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INTERLEUKIN-18/INTERLEUKIN-10 RATIO IN PREDICTING THE FURTHER COURSE OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE COMBINED WITH HYPERTENSION

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СЪОТНОШЕНИЕ ИНТЕРЛЕВКИН-18/ИНТЕРЛЕВКИН-10 ПРИ ПРЕДСКАЗВАНЕ НА ПО-НАТАТЪШНИЯ ХОД НА ХРОНИЧНА ОБСТРУКТИВНА БЕЛОДРОБНА БОЛЕСТ В КОМБИНАЦИЯ С ХИПЕРТОНИЯ

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Abstract. *The article presents the results of analysis of main prognostically significant criteria depending on the values of interleukin-18/interleukin-10 (IL-18/IL-10) ratio in patients with chronic obstructive pulmonary disease (COPD) combined with hypertension (HT). Growth of IL-18/IL-10 ratio was associated with emphysematous changes in chest X-ray, increase in the degree of dyspnea, decreased exercise tolerance, increased levels of desaturation, lower body mass index, waist and mid-arm circumferences. The results of echocardiography revealed that all patients with comorbid pathology had signs of myocardial overload. Patients of the first tertile (IL-18/IL-10 < 23) had more pronounced signs of an overload of the left heart. Instead, patients of the third tertile (IL-18/IL-10 ≥ 59) had more pronounced signs of an overload of the right heart by pressure. Prognostically unfavorable types of left ventricular geometry (concentric hypertrophy and eccentric hypertrophy) were more common in patients of the first tertile.*

Key words: *chronic obstructive pulmonary disease, hypertension, interleukin-18/interleukin-10 ratio, desaturation, left ventricular geometry*

Резюме. *В статията са представени резултатите от анализа на основните прогностично значими критерии в зависимост от стойностите на съотношението интерлевкин-18/интерлевкин-10 (ИЛ-18/ИЛ-10) при пациенти с хронична обструктивна белодробна болест (ХОББ) в комбинация с хипертония. С увеличаване на ИЛ-18/ИЛ-10 се наблюдават по-често емфизематозни промени при рентгенография на гръдния кош, повишен задух, намален толеранс при усилие, повишена десатурация, намален индекс на телесна маса, обиколка на талията и рамото. Според резултатите от ехокардиографията се установява, че всички пациенти със съпътстваща патология показват признаци на претоварване на миокарда. Пациентите от първия тертил (ИЛ-18/ИЛ-10 < 23) имат по-изразени признаци на претоварване на лявата сърдечна половина. Пациентите от третия тертил (ИЛ-18/ИЛ-10 ≥ 59) са с по-изразени признаци на претоварване на дясното сърце с натиск. Прогностично неблагоприятните видове левокамерно ремоделиране (концентрична и ексцентрична хипертрофия) са по-чести при пациенти от първия тертил.*

Ключови думи: *хронична обструктивна белодробна болест, хипертония, съотношение интерлевкин-18/интерлевкин-10, десатурация, геометрия на лявата камера*

The problem of combined course of chronic obstructive pulmonary disease (COPD) and hypertension (HT) is one of the most urgent due to the increasing incidence, severity of complications, tendency towards increased mortality and persistent disability [1]. Decrease in forced expiratory volume in 1 second (FEV_1) in patients with COPD is associated with the risk of adverse cardiovascular events. Abnormal inflammatory airway response to inhaled particles and gases, as well as the maintenance of low-grade inflammation, contribute to the progressive course of COPD. The combination of COPD with HT contributes to the progression of systemic inflammation. In order to timely predict future exacerbations and complications, along with to optimize the treatment of patients with COPD, proven biological markers are required. Recently, the role of cytokine imbalance in maintaining chronic inflammation in COPD is discussed [2].

