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Immunobiochemical Features of Pulmonary Hypertension in Patients with Diseases of the Bronchopulmonary System

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Abstract Relevance: The study focuses on cytokines and biochemical markers in pulmonary hypertension (PH) in patients with bronchial asthma (BA), chronic obstructive pulmonary disease (COPD), and their combination. Objective: To identify the immune and biochemical features of PH in these patients. Methods: A total of 95 patients with PH were examined, including 17 with BA, 35 with COPD, and 43 with ACOPD. Levels of IL-4, IL-17A, IL-18, TNFα, IFNγ, CRP, fibrinogen, NT-proBNP, and ET-1 were studied. Results: Statistically significant differences in the levels of these markers were found between the groups. Conclusions: Cytokines play a key role in the pathogenesis of PH and can serve as markers of disease severity. This can help in developing new treatment and diagnostic methods. The results can be used to improve clinical management of patients with PH.

Keywords Pulmonary hypertension, Bronchial asthma, Chronic obstructive pulmonary disease, Cytokines, Biochemical markers

1. Relevance

A fundamentally important question in modern practical medicine is the connection between the formation of a layer of chronic diseases, such as BA/COPD and hypertension/ CHD, with processes occurring in the cardiorespiratory system or with shifts in the immune system [3,6,7,10,11,12,24,25,26]. According to many authors, the cause of the overlap or layering of bronchial asthma and chronic obstructive pulmonary disease and the development of vascular complications are various immune disorders that cause a decrease in the body's resistance to microbial infection [1,4,8,13,14,15,16,22].

A detailed study of cytokines helps to determine their significant and diverse role in the development of immune, allergic and inflammatory reactions in diseases of the cardiorespiratory system. The understanding of the pathogenesis of pulmonary and cardiovascular diseases is complemented by increasingly new data on the nature and functions of these mediators. As the role of cytokines becomes clearer, it becomes possible to control the inflammatory process and other pathophysiological consequences of lung injury [2,5,9,17,18,19,20,21,23].

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2. Purpose of the Study

To study the features of cytokine status and biochemical markers in pulmonary hypertension in patients with bronchial asthma, COPD and the intersection of BA and COPD.

3. Materials and Research Methods

We selected 95 patients with pulmonary hypertension (PH) to study the state of the immune system. Of these, 17 patients with asthma, 35 patients with COPD and 43 patients with ACO. 20 practically healthy people made up the control group. Clinical material was collected at the Bukhara Regional Multidisciplinary Medical Center and at the Bukhara branch of the Republican Scientific and Practical Center for Emergency Medical Care.

To determine the concentrationIL-4, IL-17A, IL-18, TNFα, IFNγ, CRP, fibrinogen, NT-proBNP, EN1 in the blood serum of the study groups was used using the three-stage "sandwich" method - this is a type of three-phase ELISA.

Statistical processing of the research results was carried out using the SPSS v16.0, R, PLINK and Haploview 4.2 software packages.

4. Results of the Study and Their Discussion

In our studies, we conducted a comparative analysis of pro- and anti-inflammatory cytokines in the studied groups (IL-4, IL-17A, IL-18, TNFα, IFNγ) (Fig. 1).

According to many authors, cells that synthesize Th2-type cytokines dominate in the airways affected by asthma. CD8+ cells, eosinophils and mast cells produce IL-4, which in turn possibly causes hyperreactivity of the bronchial tree [2,8,16,23].

Analysis of IL-4 levels showed statistically significant differences between patient groups. The level of IL-4 was significantly higher in patients with bronchial asthma (BA) (26.7±0.67) than in patients with chronic obstructive pulmonary disease (COPD) (21.9±0.55) - by 2.9 times more, $p<0.05$. Also, the level of IL-4 in patients with BA (26.7±0.67) was higher than in patients with overlap of bronchial asthma and chronic obstructive pulmonary disease (ACO) (23.1±0.45) - by 1.8 times more, $P<0.05$. However, the difference in IL-4 levels between patients with COPD (21.9±0.55) and ACO (23.1±0.45) is not statistically significant. These results confirm the important role of IL-4 in the pathogenesis of bronchial asthma and chronic obstructive pulmonary disease, indicating differences in the immunological response and mechanisms of development of these diseases.

Thus, the level of IL-4 is statistically significantly higher in patients with bronchial asthma compared to chronic obstructive pulmonary disease and combined ACO, approximately 2.9 and 1.8 times, respectively.

