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ORIGINAL ARTICLE

Physical Rehabilitation in Patients with Chronic Heart Failure and Chronic Obstructive Pulmonary Disease

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ABSTRACT

Despite all the efforts of medical services, the socio-economic damage caused by chronic heart failure (CHF) is increasing. Approximately 10-40% of patients with CHF also suffer from chronic obstructive pulmonary disease (COPD). The comorbid course of these pathologies aggravates the prognosis of patients. Moderate physical activity is recommended as a non-drug therapy for both pathologies.

The aim of the study: was to evaluate the effectiveness of physical rehabilitation in patients with chronic heart failure and chronic obstructive pulmonary disease by determining the levels of NT-proBNP, high-sensitivity C-reactive protein, IL-1β, IL-6, TNF-α.

Methods: The study included 240 patients with CHF. After the initial examination, the patients were divided into groups depending on the presence or absence of COPD and the value of LVEF. Subsequently, each group was divided into a subgroup that took part in physical rehabilitation in addition to standard medical therapy and another one consist of patients that received only standard therapy. A year later, the levels of NT-proBNP, high-sensitivity C-reactive protein, IL-1β, IL-6 and TNF-α were re-determined.

Results and Conclusion: CHFpEF patients have higher levels of hs-CRP and pro-inflammatory cytokines compared to patients with CHFrEF. The combination of COPD and CHF enhances systemic inflammation and myocardial remodeling processes, determined by the level of NT-proBNP in comparison with the isolated course of CHF. Physical rehabilitation in patients with a comorbid course of COPD and CHF is accompanied by a significant decrease in the levels of pro-inflammatory cytokines, hs-CRP and NT-proBNP.

Keywords: chronic heart failure, chronic obstructive pulmonary disease, physical rehabilitation

INTRODUCTION

Despite all the efforts of medical services, the socio-economic damage caused by chronic heart failure (CHF) is increasing. [1] This can be explained, on the one hand, by the increase in the life expectancy of patients with cardiovascular diseases, and by the improvement of diagnostic capabilities in relation to CHF.

Approximately 10-40% of patients with CHF also suffer from chronic obstructive pulmonary disease (COPD). The comorbid course of these pathologies aggravates the prognosis of patients. [2,3] In order to improve the efficiency of CHF and COPD management, various methods of influencing the pathogenesis of these diseases are used [4,5]. Moderate physical activity is recommended as a non-drug therapy for both pathologies [6, 7].

The aim of the study was to evaluate the effectiveness of physical rehabilitation in patients with chronic heart failure and chronic obstructive pulmonary disease by determining the levels of NT-proBNP, high-sensitivity C-reactive protein, IL-1β, IL-6, TNF-α.

MATERIAL AND METHODS

Patients were recruited from the regional CHF registry of the Voronezh region. Out of 2000 patients, 240 ischemic CHF patients aged from 40 to 70 years were included in the study (134 men and 106 women, mean age 71.4 ± 8.4 years). The diagnosis of CHF was established in accordance with 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure, and 2020 clinical guidelines for the diagnosis and treatment of chronic heart failure of Ministry of Health of Russian Federation. The functional class (FC) of CHF patients was determined according to the classification of the New York Heart Association (NYHA) (1994) and the results of the 6-minute walk test (6MWT) using a complex of cardiorespiratory analysis. According to the presence / absence of COPD, patients were divided into two groups: the first group (n=160) - patients with isolated CHF (86 men and 74 women, mean age - 73.2 ± 8.8 years), who had no signs of lung diseases (including COPD), the second group (n=80) - patients with a comorbid course of CHF and COPD (48 men and 32 women, mean age - 67.5±5.9 years. All patients with COPD (GOLD grade 2, group D) corresponded to the "frequent exacerbation" phenotype (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, anamnesis, objective status, spirometry data in accordance with 2020 GOLD Reports. According to the LVEF, each of the two groups was divided into two more subgroups. Patients with CHF with borderline ejection fraction (LVEF 40-50%) and reduced ejection fraction (EF<40%) were merged into the group of patients with CHF with reduced ejection fraction (EF<50%). Accordingly, in the first group, chronic heart failure with preserved ejection fraction (CHFpEF, EF≥50%) was recorded in 69 patients (subgroup 1), chronic heart failure with reduced ejection fraction (CHFrEF, EF<50%) - in 91 patients (subgroup 2). In the second group, COPD and CHFpHF (EF≥50%) was observed in 36 patients (subgroup 3), COPD and CHFrHF (EF<50%) - in 44 patients (subgroup 4).

