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ABSTRACT

of the dissertation for the degree of Doctor of Science in Medicine

CHRONIC HEART FAILURE AND ANEMIA
(Diagnosis and treatment issues)

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Field of science: Medicine

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GENERAL DESCRIPSION OF THE WORK

Relevance of the study. In recent decades, there has been a continuous increase in the number of individuals with chronic heart failure (CHF). This is due to the growing proportion of elderly people in the population, as well as improved survival rates among patients with cardiovascular diseases as a result of advances in medical care.[1]

Despite the implementation of modern strategies for the prevention of cardiovascular pathology, improvements in the pharmacological treatment of ischemic heart disease (IHD), and correction of risk factors (RFs), chronic heart failure (CHF) remains one of the most pressing public health problems, associated with high morbidity and mortality[2].

According to epidemiological studies, the prevalence of CHF increased from 6.1% to 8.2% over a 20-year observation period[3].

Despite significant improvements in the treatment of almost all heart diseases, CHF remains an exception, as its prevalence continues to rise while survival rates have improved only slightly.

Thus, the prognosis of CHF remains poor[4], especially when complicated by anemia and iron deficiency (ID).

The association of CHF with anemia and ID, even in the absence of anemia, is frequently encountered in modern clinical practice and has a negative prognostic impact, reducing patients' physical capacity and increasing hospitalization costs[5].

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[1] Ткаченко Е.И., Боровкова Н.Ю., Буянова М.В. Анемия при хронической сердечной недостаточности: взгляд на патогенез и пути коррекции // Доктор.Ру, – 2019. № 2 (157), – с. 31-36

[2] Дадашова Г.М. Гендерные и возрастные особенности хронической сердечной недостаточности ассоцированной с дисфункцией почек // Кардиология в Беларуси, – 2015. 5(42), – с. 13-20

[3] Галявич А.С., Терещенко С.Н., Ускач Т.М. и др Хроническая сердечная недостаточность. Клинические рекомендации 2024 // Российский кардиологический журнал, – 2024. 29(11), с. 61-62

[4] Anand I.S., Gupta P. Anemia and Iron Deficiency in Heart Failure: Current Concepts and Emerging Therapies // Circulation, – 2018. 138(1), – p. :80-98

[5] Singer C.E., Vasile C.M., Popescu M. et al. Role of Iron Deficiency in Heart Failure-Clinical and Treatment Approach: An Overview // Diagnostics (Basel), – 2023. 13 (2), – p. 304.

Iron deficiency is a condition often associated with chronic diseases but frequently overlooked. It is estimated that iron deficiency occurs in 37–61% of patients with CHF, 24–85% of patients with chronic kidney disease (CKD), and 13–90% of patients with inflammatory bowel disease[6].

Studies have shown a relationship between iron deficiency and reduced exercise tolerance, decreased quality of life, and increased cardiovascular morbidity and mortality in heart failure patients—regardless of the presence of anemia.[7]

Although the pathophysiological mechanisms causing anemia are multifactorial, ID is the most common underlying cause of anemia in HF. Numerous randomized controlled trials have shown that correcting iron deficiency improves symptoms, quality of life, exercise tolerance, and may reduce the number of hospitalizations in patients with heart failure.[8]

In major multicenter trials such as ELITE II, Val-HeFT (16.9%), SOLVD (9.6%), COMET (14.2%), and CHARM, low hemoglobin levels were among the exclusion criteria for enrolling patients.

The reason lies in the development of resistance to basic therapy, caused by anemia. Moreover, in all or most cases, the anemia remained uncorrected. Anemia and ID[9], particularly a transferrin saturation below 20%, are associated with poor prognosis in CHF[10].

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[6] Cappellini M.D., Comin-Colet J., de Francisco A. et al. IRON CORE Group. Iron deficiency across chronic inflammatory conditions: International expert opinion on definition, diagnosis, and management // Am J Hematol., – 2017. 92(10), – p. 1068-1078

[7] Wahid M., Islam S., Sepehrvand N. e al. Iron Deficiency, Anemia, and Iron Supplementation in Patients with Heart Failure: A Population-Level Study // Circ Heart Fail, – 2024. 17 (4), – 011351

[8] Alnuwaysir R.I.S., Grote Beverborg N., Hoes M.F. et al. Additional burden of iron deficiency in heart failure patients beyond the cardio-renal anaemia syndrome: findings from the BIOSTAT-CHF study // Eur J Heart Fail., – 2022. 24 (1), – p. 192-204.