Analysis of IL-17A levels also showed statistically significant differences between patient groups. The level of IL-17A was higher in patients with bronchial asthma (BA) (13.1±0.72) compared to the control group (6.34±0.18) - 2.1 times more, $P<0.05$. Also, the level of IL-17A in patients with asthma (13.1±0.72) is higher than in patients with chronic obstructive pulmonary disease (COPD) (11.7±0.52) - by 1.1 times. However, the difference in the level of IL-17A between patients with asthma (13.1±0.72) and the crossover of bronchial asthma and chronic obstructive pulmonary disease (ACO) (12.4±0.51) is not statistically significant.

In a comparative analysis of the level of IL-18 in patients with bronchial asthma (BA), chronic obstructive pulmonary disease (COPD) and the intersection of bronchial asthma and chronic obstructive pulmonary disease (ACO) showed statistically significant differences compared to the control group. The level of IL-18 was higher in patients with asthma (207.5±6.29), COPD (259.4±4.47) and ACO (185.3±4.81) compared to the control group (74.1±2.91) – respectively 2.8, 3.5 and 2.5 times more, $P<0.05$. These results indicate an important role for IL-18 in the immunological response in these diseases. It is possible that the level of IL-18 is associated with various pathogenetic mechanisms, such as inflammation and autoimmune processes, which is significant for the understanding and treatment of bronchial asthma and chronic obstructive pulmonary disease.

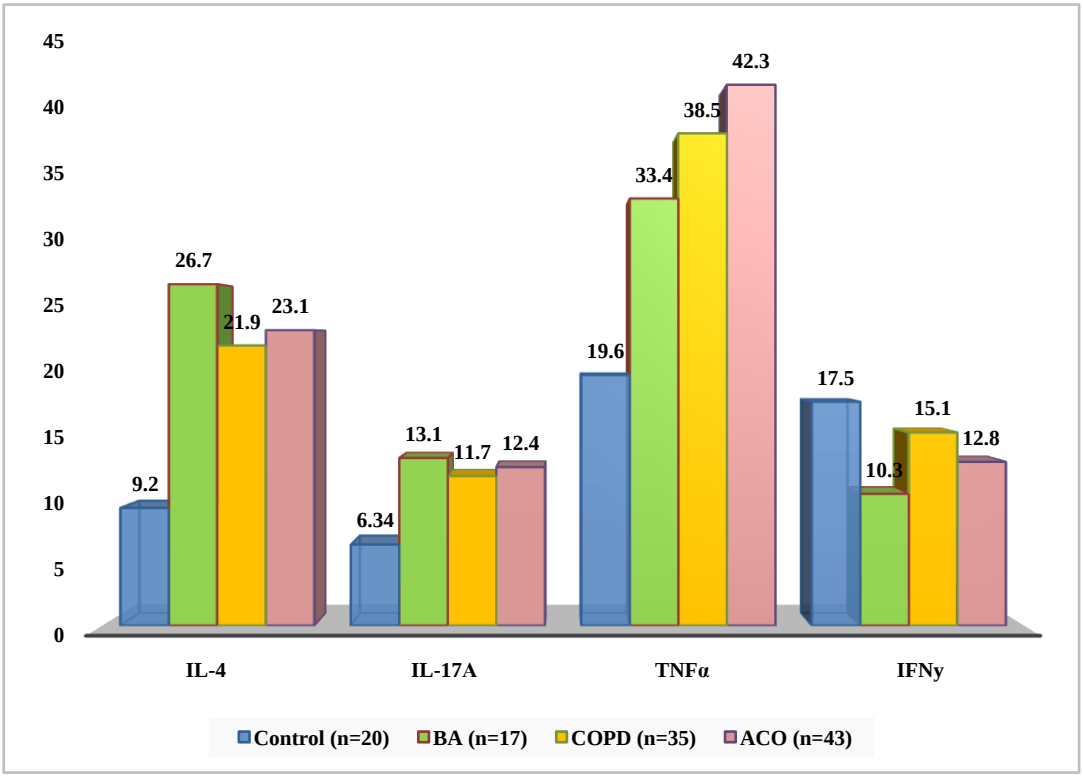

Figure 1. Comparative analysis of pro- and pro-inflammatory cytokines in the group with asthma, COPD and ACO in combination with PH

When studying the concentration of tumor necrosis factor in patients with bronchial asthma (BA), chronic obstructive pulmonary disease (COPD) and polybronchial asthma and chronic obstructive pulmonary disease (ACO), no statistically significant differences were found between groups. The level of TNFα was higher in patients with asthma (33.4±0.67) than in patients with COPD (38.5±0.48) - by 1.15 times. Also, the level of TNFα in patients with COPD (38.5±0.48) was higher than in patients with ACO (42.3±0.42) - by 1.10 times.

