ASSESSMENT OF THE DYNAMICS OF THE INFLAMMATORY CYTOKINES IN DEVELOPING OF ANEMIA WITH DIFFERENT ETIOLOGY IN CHRONIC HEART FAILURE

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Abstract: *According to the results of studies in recent years, in patients with chronic heart failure (CHF) occurs a number of neurohumoral reactions, including the activation of inflammatory cytokines (α - tumor necrosis factor, interleukin-1 and interleukin-6), are associated with anemia of chronic diseases (1,2). It is known that currently, in the development of anemia in CHF, it is important to identify hepcidin, which controls iron homeostasis, and the mechanisms of its interaction with inflammatory mediators as well as to develop effective treatment methods aimed at reducing the activity of pathogenetic factors (3,4,5,6,).*

Key words: *chronic heart failure, inflammatory cytokines, tumor necrosis factor, interleukin-1 and interleukin-6, coronary heart disease, angina pectoris, hypoxia*.

Introduction

Chronic heart failure (CHF) remains one of the leading causes of morbidity and mortality worldwide, representing a complex clinical syndrome characterized by progressive impairment of cardiac function and systemic complications. Among these, anemia is increasingly recognized as a frequent and clinically significant comorbidity, contributing to worsening symptoms, reduced exercise capacity, poor quality of life, and unfavorable prognosis. The mechanisms underlying anemia in CHF are multifactorial, involving renal dysfunction, iron deficiency, neurohormonal activation, and, importantly, chronic systemic inflammation. Inflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) have emerged as key mediators linking the chronic inflammatory state of CHF with the development of anemia of chronic disease. These cytokines not only suppress erythropoietin production and impair iron metabolism through hepcidin regulation but also inhibit erythroid progenitor cell proliferation in the bone marrow. However, the dynamics of cytokine expression and their relative contributions may vary depending on the underlying etiology of anemia in CHF patients—whether iron deficiency, renal impairment, or purely inflammation-driven pathways predominate.

Understanding the interplay between inflammatory mediators and anemia across different etiological backgrounds is essential for refining diagnostic approaches and developing targeted therapies. By assessing the dynamics of inflammatory cytokines in CHF patients with anemia of varied causes, this study aims to clarify the mechanistic

pathways involved and to highlight potential biomarkers and therapeutic targets for personalized management.

Purpose of the research. Assessment of the importance of inflammatory cytokines in the development of anemia in chronic diseases in chronic heart failure.

Materials and methods

As a research source, 115 patients with advanced coronary heart disease (CHD) who were treated in the cardiology, acute heart disease and cardiorehabilitation departments of the National Medical Center in Tashkent were selected. Their age ranged from 50 to 80, and the average was 64.6±4.9. After treatment in the hospital, all patients were followed up in an outpatient setting and divided into two main and control groups. The main group A consisted of 40 CHF with iron deficiency anemia patients and also, group B had 35 patients with anemia of chronic diseases. In the control group, 40 patients without CHF anemia were selected. In turn, each group was divided into two subgroups (II, III FC) according to the functional classes of CHF (Table 1).

Table 1. Clinical classification of patients included in the study

	The main group				The control group	
	Group A n=40		Group B n=35		Without anemia n=40	
	abs	%	abs	%	abs	%
Male	15	37,5	14	39,5	22	54,5
Female	25	62,5	21	60,5	18	45,5
FC II	14	34,5	10	28,5	16	39,5
FC III	26	65,6	25	71,5	24	61,5
CHD. Post-infarction cardiosclerosis	11	27,5	15	37,5	17	42,5
Hypertension	38	95,0	32	90,0	40	100,0
Obesity	12	30,0	17	42,5	14	35,0
Average age	64,8±1,31		65,4±1,48		63,4±1,31	

