis of cardiomyocytes, direct toxic effect on the myocardium). In this regard, identifying three categories of patients with HF (with preserved, borderline and reduced LVEF) is of particular relevance to study the effect of systemic inflammation on the clinical course, functional status and prognosis of patients with comorbid COPD and CHF with different LVEF. Thus, the high comorbidity of CHF and COPD and the increased risk of unfavorable outcomes in this combination of pathologies suggest further study of the mechanisms of CHF progression, and improvement of diagnostic methods and treatment principles for this category of patients.

The purpose of this research was to study the effect of COPD on the functional status and cytokine profile of patients with CHF with different EF.

Materials and Methods

The study involved 240 patients diagnosed with CHF (134 men and 106 women, mean age of 72.4±8.7 years), included in the regional register of CHF patients in the Voronezh region. Among them, 80 patients (48[60%] men and 32[40%] women) aged between 40 and 80 years were diagnosed with CHF and COPD (GOLD 2, group D) without exacerbation. Depending on the presence of COPD, the patients were divided into two groups: Group 1 included 160 patients with CHF who had no signs of COPD; Group 2 included 80 patients with a comorbid course of CHF and COPD. All patients with COPD corresponded to the "phenotype with frequent exacerbations" (2 or more per year) and required antibiotic therapy and/or glucocorticosteroids. The diagnosis of COPD was made on the basis of an integral assessment of symptoms, history, objective status, and spirometry data, according to GOLD, revision 2019. According to the value of LVEF, each of the two groups was divided into two more subgroups: In Group 1, CHFpEF (EF≥50%) was recorded in 69 patients (Subgroup 1) and CHFrFV (EF<50%) in 91 patients (Subgroup 2). In Group 2, CHFpEF was observed in 36 patients (Subgroup 3) and CHFrEF in 44 patients (Subgroup 4). The diagnosis of CHF was established according to 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. The functional class (FC) of CHF was determined according to the NYHA classification (1994), based on the results of the 6MWT.

The non-inclusion criteria for Groups 1 and 2 were the presence of chronic kidney disease (3b stages and higher), diabetes mellitus or taking hypoglycemic drugs, permanent atrial fibrillation, anemia, diseases of musculoskeletal system (coxarthrosis, gonarthrosis, etc., reducing motor activity), obesity (2-3 classes) and other severe somatic pathologies.

From the moment of inclusion in the study, patients were examined weekly by researchers—a cardiologist and a pulmonologist—to make sure there were no symptoms of CHF decompensation and exacerbation of COPD. After 12 weeks, the study participants underwent a standard examination, which included clinical, laboratory and instrumental methods. Exercise tolerance was determined using a complex of cardiorespiratory analysis and register of patients with CHF [13,14]) and 6MWT.

The 6MWD was measured in meters and compared with the proper 6MWD(i). The 6MWD(i) value was calculated using the formulas below, which take into account age and BMI. The formula for calculating 6MWD(i) for men: 6MWD(i)=1140-5.61×BMI-6.94×age. The 6MWD (i) value for women was defined as: 6MWD(i)=(1017-6.24×BMI-5.83×age.[1]

The serum levels of NT-proBNP, hs-CRP, IL-1β, IL-6, and TNF-α were determined using an automatic analyzer IMMULITE 2000 (Siemens Diagnostics, USA) and quantitative ELISA kits: NT-proBNP - using the Biomedica human NT-proBNP Sandwich ELISA kit (Austria), hs-CRP - using the SRB-IFA-BEST highly sensitive kit (Vector-Best, Russia), IL-1β using the Interleukin-1 beta - ELISA-BEST kit (Vector-Best, Russia), IL-6 using the Interleukin-6- ELISA-BEST kit (Vector-Best, Russia), and TNF-α using the alpha-TNF-ELISA-BEST (Vector-Best, Russia). Comprehensive two-dimensional and Doppler echocardiography were performed using an EPIQ5 ultrasound system (Phillips, USA) equipped with S5-1 Pure-Wave Cardiac Transducer. All patients included in the study underwent the Borg test to assess dyspnea after 6MWT.

All patients received treatment according to the standards for the treatment of CHF and COPD.

The study was approved by the Ethics Committee of Voronezh State Medical University named after N.N. Burdenko. Written informed consent was obtained from each patient.