The first group (patients with isolated CHF) did not include patients with bronchopulmonary diseases (including asthma, chronic obstructive pulmonary disease), chronic kidney disease (stage 3b and above), diabetes mellitus, a permanent form of atrial fibrillation, anemia, diseases of the musculoskeletal system (that reduce movement), obesity (2-3 degrees), oncological diseases with a chronic pulmonary hear disease. The exclusion criteria in

the second group (patients with comorbid CHF and COPD) were the same, except for the presence of COPD.

After the initial examination, each of the 4 groups was divided into 2 subgroups: the first subgroups included patients who received standard drug therapy and underwent additional physical rehabilitation; the second subgroups included patients who received only standard drug therapy. The distribution of patients into groups and subgroups is shown on the figure 1.

All patients included in the study had the opportunity to communicate with a cardiologist during the year. During that period of time, 21 people discontinued participation in the study due to the onset of one of the endpoints (death). The remaining 219 patients underwent a second examination, which included clinical, laboratory and instrumental research methods. Repeated laboratory methods included: complete blood cell count, ELISA blood tests with the determination of the levels of NT-proBNP, high-sensitivity C-reactive protein (hs-CRP), IL-1β, IL-6, TNF-α.

Informed consent was obtained from all participants of the study. The study was reviewed and approved by the ethics committee of VSMU named after N.N. Burdenko.

Statistical analysis was carried out using the Statistica 10 software package. Normality of data distribution was assessed using the Shapira-Wilk test. The original continuous variables were presented as mean ± standard deviation and compared using Student's t-test, as median and interquartile range and compared using the Mann-Whitney and Kruskal-Wallis test. Categorical comparisons were made using Fisher's exact method. The Spirmen rank correlation coefficient was used to assess the relationship between NT-proBNP, hs-CRP levels and echocardiography (ECHO) parameters. Differences between subgroups were considered statistically significant p<0.05.

RESULTS

The mean level of NT-proBNP in patients with CHFrEF who underwent additional physical rehabilitation (subgroup 2.1) was 897 ± 136 ng/l, which significantly exceeded its value in patients with CHFpEF (subgroup 1.1) - 476 ± 82 ng/l (p<0.001). The mean level of NT-proBNP in patients with CHFrEF (subgroup 2.2) was 1129±185 ng/l, which also was significantly higher than in patients with CHFpEF (subgroup 1.2) – 796±121 ng/l (p<0.001). The same trend was obtained in patient with comorbid course of COPD and CHF. The level of NT-proBNP in blood serum in subgroup 4.1 (patients with COPD and CHFpEF who underwent additional physical rehabilitation) was 1401±211 ng/l, which also exceeded its value in patients of subgroup 3.1 with COPD and CHFpEF 981±156 ng/l (p <0.001). Serum NT-proBNP level in subgroup 4.2 (patients with COPD and CHFpEF who received drug therapy only) was 1835±241 ng/l, which also exceeded its value in patients of subgroup 3.2 with COPD and CHFpEF 1209±203 ng/l (p <0.001). It was noted that in patients who had a combination of COPD and CHF, the level of NT-proBNP remained statistically significantly higher than in the group of patients with isolated CHF, which may indicate a negative impact of COPD on the course of cardiovascular diseases (diagram 1).