FC- functional class. CHD – chronic heart disease

Determining the level of inflammatory markers

Cytokines are protein mediators with a low molecular weight in the cell, they participate in the mechanism of intercellular interaction and biological processes (immune reactions in homopoietic, lymphoid and mesenchymal cells, tissue repair, angiogenesis, growth of inflammation etc.) controls. They are synthesized by the activated immune system, fibroblasts, epithelium, endothelium and bone marrow stromal cells. In our study, pro-inflammatory cytokines such as tumor necrosis factor, interleukin-1, interleukin-6 were determined. α-TNF, this cytokine causes left ventricular dysfunction and remodeling, stimulates the development of cardiomyopathies, has a negative effect on energy processes in mitochondria, and creates conditions for the development of lung tumors. Some authors claim that the amount of α-TNF in the blood is considered an independent predictor in determining the prognosis of the disease, and this indicator is more important than that of the indicators of left ventricular ejection fraction and CHF FC. The circulating α-TNF indicator in the blood of patients with CHF is directly related to the functional class of the disease, and is reliably related to early death (within 1.4 years). The eBioscience (Bender MedSystems) company's reagent was used in order to determine the parameters of α-TNF in blood serum, a pack of 96 tests. The package is based on the quantitative determination of the above-mentioned cytokines in human blood serum using immunoenzymatic analysis. Test range: 0.03-5 pg/ml. Sensitivity: 0.03 pg/ml. All laboratory parameters were determined before and after 6 months of adding iron medications to the standard care of the observation patients in order to evaluate the effectiveness of the iron medication.

Statistical analysis of numerical figures

MS Excel (2013) computer software was used for statistical processing of the data obtained in the study. Arithmetic mean and standard deviation (M±m) of the indicators presented in all tables were calculated. The reliability of differences between groups was determined by applying Student's criteria for odd and even differences. Correlation analysis was conducted using Pearson's correlation coefficient and determining its significance established on reliability tables. Based on the sources in the literature, the systemic hypoxia process in the body, the activation of neurohumoral local tissue hormones stimulates the expression of pro-inflammatory cytokines during the exacerbation of CHF and the occurrence of unpleasant complications due to the disease. The increased expression of cytokines is consistent with increasing functional classes of CHF and severity, and in both the main and control groups of patients included in our study, as the functional classes of CHF increase, the amount of cytokines increases compared to normal values, especially in the groups with anemia. compared to groups without anemia, a reliable increase was returned.

Resuts of the study

According to the results of our conducted study, in the control group of CHF patients without anemia, the levels of IL-1 in blood serum at II – III FC were 16.4±0.72 -

18.6±1.93 ng/ml, IL-6 levels were 17.2±1.78 - 18.9±1.3 ng/ml, and α -TNF levels were 15.9±0.72 - 17.4±1.93 ng/ml, respectively.

In group I A, consisting of CHF patients with iron deficiency anemia, the levels of IL-1 in blood serum at II – III FC were 17.9±2.1 - 20.8±1.3 ng/ml, IL-6 levels were 20.4±1.8 - 22.6±1.3 ng/ml, and α -TNF levels were 19.6±0.62 - 21.8±1.64 ng/ml (Table 2).

In group I B, consisting of CHF patients with anemia of chronic disease, the levels of IL-1 in blood serum at II – III FC were 18.2±0.72 - 21.1±1.93 ng/ml, IL-6 levels were 26.6±1.7 - 29.7±1.3 ng/ml, and alp α -TNF levels were 20.2±0.72 - 24.7±1.93 ng/ml, respectively. In patients of group I A, compared to the control group, the levels of IL-1 increased by 9.1 – 11.8% (P<0.05), IL-6 by 18.6 – 19.5% (P<0.001), and α-TNF by 27.1 – 41.0% (P<0.01).