Interferon gamma is an indicator of a Th1 immune response, which is more characteristic of a non-allergic inflammatory process [3,7,11,16]. The level of IFNγ was lower in patients with asthma (10.3±0.77) than in patients with COPD (15.1±0.47) - by 1.5 times, $P<0.05$. Also, the level of IFNγ in patients with ACO (12.8±0.44) was lower than in patients with COPD - by 1.2 times. Differences in IFNγ levels between patients with AD and ACO were not statistically significant. Thus, at level IFNγ was reduced in all study groups, but its lowest concentration was observed in the group of patients with asthma in combination with PH.

The results obtained reflect the type and intensity of inflammation of the respiratory tract and vascular bed in the pulmonary circulation. High values of the studied cytokines confirm their role in the remodeling of the bronchi and vascular intima, which contributes to the irreversibility of obstruction in these pathologies. This may be due to the chronic course of both eosinophilic and neutrophilic inflammation of the airways. Undoubtedly, these cytokines play an important role in the pathogenesis of asthma, COPD, ACO in combination with pulmonary hypertension and can serve as markers of the severity of the pathological process.

Pulmonary hypertension (PH) is a pathological condition characterized by increased pressure in the pulmonary arteries, which can develop in various diseases, such as bronchial asthma (BA), chronic obstructive pulmonary disease (COPD) and cross-sectional asthma and COPD (BACO). Inflammatory markers and biomarkers, such as C-reactive protein (CRP), fibrinogen, NT-proBNP and endothelin-1 (EN1), play an important role in the development and progression of PH.

C-reactive protein (CRP) is a marker of systemic inflammation and plays an important role in the pathogenesis of PH [4,8,10,13]. The study found that CRP levels were significantly higher in patients with PH compared to controls. In particular, the average values of CRP were: control - 4.25±0.11mg/l, BA - 11.9±0.64mg/l, COPD - 7.76±0.44mg/l, ACOH - 9.82±0.46mg/l. Thus, the level of CRP in patients with BA was 2.8 times higher than in the control group ($p<0.05$), in patients with COPD it was 1.8 times higher ($p<0.05$), and in in patients with ACO – 2.3 times higher ($p<0.05$).

Fibrinogen is an important plasma protein that plays a key role in the blood clotting process and is a marker of inflammation. Elevated fibrinogen levels are associated with an increased risk of cardiovascular disease, including pulmonary hypertension (PH). [11,15,22,25]. Its increase is also associated with the risk of developing PH. In our study, fibrinogen values were: control - 1.93±0.06g/l, BA - 2.43±0.14g/l, COPD - 3.97±0.09g/l, ACOH - 3.25±0.08g/l. Thus, the fibrinogen level in patients with asthma was 1.3 times higher compared to the control group ($p<0.05$), in patients with COPD it was 2.1 times higher ($p<0.05$), and in patients with ACO – 1.7 times higher ($p<0.05$) (Fig. 2).

The study showed that fibrinogen levels in patients with PH associated with asthma, COPD and ACO are significantly increased compared to the control group. The greatest increase in fibrinogen levels is observed in patients with COPD, indicating a more pronounced inflammatory process and hypercoagulability in this group. In patients with ACO, fibrinogen levels are also significantly elevated, confirming the severity of the overlap between these diseases. In patients with asthma, fibrinogen levels are increased to a lesser extent, indicating less severe inflammation and hypercoagulation.

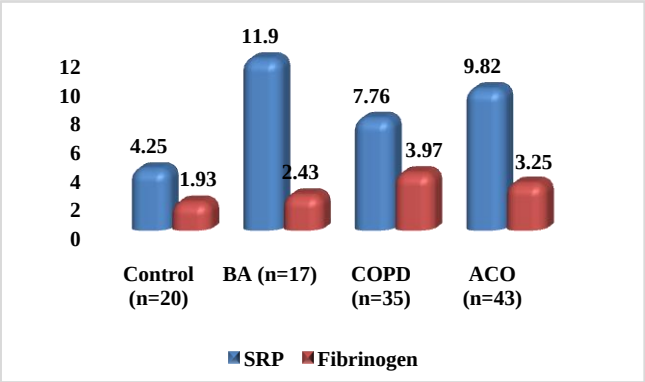

Figure 2. Levels of CRP and fibrinogen in those examined (mg/l, g/l)