[9] Anand I.S. Heart failure and anaemia: machanisms andm pathophysiology // Heart Fail Rev, – 2008. 13, – p. 377-378.

[10] Martens P., Mullens W. Treating iron deficiency in heart failure // N Engl J Med., – 2023. 389, – p. 1041-2.

Various authors have identified a correlation between the severity of anemia and the degree of impaired cardiac contractility, which is linked to an increased risk of patient mortality. According to the literature, among patients hospitalized for heart failure with coexisting iron deficiency anemia, mortality reached up to 32%. Iron deficiency is detected in 30–40% of patients, and their survival rate is lower compared to individuals with normal iron levels[11].

Erythropoietin (EPO) is a hormone synthesized in the cortical and medullary regions of the kidneys, which induces erythropoiesis under hypoxic conditions. Hypoxia-inducible factor 1-alpha plays a regulatory role in the cellular response to hypoxia[12].

Methods for treating anemia in CHF that have been evaluated as effective include blood transfusions, iron therapy, and erythropoiesis-stimulating agents (ESAs). ESAs in patients with heart failure[13] have demonstrated efficacy in various types of anemia, including anemia caused by chronic kidney disease, chemotherapy, and zidovudine use in HIV infection; however, they—particularly α-epoetin, β-epoetin, and darbepoetin-α—are currently not approved for the treatment of anemia caused by CHF[14].

This is because the studies used short-acting ESAs such as α-epoetin, β-epoetin, and darbepoetin-α, but did not use MPG-epoetin beta, which induces physiological erythropoiesis — that is, it stimulates EPO receptors smoothly and continuously, avoiding fluctuations in hemoglobin levels.

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[11] Рагимова Э.С., Бахшалиев А.Б., Бабаева Н.З.и др. Железодефицитная анемия у больных с хронической сердечной недостаточностью и пути ее коррекции // Медицинские новости, – 2017. №8, – с.65-68

[12] Güven Bağla A., Içkin Gülen M., Ercan F. et al. Changes in kidney tissue and effects of erythropoietin after acute heart failure // Biotech Histochem., – 2018. 93 (5), – p. 340-353

[13] Alnuwaysir R.I.S., Grote Beverborg N., Hoes M.F. et al. Additional burden of iron deficiency in heart failure patients beyond the cardio-renal anaemia syndrome: findings from the BIOSTAT-CHF study // Eur J Heart Fail., – 2022. 24 (1), – p. 192-204.

[14] Lindquist D.E., Cruz J.L., Brown J.N. Use of erythropoiesis-stimulating agents in the treatment of anemia in patients with systolic heart failure // J Cardiovasc Pharmacol Ther., – 2015. 20 (1), – p. 59-65.

To diagnose ID in HF and other conditions, it is necessary to measure iron parameters: serum iron, serum transferrin, transferrin saturation, and serum ferritin in any patient suspected of having iron deficiency. The two most used tests to detect iron deficiency are transferrin saturation and serum ferritin[15].

Absolute ID may be caused or aggravated using anti-coagulants or antiplatelet agents, which are commonly prescribed to patients with heart failure.

In contrast, the pathophysiology of functional iron deficiency lies in iron restriction associated with inflammation, which leads to reduced iron availability for erythropoiesis and other metabolic processes.

Current definitions of iron deficiency do not consider the multiple factors affecting patients with heart failure and, therefore, do not allow the identification of those with a truly unmet need for iron.

This issue is highly relevant, as there are no published data on the use of -EPO beta in patients with CHF and anemia for the correction of anemia caused by erythropoietin deficiency. MPG-EPO beta, a continuous EPO receptor stimulator that maintains stable hemoglobin levels without fluctuations, has not yet been studied in CHF patients with anemia.