Interleukin-18 (IL-18) is an inflammatory cytokine of the family IL-1, which produces various cells of the body, including alveolar macrophages and respiratory epithelial cells. There is evidence of participation of IL-18 in the formation of COPD, emphysema and pulmonary fibrosis [3]. Interleukin-10 (IL-10) is a major anti-inflammatory cytokine. The physiological function of IL-10 is associated with regulation of inflammation processes, restoring the balance of pro- and anti-inflammatory cytokines and inhibition of excessive production of pro-inflammatory cytokines, including cytokines IL-1 family. IL-18/IL-10 ratio reflects the balance of pro- and anti-inflammatory components of inflammation. Lack of data on imbalance of cytokines in the formation of COPD in combination with HT and predicting further outcomes requires further research.

The study aim is to analyze the dependence of IL-18/IL-10 ratio on the clinical course and features of the myocardial remodeling of patients with COPD combined with HT.

Material and Methods

The study included 69 occupational COPD patients (GOLD 2, group B) in combination with HT stage II (57 males and 12 females), 55.80 ± 5.51 years old. Duration of dust exposure was 25.36 ± 7.65 years. The patients were divided into three groups (tertiles) by the value of IL-18/IL-10.The study also included 20 healthy volunteers (12 males and 8 females), 44.35 ± 6.91 years old. All patients expressed their consent to participate in the study and were fully aware of the scope and methods of research.

The exclusion criteria were the presence of symptomatic hypertension, oncological, endocrine, renal and autoimmune pathologies; exacerbation of chronic or acute inflammation processes; diffuse connective disorders.

All patients performed general clinical and laboratory examinations, 6-min walk test (6MWT), pulse oximetry, spirometry, electrocardiography, echocardiography and chest X-ray. The examination was carried out in remission which is characterized by stable clinical symptoms and spirometry indices. Severity of such symptoms as coughing, sputum secretion, weakness was evaluated using visual analog scales. Echocardiography was performed on ultrasound device RADMIR (Ultima PA).The following hemodynamic parameters were calculated: dimensions of left atrium (LA), left ventricular (LV) posterior wall thickness at end diastole (LVPWd), interventricular septal wall thickness at end diastole (IVSd), LV volumes – end-systolic (LVVs) and end-diastolic (LVVd), LV dimensions – end-systolic (LVDs) and end-diastolic (LVDd), LV mass index (LVMI), LV ejection fraction(LVEF), dimensions of right atrium (RA), right ventricle (RV) diameter, RV wall thickness, pulmonary artery diameter (PAD) and mean pulmonary artery pressure (mPAP). LV geometry was divided into four patterns based on LVMI and relative wall thickness (RWT) values according to the classification of A. Ganau. These are: 1. Normal geometry (NLVG) – normal LVMI and RWT ≤ 0.42; 2. Concentric remodeling (CLVR) – normal LVMI and RWT > 0.42; 3. Concentric hypertrophy (CLVH) – increased LVMI and RWT > 0.42; 4. Eccentric hypertrophy (ELVH) – increased LVMI and RWT ≤ 0.42. The relative wall thickness (RWT) was calculated using the formula (IVSd + LVPWd)/LVDd. According to the European guidelines for the management of patients with hypertension in 2013 – exceeding the LVMIover 115 g/m^2 for men and over 95 g/m^2 for women according to echocardiography is the criterion of high-risk cardiovascular complications [4]. IL-18 and IL-10 in peripheral blood were determined by ELISA using a test system Bender MedSystems, GmbH (Austria).

Statistical analysis of the data was performed by non-parametric statistics methods. The central pattern and variability of quantitative indicators were calculated by bringing the arithmetic mean value (M) and standard deviation (m) or median (me) and interquartile range – lower quartile (LQ), upper quartile (UQ); results are presented in the form of: **M ± m** or **me** (LQ; UQ). The probability of differences in independent groups was estimated using Mann-Whitney U-test and Kruskal-Wallis H-test for quantitative indicators, χ^2-test for

qualitative indicators. All statistical tests were bilateral, differences were considered significant for p < 0,05.