All data was evaluated with STATGRAPHICS Plus 5.1. Baseline characteristics were summarized as frequencies and percentages for categorical variables and as mean±SD, median (Me) and interquartile range (IQR; 25th to 75th percentiles) for continuous variables. Student's unpaired t-test was used to compare two groups for data with normal distribution. Mann-Whitney U test was used to compare means of 2 groups of variables not normally distributed. A probability value of $P<0.05$ was considered statistically significant.

Results

The median NT-proBNP value in Subgroup 2 was 1804(608-4908) ng/L, which significantly exceeded its value in Subgroup 1 - 980(301;2677) ng/L ($P<0.001$). The median NT-proBNP level in Subgroup 4 was 2046(1103;2806) ng/L, which also exceeded its value in Subgroup 3 - 1280(601;3150) ng/L ($P<0.001$) (Fig. 1). This result allows us to conclude that the NT-proBNP biomarker does not lose its sensitivity in the case of a combined course of COPD and CHF.

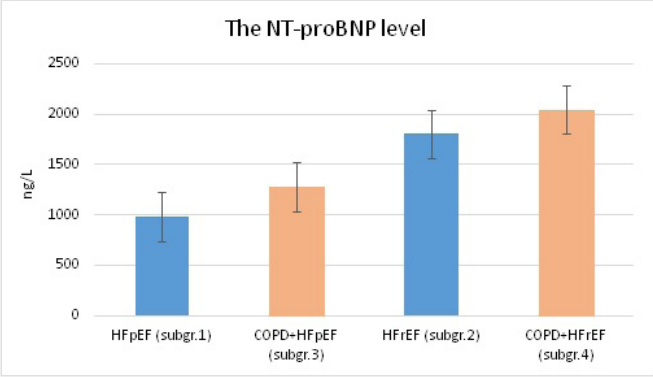

Fig. 1. *The NT-proBNP level in the study subgroups.*

It was also noted that in patients of Group 2 who had a combination of COPD and CHF, the NT-proBNP level, equal to 1593(601;3150) ng/L, was higher than in Group 1 patients with isolated CHF - 1064(301;4908) ng/L ($P=0.049$).

The level of hs-CRP, known as a biomarker of endogenous inflammatory processes, in patients with CHFpEF was 3.4(1.2; 8.1) mg/L, while in patients with CHFrEF it was statistically significantly lower - 2.9(1.6;5.4) mg/l ($P<0.001$). The level of hs-CRP in Subgroup 4 was 4.1(2.3;15.6) mg/L, which was also lower than in patients of Subgroup 3 - 4.8(1.9;13.5) ng/L ($P<0.001$). The hs-CRP levels obtained in the study in isolated cardiac pathology in patients with various NYHA FC indicate an increase comparable to that in patients with FCII (3.2[1.2;7.1] mg/l), a more pronounced FCIII (3.3[1.4;7.8] mg/l) and severe FCIV (3.5[1.8;8.1] mg/l) ($P=0.06$) (Fig. 2).

We found an increase in the level of pro-inflammatory cytokines in all studied subgroups (Table 1). At the same time, the content of IL-1β, IL-6, and TNF-α was significantly higher in Group 2.

A higher level of IL-1β, IL-6, and TNF-α, hs-CRP (Table 1) in Subgroups 1 and 3 compared with Subgroups 2 and 4 reflects how important the contribution of systemic inflammation is to the development and progression of heart failure. At the same time, a higher level of pro-inflammatory cytokines was observed in Group 2 than in Group 1, which demonstrates a close pathogenetic relationship between the two pathologies.

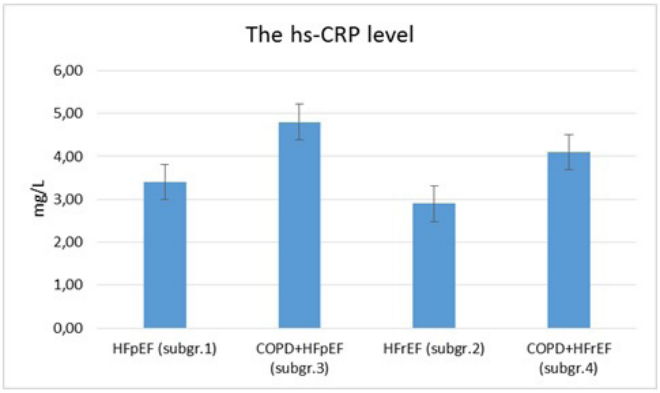

Fig. 2. *The Hs-CRP level in the study subgroups.*

Table 1.