In addition, none of the aforementioned studies reported plasma erythropoietin levels, nor were there data on the development of therapeutic strategies based on EPO levels. Furthermore, there is a lack of data regarding differences in the effectiveness of therapy among CHF patients with anemia depending on the severity of the disease. Ongoing studies contribute to the targeted selection of patients who are likely to benefit from iron and erythropoietin therapy, helping to determine the optimal route of iron administration, as well as the timing and duration of treatment.

Thus, there has been no differentiated approach to the treatment of patients with CHF and anemia. Recent studies

[15] Silverberg D.S., Wexler D., Schwartz D. Is Correction of Iron Deficiency a New Addition to the Treatment of the Heart Failure? // Int J Mol Sci., –2015. 16 (6), – p. 14056-74

contribute to the more precise selection of patients who are likely to benefit from intravenous iron therapy (IVIT) and MPG-EPO beta, aiming to determine the optimal method of iron administration, as well as the initiation and duration of therapy.

Thus, there has been no differentiated approach to treating patients with CHF and anemia, where the therapeutic strategy should be specifically targeted at anemia caused by iron deficiency, erythropoietin deficiency, or a combination of both.

Object and subject of the study:

The object of the study consists of 207 patients with CHF who were examined in the cardiology department of City Clinical Hospital No. 3 of the Ministry of Health of the Azerbaijan Republic, which serves as the clinical base for the Department of Cardiology at the Azerbaijan State Institute for Advanced Medical Studies named after A. Aliyev. The study was conducted during the period from 2008 to 2013.

Patients had CHF classified as NYHA functional classes I-IV according to the recommendations of the European Society of Cardiology 2012; among them, anemia was diagnosed in 173 patients. All 173 patients were divided into 4 groups depending on their levels of ferritin, transferrin saturation, erythropoietin, and the therapeutic strategy being applied.

The subject of observation were the levels of Hb, Htc, ferritin, transferrin saturation, erythropoietin, NTproBNP, IL-1, IL-6, TNF-α, GFR, parameters of systolic and diastolic function of the LV myocardium, 6MWT, clinical assessment scales.

Aim of research based on improved and more informative diagnostic approaches, to develop and justify new, differentiated therapy schemes for patients with chronic heart failure complicated by anemia, which include not only iron preparations but also erythropoietin-related drugs in combination with basic therapy.

Research objectives

1. To analyze the impact of anemic syndrome on the clinical presentation and progression of CHF.
2. To investigate kidney function in the context of erythropoietin synthesis in patients with CHF complicated by anemia and signs of iron deficiency.

3. To determine the plasma level of N-terminal pro-brain natriuretic peptide (NT-proBNP) in patients with CHF and anemia, with iron deficiency, considering transferrin saturation with iron.
4. To assess the level of proinflammatory cytokines in peripheral blood in patients with CHF and anemia in the presence of iron deficiency, with determination of transferrin saturation.
5. To study the features of systolic and diastolic dysfunction of the left ventricle (LV) in patients with CHF and anemia, with iron deficiency.
6. To analyze the relationships between laboratory parameters — hemoglobin, ferritin, transferrin saturation, erythropoietin levels — and NT-proBNP, cytokine profiles, and doppler echocardiography parameters in patients with CHF complicated by anemic syndrome.
7. To determine the therapeutic effectiveness of standard medical treatment in patients with CHF and anemia, with iron deficiency, based on laboratory, diagnostic, and echocardiographic data.
8. To investigate the effectiveness of including methoxy polyethylene glycol-epoetin beta (MPG-EPO beta) in the standard treatment of patients with chronic heart failure (CHF) accompanied by anemia and hypoerythropoietinemia, in patients with CHF functional classes I–II and III–IV.
9. To analyze the clinical effectiveness of a of a combined approach in the treatment of CHF patients with anemia due to iron deficiency, who receive standard therapy along with intravenous administration of iron (III) in the form of a polysaccharide complex, considering TS in patients with CHF functional classes I–II and III–IV.
10. To provide a comprehensive assessment of the effectiveness of triple therapy, including standard heart failure medications, MPG-epoetin beta and intravenous administration of iron (iron(III) polysaccharide complex), in patients with CHF and anemia, iron deficiency, and hypoerythropoietinemia, taking into account laboratory and echocardiographic parameters in patients with CHF functional classes I–II and III–IV.