Table 2. The amount of pro-inflammatory cytokines before treatment

Categories	Main group A CHF patients with iron deficiency anemia (n=40)		Main group B CHF patients anemia with chronic diseases (n=35)		Control group, CHF patients without anemia (n=40)	
	CHF FC II, n=14	CHF FC III, n=26	CHF FC II, n=12	CHF FC III, n=28	CHF FC II, n=16	CHF FC III, n=24
IL-1	17,9± 2,1	20,8±1, 3	18,2±0, 72	21,1±1,93 *	16,4± 0,72	18,6± 1,93
IL-6	20,4± 1,8	22,6±1, 3*	26,6±1, 7**	29,7±1,3* **^	17,2± 1,78	18,9± 1,3
α -TNF	19,6± 0,62	21,8±1, 64*	20,2±0, 72*	24,7±1,93 **	15,9± 0,72	17,4± 1,93

Note: differences are significant compared to the indicators of the control group (- P<0.05, ** -P <0.01, *** - P<0.001), - differences are significant compared to the indicators of group A (* - P <0.5. - P <0.01 (P<0.001).*

FC- functional class. CHF – chronic heart failure, IL-1 – interleukin – 1, IL-6 – interleukin – 6, α –TNF – alpha tumor necrosis factor.

Compared to the control group, the amount of IL-1 in patients of group I A went up from 9.1 to 11.8% (P<0.05), and IL-6 accelerated from 18.6 to 19.5% (P<0.01), α -TNF increased from 23.2 % from 25.0% (P<0.01), and in patients of group I B, the amount of IL-1 was 10.9 - 13.4% (P<0.05), and IL-6 was 54.6 - 57.1 % (P<0.001), α - TNF increased from 27.1 to 41.0% (P<0.01).

Table 3. The dynamics of pro-inflammatory cytokines in the serum after treatment (Group A)

Categories	Types of treatment	Group A		Control group	
		CHF FC II, n=12	CHF FC III, n=28	CHF FC II, n=16	CHF FC III, n=24
IL-1	Before	17,9±2,1	20,8±1,3	16,4±0,72	18,6±1,93
	After	9,6±1,2^^	10,8±1,23 ^^^	7,4±1,3^^	8,7±0,92^ ^^
IL-6	Before	20,4±1,8	22,6±1,3*	17,2±1,78	18,9±1,3
	After	10,3±0,98 ^^^	12,2±1,43 ^^^	7,7±1,43^ ^^	8,6±1,2^^ ^
α -TNF	Before	19,6±0,62	21,8±1,64 *	15,9±0,72	17,4±1,93
	After	9,6±1,33^^ ^	11,4±1,67^ ^	6,8±2,1	8,2±2,3

Note: *- differences are significant compared to the indicators of the control group (*- P<0.05, ** -P <0.01, *** - P<0.001), - differences are significant compared to the indicators of group A (^ - P <0.5. ^^- P <0.01, ^^^-P<0.001).

Table 4. The dynamics of pro-inflammatory cytokines in the serum after treatment (Group B)

Categories	Types of treatment	Group B		Control group	
		CHF FC II, n=12	CHF FC III, n=28	CHF FC II, n=16	CHF FC III, n=24
IL-1	Before	18,2±0,72	21,1±1,93*	16,4±0,72	18,6±1,93
	After	16,2±1,12** **	18,3±1,21** **	7,4±1,3^^	8,7±0,92^ ^^
IL-6	Before	26,6±1,7**	29,7±1,3** *	17,2±1,78	18,9±1,3
	After	19,7±0,98** **^	22,8±1,32** **	7,7±1,43^ ^^	8,6±1,2^^ ^
α -TNF	Before	20,2±0,72*	24,7±1,93** *	15,9±0,72	17,4±1,93
	After	15,6±1,42** ^	19,3±0,89** **^	6,8±2,1^^ ^	8,2±2,3^^

Note: *- differences are significant compared to the indicators of the control group (*- P<0.05, ** -P <0.01, *** - P<0.001), - differences are significant compared to the indicators of group A (^ - P <0.5. ^^- P <0.01, ^^^-P<0.001).

Accoding to the treatment, it was found that the amount of pro-inflammatory cytokines in the blood serum of patients in the I A group and the control group with CHF iron deficiency anemia was marginally reduced. The main group of patients with anemia of chronic diseases, CHF I B group, the amount of pro-inflammatory cytokines in the blood serum remained at a high level compared to the other groups, while the trend of declining dynamics was observed. The dynamics of pro-inflammatory cytokines in blood serum of patients in post-treatment follow-up after 6 months are given.