Cytokine profile in study subgroups

Subgroup	IL-1β	*P*-value	IL-6	*P*-value	TNF-α	P-value
1	121.9±25.4	0.03	298.2±35.8	0.006	163.4± 27.2	0.04
2	103.1± 21.0		186.5± 29.6		143.0± 24.9	
3	139.3± 26.1*	0.04	408.3± 61.3*	0.005	256.8± 33.7*	0.02
4	122.1± 24.8^		312.7 ± 41.1^		198.4± 28.1^	

** - P<0.05 between Subgroups 1 and 3; ^- P<0.01 between Subgroups 2 and 4.*

The 6MWD level (Table 2) in patients with comorbid COPD and CHF, regardless of EF, was less than in CHF without COPD ($P<0.05$ in both cases). This fact can be explained by a combination of obstructive and restrictive breathing disorders.

Assessment of the 6MWD/6MWD(i) ratio showed that in Group 2, the average value of this indicator was significantly less than in Group 1, regardless of EF ($P<0.05$ in both cases). In previous studies, we found that in patients with COPD, a decrease in physical activity was apparently associated not only with lung dysfunction at rest, but also depends on a number of other factors. Thus, in COPD patients, a decrease in lean body mass is often observed, which is a

consequence of systemic inflammation and muscle atrophy due to low physical activity. In turn, this study showed that the comorbid course of CHF and COPD is accompanied by a higher activity of pro-inflammatory cytokines than with isolated CHF. Therefore, it can be assumed that one of the components that reduce exercise tolerance in such patients is the activation of systemic subclinical inflammation, leading, among other things, to a decrease in lean body mass.

The values of heart rate both before and immediately after performing 6MWT in patients in the study groups did not differ significantly. At the same time, in the process of performing 6MWT, the device did not record any excess of the submaximal values of this parameter in any of the subjects.

Before the start of the test, the studied subgroups did not differ in the level of SpO_2. However, this parameter was significantly lower in patients with CHF and COPD immediately after 6MWT, regardless of EF (Table 2). In turn, in patients in Subgroups 3 and 4 (CHF patients with COPD), higher scores on the Borg test, reflecting the degree of dyspnea after 6MWT, compared with Subgroups 1 and 2 (CHF patients without COPD), indicate a lower tolerance to physical activity (Table 2).

Table 2.

Comparative characteristics of 6MWT parameters, dynamic pulse oximetry in patients in the studied subgroups

Indicator	Subgr. 1	Subgr. 3	P_{1-3}	Subgr. 2	Subgr. 4	P_{2-4}
6MWD, m	301.5 ±153.5	264.6 ±120.6	0.04	251.5 ±183.5	202.4 ±130.2	0.03
6MWD(i), %	53.0 ±29.2	47.2 ±25.6	0.01	48.1 ±30.5	42.8 ±22.4	0.02
HR before test, bpm	76.1 ±15.2	77.8 ±17.3	0.18	86.1 ±15.2	87.8 ±17.3	0.16
HR after test, bpm	102.4 ±17.5	107.3 ±18.8	0.15	109.4 ±17.2	115.1 ±14.8	0.15
SpO2 before test, %	97.9 ±2.0	97.5 ±2.1	0.12	95.2 ±2.4	94.9 ±2.6	0.26
SpO2 after test, %	95.5 ±3.0	93.3 ±3.1	0.001	94.1 ±3.3	91.2 ±2.5	0.001
Borg test, points	2.41 ±0.17	3.22 ±0.29	0.01	3.83 ±0.32	5.19 ±0.37	0.001

Conclusion

The patients with CHFpEF have higher levels of hs-CRP, pro-inflammatory cytokines than patients with CHFrEF. This reflects more pronounced subclinical inflammation. The combination of COPD and CHF amplifies systemic inflammation(hs-CRP, proinflammatory cytokines) and myocardial remodeling processes (NT-proBNP) in comparison with the isolated course of CHF. COPD negatively affects the functional status of patients with CHF with different EF by lower values of 6MWD, 6MWD/6MWD(i) ratio, and higher results on the Borg dyspnea test.

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Competing Interests

The authors declare that they have no competing interests.

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