11. To develop and justify an individualized pharmacotherapeutic management plan for CHF patients with anemia and iron deficiency, considering transferrin saturation levels and hypoerythropoietinemia

MATERIALS AND METHODS OF THE STUDY

Study design and methodology

At City Clinical Hospital No. 3 of the Ministry of Health of the Azerbaijan Republic, which serves as the clinical base for the Department of Cardiology at the Azerbaijan State Institute for Advanced Medical Studies named after A. Aliyev, a total of 207 patients with chronic heart failure (CHF) of NYHA functional classes I–IV were examined during the period from 2008 to 2013, in accordance with the recommendations of the European Society of Cardiology 2012. Among them, anemia was diagnosed in 173 patients.

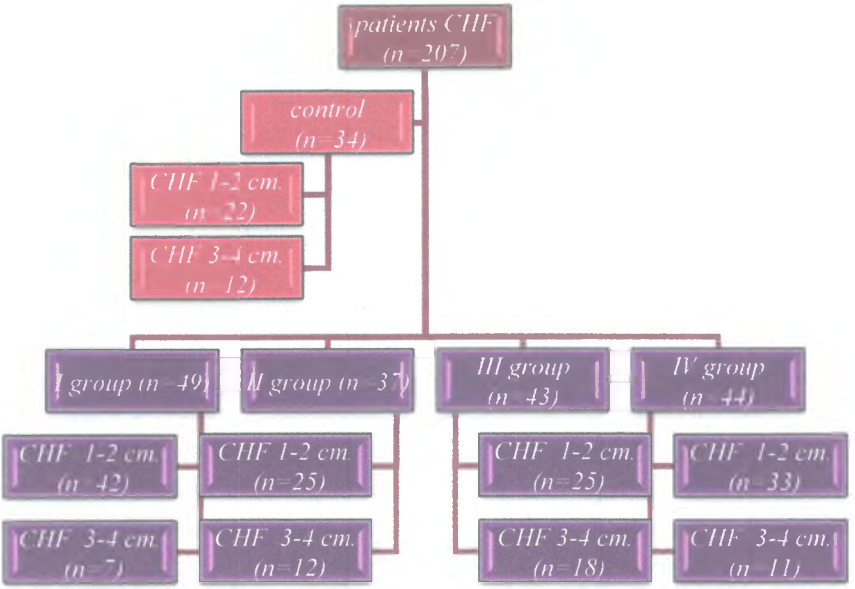
As a control group, 34 patients of both sexes, middle-aged and elderly (aged 36 to 75 years), with ischemic CHF without anemia were examined (21 women, 13 men). Like the main groups, the control group was subdivided into two subgroups: the first subgroup included 22 patients with ischemic CHF of NYHA class I–II without anemia, with a mean age of 57.8 ± 2.1 years; the second subgroup included 12 patients with ischemic CHF of NYHA class III–IV without anemia, with a mean age of 59.7 ± 2.5 years (see Table 1). The average disease duration in patients with CHF class I–II was 4.2 ± 2.1 years, while for those with CHF class III–IV it was 18.7 ± 3.2 years.

Among the 173 CHF patients with anemia, 78 (44.8%) were men and 95 (55.2%) were women, aged from 41 to 75 years. The mean age was 60.6 ± 1.4 years. The average disease duration was 16.5 ± 1.2 years. Patients with CHF NYHA classes I–II were grouped into subgroup I (125 patients), and those with CHF classes III–IV formed subgroup II (49 patients). Patients with CHF NYHA classes I–II had a left ventricular ejection fraction (LVEF) of 44.6 ± 2.3%, and according to the 2021 CHF classification, were classified

as having heart failure with mildly reduced ejection fraction (HFmrEF). Patients in NYHA classes III–IV had an LVEF of 35.5 ± 2.5% and were classified as having heart failure with reduced ejection fraction (HFrEF).