The dynamics of the level of hs-CRP (highly sensitive C-reactive protein) as a biomarker of endogenous inflammatory processes in all 8 subgroups of patients was studied. Re-examination of patients revealed that in the subgroup of patients with CHFpEF who underwent additional physical rehabilitation (subgroup 1.1), the level of hs-CRP significantly decreased by 2.9±0.56 mg/l (p<0.05 compared to subgroup 1 in 2020 year), while in patients who received drug therapy only (subgroup 1.2), no statistically significant changes were detected (3.6±0.62 mg/l). In patients with CHFrEF who underwent additional physical rehabilitation (subgroup 2.1), the level of hs-CRP was statistically significantly lower - 2.05±0.48 mg/l (p<0.01, compared with subgroup 1.1; p<0.05 in comparison with subgroup 2 in 2020). It should be noted that in patients with CHFrEF who haven't participated in physical rehabilitation the level of hs-CRP also significantly decreased and was 2.2±0.51 mg/l (p<0.001, compared with subgroup 1.2; p<0.01, compared with subgroup 1.2 in 2020). The level of hs-CRP in subgroup 4.1 (patients with COPD and CHFrEF who underwent additional physical rehabilitation) was 3.1±0.6 mg/l, which also reflected a statistically significant decrease in this biomarker of endogenous inflammation (p<0.05 compared with subgroup 4 in 2020). In subgroup 4.2, no statistically significant changes could be detected (hs-CRP level = 3.9±0.73 mg/l, p>0.05). In turn, in the subgroups of patients with COPD and CHFpEF, the level of highly sensitive C-reactive protein was higher than in patients of the fourth subgroup with COPD and CHFrHF. So in subgroup 3.1 it was 4.4±0.78 mg/l (p<0.03; p<0.001 compared to subgroup 3 in 2020), in subgroup it was 3.2 - 4.6±0.8 mg/l (p<0.05 ; p<0.02 compared to subgroup 3 in 2020) (diagram 2).

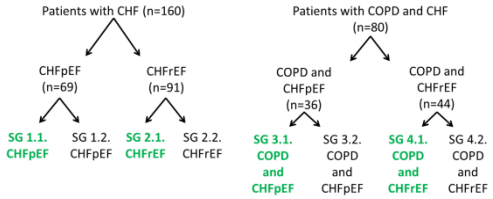

Figure 1: The distribution of patients into groups and subgroups.

Those groups of patients who underwent additional physical rehabilitation are highlighted in green. CHFpEF - chronic heart failure with preserved ejection fraction, CHFrEF - chronic heart failure with reduced ejection fraction, COPD - chronic obstructive pulmonary disease, SG – subgroup.

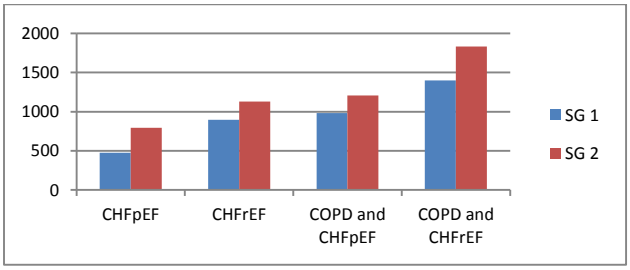

Diagram 1: Comparative characteristics of NT-proBNP levels (ng/l) in subgroups.

CHFpEF - chronic heart failure with preserved ejection fraction, CHFrEF - chronic heart failure with reduced ejection fraction, COPD - chronic obstructive pulmonary disease, SG – subgroup.

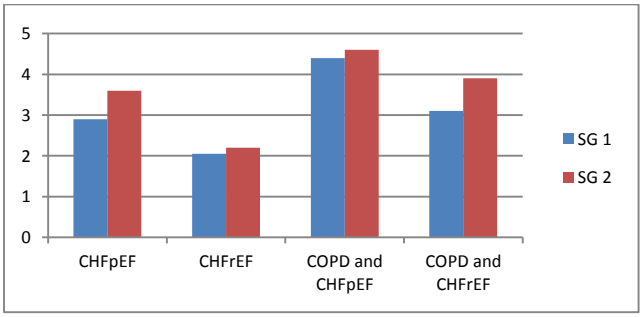

Diagram 2: Comparative characteristics of hs-CRP levels (mg/l) in subgroups.

CHFpEF - chronic heart failure with preserved ejection fraction, CHFrEF - chronic heart failure with reduced ejection fraction, COPD - chronic obstructive pulmonary disease, SG – subgroup.