N-terminal fragment of brain natriuretic peptide (NT-proBNP) is an important biomarker used for the diagnosis and monitoring of heart failure and pulmonary hypertension (PH). NT-proBNP levels increase in response to increased cardiac wall tension, which occurs with increased pulmonary artery pressure. NT-proBNP is released by ventricular cardiomyocytes in response to stretch and stress on the heart wall, which may be caused by volume overload or increased pressure. The main actions of NT-proBNP include: Diuresis - increasing sodium and water excretion by the kidneys. Vasodilation is the widening of blood vessels. Antihypertrophic effect - preventing thickening of the heart walls. These effects are aimed at reducing circulating blood volume and pressure, which facilitates the work of the heart and reduces pressure in the pulmonary arteries. NT-proBNP is a marker of heart failure and one of the key indicators of PH [4,14,21,24]. The study established the following NT-proBNP values: control - 113.6±6.13pg/ml, BA - 526.3±6.68pg/ml, COPD - 1206.8±9.43pg/ml, ACOC - 1103.7±8.39pg/ml. The level of NT-proBNP in patients with asthma was 4.6 times higher compared to the control group ($p<0.05$), in patients with COPD it was 10.6 times higher ($p<0.05$), and in patients with ACOH - 9.7 times higher ($p<0.05$) (Fig. 3).

When comparing groups of patients with different diseases, it is clear that the level of NT-proBNP is highest in patients with COPD, which indicates a more pronounced load on the heart and a more severe form of PH. The level of NT-proBNP in patients with ACO is also significant, which confirms the severity of the overlap of these diseases. In

patients with asthma, the level of NT-proBNP is also increased, but to a lesser extent, indicating a less pronounced load on the right ventricle compared with other groups.

A study of the level of NT-proBNP in patients with PH associated with BA, COPD and ACO shows a significant increase in this marker, which indicates a high load on the right ventricle and the severity of the disease. The greatest increase in NT-proBNP levels is observed in patients with COPD, followed by patients with ACO and BA. This highlights the importance of using NT-proBNP to diagnose and monitor PH in patients with these diseases, as well as to determine the severity of the condition and prognosis.

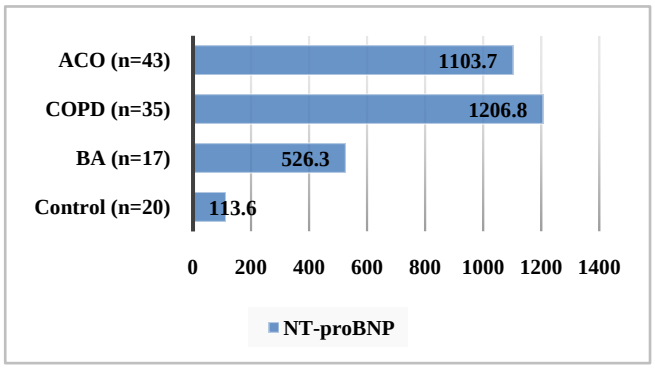

Figure 3. NT-proBNP level in those examined (pg/ml)

Endothelin-1 (EN1) is a vasoconstrictor peptide that plays an important role in the pathogenesis of PH. It is synthesized by vascular endothelial cells and has various biological effects, including vasoconstriction, smooth muscle cell proliferation, and inflammation. Let us consider the role and significance of EN1 in patients with bronchial asthma (BA), chronic obstructive pulmonary disease (COPD) and the crossover of BA and COPD (ACPD). EN1 acts on vascular smooth muscle cells through endothelin type A and B receptors (ET_A and ET_B), causing: Vasoconstriction: Constriction of blood vessels, which leads to increased pressure in the pulmonary arteries. Proliferation: Increase in the number of smooth muscle cells and endothelial cells, which promotes vascular remodeling. Inflammation: Stimulates the production of inflammatory cytokines and attracts inflammatory cells. [7,16,18,23]. EN1 values in the study were: control - 0.83±0.06pg/ml, BA - 1.41±0.07pg/ml, COPD - 3.81±0.09pg/ml, ACOC - 3.07±0.08pg/ml. The level of EN1 in patients with asthma was 1.7 times higher compared to the control group ($p<0.05$), in patients with COPD it was 4.6 times higher ($p<0.05$), and in patients with ACO - 3.7 times higher ($p<0.05$) (Fig. 4).