Results and Discussion

Levels of IL-18 in serum were significantly higher in patients with COPD combined with HT compared to the healthy controls (2641.28 (2171.34; 3550.16) pg/ml vs. 207.22 (195.29; 272.74) pg/ml, p < 0,001). Levels of IL-10 in serum were significantly higher in patients with COPD combined with HT compared to the healthy controls: 77.93 (55.27; 112.34) pg/ml vs. 47.10 (44.00; 49.18) pg/ml, p < 0,001). IL-18/IL-10 ratios also were significantly higher in patients with COPD combined with HT compared to the healthy controls (40.23 (20.67; 66.11) vs. 4.36 (3.98; 6.10), p < 0,001).

We analyzed the main features of the patients depending on the level of IL-18/IL-10 ratio. Patients were divided into three groups – tertiles (Table 1). It was found that in the studied patients, the growth of IL-18/IL-10 ratio is significantly (p < 0.05) associated with reducing the body mass index (BMI), waist and mid-arm circumferences, 6MWT distance; increasing the degree of dyspnea before and after 6MWT, a lower level of saturation after 6MWTand a higher degree of desaturation, less cough and more severe

Table 1. Characteristics of patients depending on the level of IL-18/IL-10 ratio

Features	First tertile (IL-18/IL-10 < 23) n = 23	Second tertile (23 ≥ IL-18/IL-10 < 59) n = 23	Third tertile (IL-18/IL-10 ≥ 59) n = 23	p
BMI, kg/m^2	30.19 ± 4.10	29.16 ± 3.19	25.73 ± 2.17	p < 0,001
Waist circumference, cm	100.52 ± 10.00	94.48 ± 10.31	85.17 ± 8.89	p < 0,001
Mid-arm circumference, cm	33.83 ± 1.72	32.43 ± 1.95	30.26 ± 1.89	p < 0,001
6MWT distance, m	387.30 ± 15.80	387.48 ± 13.61	375.43 ± 12.11	p = 0,007
Dyspnea before 6MWT, points	2.83 ± 0.72	2.96 ± 0.77	3.35 ± 0.65	p = 0,016
Dyspnea after 6MWT, points	3.52 ± 0.90	3.57 ± 0.95	4.48 ± 0.73	p < 0,001
Saturation before 6MWT, %	98.00 ± 0.52	97.87 ± 0.76	97.70 ± 0.56	p = 0,245
Saturation after 6MWT, %	94.57 ± 1.38	3.57 ± 0.95	92.57 ± 1.20	p < 0,001
Desaturation, %	3.43 ± 1.24	3.87 ± 1.36	5.13 ± 1.18	p < 0,001
Severity of cough, points	3.87 ± 1.58	2.93 ± 1.80	1.43 ± 1.11	p < 0,001
Severity of weakness, points	3.04 ± 1.07	3.09 ± 1.12	4.13 ± 1.06	p = 0,001
Emphysema on chest X-ray	16	12	23	p = 0,161
LA, mm	42.13 ± 3.17	41.35 ± 3.20	38.04 ± 2.65	p < 0,001
IVSd, cm	1.25 ± 0.12	1.22 ± 0.08	1.17 ± 0.06	p = 0,012
LVDd, cm	5.60 ± 0.44	5.39 ± 0.39	5.11 ± 0.34	p = 0,002
LVPWd, cm	1.19 ± 0.10	1.13 ± 0.08	1.07 ± 0.08	p < 0,001
LVDs, cm	3.66 ± 0.37	3.55 ± 0.39	3.27 ± 0.30	p = 0,002
LVVd, ml	149.00 ± 23.03	142.70 ± 20.71	129.91 ± 17.27	p = 0,01
LVVs, ml	56.26 ± 12.62	53.09 ± 10.69	45.04 ± 10.54	p = 0,005
LVEF, %	61.57 ± 3.38	61.87 ± 3.03	61.96 ± 2.99	p = 0,794
LVMI, g/m^2	142.54 ± 24.01	132.90 ± 19.48	116.85 ± 18.57	p < 0,001
RA, mm	37.65 ± 5.05	38.13 ± 3.98	38.43 ± 3.54	p = 0,996
RV diameter,mm	28.35 ± 2.27	28.17 ± 2.29	26.43 ± 2.15	p = 0,013
RV wall thickness, mm	5.28 ± 0.60	5.39 ± 0.58	5.59 ± 0.639	p = 0,153
PAD, mm	24.78 ± 1.78	24.52 ± 1.24	24.39 ± 1.33	p = 0,843
mPAP, mmHg	25.87 ± 3.20	25.65 ± 2.01	25.61 ± 1.73	p = 0,976
NLVG	0 (0%)	1 (4%)	3 (13%)	p = 0,223
CLVR	1 (4%)	4 (17%)	9 (39%)	p = 0,059
CLVH	14 (61%)	15 (65%)	6 (26%)	p = 0,187
ELVH	8 (35%)	3 (13%)	5 (22%)	p = 0,779
NLVG and CLVR	1 (4%)	5 (22%)	12 (52%)	p = 0,006
CLVH and ELVH	22 (96%)	18 (78%)	11 (48%)	p = 0,161