The study design was determined by the stated aim and objectives. Anemia was diagnosed in all patients by hemoglobin (Hb) levels of less than 120 g/L for men and less than 110 g/L for women, according to WHO criteria.

Of the total 173 CHF patients with anemia examined, they were divided into 4 randomized groups according to treatment strategy (Chart 1):



Graph 1. Study design.

Group I - 49 patients with CHF and anemia who received only basic therapy, including ACE inhibitors, angiotensin II receptor blockers, β-blockers, mineralocorticoid antagonists, diuretics, digoxin, and nitrates. Of these, 26 were men and 23 women, with an average age of 61.1 ± 1.4 years. As noted above, Group I was further

subdivided according to NYHA functional class (FC) into two subgroups: CHF NYHA I–II FC (42 patients) and CHF NYHA III–IV FC (7 patients). Among these 49 patients, CHF developed in 34 cases due to stable angina (SA) NYHA III–IV FC, and in 15 cases due to post-infarction cardiosclerosis (PIC). Eight patients had concomitant type 2 diabetes mellitus (T2DM), and one patient had arterial hypertension (AH). The average disease duration was 5.2 ± 2.5 years in the CHF NYHA I–II FC subgroup and 15.5 ± 3.2 years in the CHF NYHA III–IV FC subgroup.

Group II - 37 patients with CHF and anemia who received combined therapy with MPG-EPO beta at a dose of 0.60 μg/kg (50 IU) once per month along with basic therapy. If hemoglobin (Hb) increased by less than 10 g/L in one month, the dose was increased by approximately 25% monthly until the individual target Hb level was reached. If Hb rose by more than 20 g/L per month or approached 120 g/L, the dose was reduced by about 25%. If Hb continued to increase, treatment was paused until Hb began to decline. However, no Hb decreases were observed; Hb levels remained stable without fluctuations. MPG-EPO beta was administered to patients without iron deficiency (ID). ID was defined as ferritin less than 100 μg/L, or less than 299 μg/L if transferrin saturation was below 20%. The average age was 59 ± 1.5 years; 18 men and 20 women. Group II was also subdivided by NYHA FC: 25 patients in NYHA I–II and 12 in NYHA III–IV. Among the 37 patients, CHF was caused by stable SA NYHA III–IV FC in 19 cases and PIC in 19 cases. Fourteen patients had concomitant T2DM and 26 had AH. Disease duration averaged 4.1 ± 1.7 years for NYHA I–II and 16.2 ± 1.5 years for NYHA III–IV patients.

Group III - 43 patients with CHF and anemia who received combined intravenous iron therapy with basic drugs. Ferric (III) hydroxide sucrose complex (Venofer) was administered intravenously at 200 mg twice weekly for 5 weeks. Intravenous iron was prescribed to CHF patients with anemia and iron deficiency. The average age was 62.5 ± 1.4 years, including 16 men and 27 women. Group III was subdivided by NYHA FC: 25 patients with NYHA I–II and 18 with NYHA III–IV. Among the 43 patients, CHF

developed due to stable SA NYHA III–IV FC in 15 cases and PIC in 28 cases. Thirteen patients had T2DM and 31 had AH. Disease duration was 6.3 ± 2.3 years for NYHA I–II and 14.8 ± 1.75 years for NYHA III–IV.

Group IV - 44 patients with CHF and anemia who received combined therapy of MPG-EPO beta and intravenous iron along with basic therapy. MPG-EPO beta was administered at 50 IU once monthly, and intravenous ferric (III) hydroxide sucrose complex at 200 mg twice weekly for 5 weeks. Intravenous iron was given to patients with CHF, anemia, and iron deficiency combined with reduced erythropoietin (EPO) levels. The average age was 59.9 ± 1.2 years; 19 men and 25 women. Group IV was subdivided by NYHA FC: 33 patients in NYHA I–II and 11 in NYHA III–IV. Among 44 patients, CHF was caused by stable SA NYHA III–IV FC in 17 cases and PIC in 27 cases. Nineteen patients had T2DM and 30 had AH. Group IV included CHF patients with anemia due to iron deficiency and decreased EPO levels. Disease duration was 4.5 ± 1.6 years for NYHA I–II and 16.2 ± 2.1 years for NYHA III–IV.