Among those monitored during treatment, the amount of cytokines in the blood serum in the follow-up in the dynamics of CHF FC II without anemia, the amount of IL-1 decreased from 16.4 to 7.4 ng/ml (p<0.01), the amount of IL-6 declined from 17.2 to 7,7 ng/ml (P<0.001), α -TNF dropped reliably from 15.9 to 6.8 ng/ml (p<0.001). And in CHF FC III, the amount of IL-1 increased from 18.6 to 8.7 ng/ml (p<0.001), the amount of IL-6 from went down 18.9 to 8.6 ng/ml (p<0.001), α -TNF significantly positive changed from 17.4 to 8.2 ng/ml (P<0.01).

In patients with iron deficiency anemia in group I A with CHF FC II the plasma level of IL-1 decreased significantly from 17.9 to 9.6 ng/ml (P<0.01) IL-6 decreased from 20.4 to 10.3 ng/ml (P<0.001) and α - TNF decreased from 19.6 to 9.2 ng/ml (P<0.001). In CHF FC III plasma level of IL-1 dropped significantly from 20.8 to 10.8 ng/ml (P<0.001) IL-6 declined from 22.6 to 12.2 ng/ml (P<0.001) and α - TNF went down from 21.8 to 11.4 ng/ml (P<0.01) (Table 3).

In group I B consisting of patients with chronic disease anemia with CHF II FC plasma level of IL-1 changed from 18.2 to 16.2 ng/ml (P>0.05) IL-6 decreased from 26.6 to 19.7 ng/ml (P<0.05) and α - TNF reduced from 20.2 to 15.6 ng/ml (P<0.05) showing a lowering tendency. In CHF III FC IL-1 changed from 21.1 to 18.3 ng/ml (P>0.05) IL-6 altered from 29.7 to 22.8 ng/ml (P>0.05) and α - TNF changed from 24.7 to 19.3 ng/ml (P>0.05) (Table 4).

Conclusion

Summing up from the obtained data, it was found that the quantitative indicators of pro-inflammatory cytokines in the blood serum were high in both groups of CHF with and without anemia. In this case, it is clear that these indicators were high in severe functional classes of CHF, in CHF patients with anemia, especially when they suffer from anemia of chronic diseases, and it can be caused by the activation of local hormones due to chronic ongoing systemic hypoxia in the body.

REFERENCES

1. 1. Gadayev A.G., Turakulov R.I., Kurbanov A.K., Rakhimova M.E. Role of Hepcidin and ProInflammatory Cytokines in Chronic Heart Failure in Combination with Anemia. Central Asian Journal of Medicine 2019.
2. Sorokova N.F., Zilabova T. S. Rol activatsii sitokinov v razvitii i progressirovani hronicheskoy serdechnoy nedastatochnosti // Meditsinskie novosti. -2015, - №1. –C. 12-15.
3. Shilov A . M., Melnik M. B., Saricheva A.A. Anemia pri serdechnoy nedastatochnosti // Russkiy medidsinskiy jurnal. – 2015. – Tom 11. №9. – C. 545-548.
4. 10. Vatutin N. T., Sklyannaya E. V. Kirienko T, S, Anemii u bolnih s xronicheskoy serdechnoy nedastatochnostyu / Ukrainskiy Kardiologicheskiy Jurnal. - 2016,-№3, C - 1-11
5. 14. Isakova D.Z. [i dr.]. Xronicheskoe sistemnoe vospalenie v patogeneze serdechnoy nedostatochnosti. I] Uzbekiston terapiya axborotnomasi, 2017.-№3.C-.22
6. Solomaxina N. I., Naxodnova E. S, Ershov V. I. Anemiya pri xronicheskoy serdechnoy nedostatochnosti: rol gepsidina kak universalnogo regulyatora metabolizma jeleza] Jurnal Serdechnaya nedostatochnost. - 2015.- Tom 15, №4. C. 254-260.