weakness. Desaturation is decreased in SpO_2 during 6MWT more than 4% of the initial value, or starting SpO_2 below 90% is associated with more rapid decrease in lung function, twice more frequent adverse events [7].

The majority of the first tertile patients resemble classical representatives of the bronchial phenotype COPD, while many patients of the third tertile are similar to the emphysematous phenotype COPD.

Excessive production of IL-18 promotes remodeling of lung parenchyma. Mechanisms of alveolar destruction are also associated with interferon-γ (IFN-γ). IL-18 induces the production of IFN-γ, which causes changes in the balance of lung proteases and proteases. Thus, high levels of IL-18 indicate significant activity reconstruction process in airways, alveoli and pulmonary vessels with the formation of emphysematous and fibrotic changes [3].

Most patients with mild and moderate COPD suffer from adverse cardiovascular events [5,6]. To predict the risk of unwanted cardiovascular outcomes, it is necessary to timely analyze hemodynamic parameters by evaluating echocardiographic data. Signs of an overload of the left heart were significantly more common among patients in the first tertile. IVSd, LVDd, LVPWd, LVDs, LVVd, LVVs, LVMI were significantly ($p \leq 0,01$) higher in patients of the first tertile. Increased left ventricular mass every 39 g/m^2 is accompanied by an increased risk of adverse cardiovascular events by 40% [8]. Patients of the third tertile had more pronounced signs of overloading the right heart by pressure (RV wall thickness> 5 mm, RV diameter < 30 mm and IVSd > 1.1 cm).

LV geometry analysis enables to distinguish patients with a higher risk of cardiovascular complications. In the first tertile CLVH and ELVH were prevalent. Instead, in the third tertile CLVR were dominant. Concentric and eccentric hypertrophy indicates a deeper and prognostically adverse remodeling of the myocardium. Prognostically unfavorable types of LV geometry (CLVH and ELVH) were observed in 22 patients (96%) of the first tertile. Prognostically favorable types of LV geometry (NLVG and CLVR) were significantly ($p = 0,006$) more common in patients of the third tertile. Myocardial remodeling is associated with a higher risk of cardiovascular complications.

Conclusions

1. Increased IL-18/IL-10 ratio in patients with COPD combined with HT was associated with decreased exercise tolerance, desaturation, low values of BMI, waist and mid-arm circumferences, and increased frequency of emphysema on X-rays.

2. All patients with comorbid pathology had signs of myocardial overload. Patients of the first tertile (IL-18/IL-10 < 23) had more pronounced signs of an overload of the left heart. Instead, patients of the third tertile (IL-18/IL-10 ≥ 59) had more pronounced signs of an overload of the right heart by pressure. Prognostically unfavorable types of LV geometry (CLVH and ELVH) were more common in patients of the first tertile.

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