Table 1: Comparative characteristics of pro-inflammatory cytokines levels in subgroups

Subgroups	Cytokine profile					
	IL -1β	p	IL -6	p	TNF-α	p
SG 1 (CHFpEF)	106,9± 21,8		261,4±31,4		145,4± 25,1	
SG 2 (CHFpEF)	121,9± 25,4	0,04	295,2±35,1	0,001	163,4± 27,2	0,005
SG 1 (CHFrEF)	95,8±20,1	0,05	167,6±26,3	0,05	130,7± 22,8	0,05
SG 2 (CHFrEF)	103,1± 21,0		182,1± 28,8		143,0± 24,9	
SG 1 (COPD and CHFpEF)	117,4± 22,3		376,7± 55,7*		235,9± 31,6*	
SG 2 (COPD and CHFpEF)	139,3± 26,1	0,004	399,8± 60,5*	0,005	256,8± 33,7*	0,01
SG 1 (COPD and CHFrEF)	106,2± 22,6	0,05	290,1 ± 37,6**	0,04	177,2± 26,5**	
SG 2 (COPD and CHFrEF)	122,1± 24,8		302,7 ± 39,1**		198,4± 28,1**	0,03

CHFpEF - chronic heart failure with preserved ejection fraction, CHFrEF - chronic heart failure with reduced ejection fraction, COPD - chronic obstructive pulmonary disease, SG – subgroup.

The results of the repeated analysis of the cytokine profile in patients with CHF, CHF and COPD are presented in Table 1.

Higher levels of IL-1β, IL-6, TNF-α, hs-CRP (Table 1) in subgroups of patients with CHFpEF and comorbid CHFpEF and COPD (subgroups 1.1, 1.2, 3.1 and 3.2) compared with subgroups with reduced EF (subgroups 2.1, 2.2, 4.1 and 4.2) may reflect the importance of the contribution of systemic inflammation to the development and progression of CHF. At the same time, a higher level of pro-inflammatory cytokines was observed in patients with a comorbid course of COPD and CHF in comparison with patients with an isolated course of CHF, which demonstrates the amplification of systemic inflammation (hs-CRP, pro-inflammatory cytokines) and, accordingly, a close pathogenetic relationship between the two pathologies.

DISCUSSION

The success of using NT-proBNP in practical medicine and science, including as a standard, is limited by many factors that can affect its level [8]. However, decrease in the level of biomarker obtained during research in groups of patients undergoing physical rehabilitation may indicate a positive effect of properly selected physical activity on the course of CHF.

Patients with comorbid COPD and CHF are in a state of prolonged hypoxia: permanent (chronic respiratory failure) or intermittent [9,10,11]. Intermittent hypoxia can occur during exercise, exacerbation of COPD or CHF decompensation and during sleep. Hypoxia can lead to a relaxation and contraction dysfunction due to changes in the metabolism of cardiomyocytes. One of the main factors of impaired relaxation and the formation of diastolic dysfunction is a violation of intracellular calcium transport in cardiomyocytes against the background of hypoxia (calcium overload). Hypoxia is involved in the pathogenesis of atherosclerosis and cardiosclerosis: systemic and vascular inflammation, increased levels of C-reactive protein, oxidative stress [12].

Thus additional information about the possibility of adverse outcomes can be obtained through the determination of hs-CRP. Its increase (simultaneously with an increase in NT-proBNP) may indicate a non-infectious inflammatory process in the myocardium, which may be one of the pathophysiological mechanisms of myocardial remodeling, which differs from changes in the heart during its hypertrophy and ischemia.

The main systemic effect of COPD is systemic inflammation. At the same time, the underlying mechanism is quite diverse and has not yet been sufficiently studied. The repeated analysis of the cytokine status indicators showed that the elevated level of pro-inflammatory cytokines in all the studied subgroups, both in isolated CHF and in the comorbid course of CHF and COPD, persists. At the same time, the content of IL-1β, IL-6, TNF-α was also significantly higher in comorbidity. In groups of patients who additionally underwent physical rehabilitation, the content of systemic inflammation biomarkers significantly decreased in comparison with the group who received drug therapy only.

CONCLUSION

CHFpEF patients have higher levels of hs-CRP and pro-inflammatory cytokines compared to patients with CHFrEF, which reflects more pronounced subclinical inflammation and the importance of the contribution of the immune-inflammatory component to the development of early stages of CHF.

The combination of COPD and CHF enhances systemic inflammation and myocardial remodeling processes, determined by the level of NT-proBNP in comparison with the isolated course of CHF.

In addition, physical rehabilitation in patients with a comorbid course of COPD and CHF is accompanied by a significant decrease in the levels of pro-inflammatory cytokines, hs-CRP and NT-proBNP.

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