A comparative analysis of EN1 levels among patients with various diseases shows the following results: The EN1 level in patients with asthma is 1.41±0.07 pg/ml, which indicates a moderate increase compared to the control group: The EN1 level in patients with COPD is significantly higher and amounts to 3.81±0.09pg/ml, indicating more pronounced vascular remodeling and inflammation. The EN1 level in patients with ACO is 3.07±0.08pg/ml, which also indicates a significant increase, but slightly lower than in patients with COPD. The pathogenesis of PH in patients with asthma, COPD and ACO includes the following mechanisms associated with EN1: Increased synthesis of EN1: In response to hypoxia and inflammation, pulmonary vascular endothelial cells increase synthesis of EN1. Vasoconstriction: EN1 causes narrowing of the pulmonary arteries, which leads to increased pressure in them. Vascular remodeling: Chronic exposure to EN1 leads to proliferation and hypertrophy of vascular smooth muscle cells, which contributes to thickening of arterial walls and increased resistance to blood flow. Inflammation: EN1 stimulates the production of inflammatory cytokines and the recruitment of inflammatory cells, which exacerbates vascular damage and contributes to the development of PH.

The study showed that the level of EN1 in patients with PH associated with asthma, COPD and ACO is significantly increased compared to the control group. The greatest increase in EN1 levels is observed in patients with COPD, indicating more pronounced vascular remodeling and inflammation in this group. In patients with ACO, EN1 levels are also significantly elevated, confirming the severity of the overlap between these diseases. In patients with asthma, EN1 levels are increased to a lesser extent, indicating less pronounced vasoconstriction and inflammation.

These data highlight the importance of EN1 as a marker of PH and its significance in assessing disease severity and prognosis in patients with asthma, COPD and ACO. They also highlight the need to develop targeted therapies aimed at reducing EN1 levels and attenuating its effects to improve the condition of patients with PH.

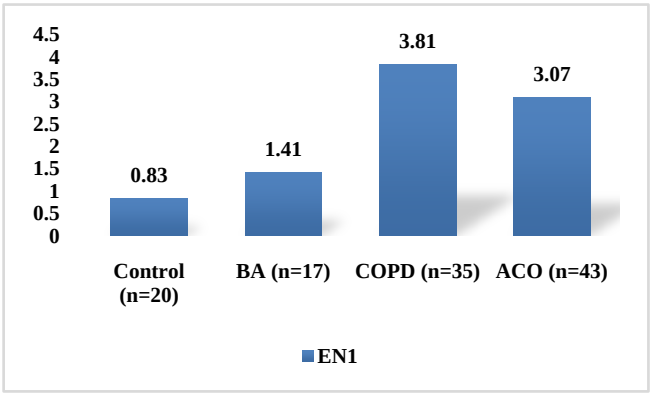

Figure 4. Endothelin-1 level a mong those examined (pg/ml)

Based on the data obtained, conclusions can be drawn about differences in the levels of inflammatory markers and biomarkers among patient groups:

1. CRP: CRP level was highest in patients with asthma (11.9±0.63mg/l), followed by patients with ACO (9.82±0.46mg/l) and COPD (7.76±0.44mg/l).
2. Fibrinogen: Fibrinogen levels were highest in patients with COPD (3.97±0.09g/l), then in patients with ACO (3.25±0.08g/l) and BA (2.43±0.14g/l).
3. NT-proBNP: the highest NT-proBNP values were observed in patients with COPD (1206.8±9.43pg/ml), followed by patients with ACO (1103.7±8.39pg/ml)

and BA (526.3±6.68pg/ml).

4. EN1: EN1 level was highest in patients with COPD (3.81±0.09pg/ml), followed by patients with ACO (3.07±0.08pg/ml) and BA (1.41±0.07pg/ml).

Inflammatory processes play a key role in the pathogenesis of PH. Increases in CRP and fibrinogen indicate the presence of chronic inflammation, which leads to vascular remodeling and increased vascular resistance. An increase in NT-proBNP indicates strain on the right side of the heart associated with increased pulmonary artery pressure. EN1 promotes vasoconstriction and further increases in pulmonary vascular pressure.

5. Conclusions

The study showed that patients with PH associated with asthma, COPD and ACO experienced significant changes in the levels of CRP, fibrinogen, NT-proBNP and EN1 compared with the control group. These markers can be used to assess disease severity and prognosis in patients with PH. Higher levels of these markers in patients with COPD and ACO compared with patients with asthma indicate greater inflammation and vascular damage in these patient groups. This highlights the need for early diagnosis and adequate treatment to prevent the progression of PH and its associated complications.

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