The choice of treatment strategy for all CHF patients with anemia was based on EPO, ferritin, and transferrin saturation levels. According to the study protocol, exclusion criteria included severe or malignant arterial hypertension, acute cerebrovascular accident within the last 12 months, acute myocardial infarction, acute coronary syndrome, chronic obstructive pulmonary disease, and psychiatric disorders.

Within each group, patients were distributed by sex, age, disease duration, and treatment strategy. The mean ages in the groups were: Group I — 61.1 ± 1.4 years, Group II — 59 ± 1.5 years, Group III — 62.5 ± 1.4 years, and Group IV — 59.9 ± 1.2 years. Thus, no significant differences in age were observed between groups, facilitating subsequent comparative analysis without the confounding effect of age on laboratory and echocardiographic parameters.

At the initial stage of inpatient examination, patients' medical histories and complaints were carefully studied; pulse and heart rate were measured.

All patients had levels of Hb, serum iron, ferritin, transferrin, erythropoietin, NT-proBNP, IL-1, IL-6, and TNF-α measured, as well as parameters of left ventricular systolic and diastolic function before and after treatment. All patients performed the 6-minute walk test, and clinical condition was assessed using the SHOKS scale. Repeat laboratory tests were conducted 6 weeks after treatment, and Doppler echocardiography was repeated after 20 weeks.

The left ventricular ejection fraction (LVEF) thresholds for CHF patients were: NYHA I FC: ≤50% , NYHA II FC: ≤45%, NYHA III FC: ≤35%,NYHA IV FC: ≤25%.

Before starting the treatment program, all patients received the following medication: ACE inhibitors, angiotensin II receptor blockers, β-blockers, mineralocorticoids reseptors antagonistes, prolonged nitrates, diuretics, and digoxin, individually dosed and according to national guidelines for CHF treatment.

Patients with arrhythmias were prescribed antiarrhythmic drugs. Those with ventricular extrasystoles additionally received amiodarone; patients with sinus tachycardia received ivabradine; and patients with atrial fibrillation were treated with amiodarone and digoxin. CHF patients with NYHA III–IV FC and LVEF below 40% received digoxin as per clinical protocols. Among ACE inhibitors, perindopril and ramipril were prescribed for CHF patients with anemia. Bisoprolol was the β-blocker used. Diuretics were prescribed depending on FC: for CHF NYHA I–II FC, hydrochlorothiazide 25–100 mg was given; patients with concomitant diabetes received indapamide 1.25–2.5 mg. For CHF NYHA III–IV FC, hydrochlorothiazide 25–100 mg combined with loop diuretics -furosemide 40–160 mg or torasemide 5–10 mg — were used, along with spironolactone 25–50 mg or eplerenone 15–20 mg.

Given the ischemic etiology of CHF, patients were prescribed isosorbide dinitrate or isosorbide mononitrate. Some CHF patients with anemia and concomitant hypertension took calcium channel blockers. Patients with type 2 diabetes mellitus received gliclazide (Diabeton MR), metformin, or prolonged insulin preparations in insulin-dependent stages.

Dynamic monitoring of patients was carried out over a period of 4–8 weeks up to 6 months. Doppler echocardiographic examinations were performed at the time of inclusion and after 4 weeks, then again after 6–8 weeks. To address the research objectives, the following clinical, laboratory, and functional studies were used:

a) Determination of hemoglobin level by the cyanmethemoglobin (hemiglobincyanide) method and hematocrit by separation of plasma and erythrocytes using centrifugation.

b) Determination of serum iron and ferritin levels by colorimetric photometric test on automatic analyzers of the AU 480 series (Beckman Coulter, USA) and transferrin saturation.

c) Determination of erythropoietin level was performed by enzyme-linked immunosorbent assay (ELISA). A test kit for quantitative determination of EPO in serum was used, including reagents for erythropoietin ELISA-BEST; one variant is the immunochemiluminescent method on an automatic immunochemiluminescent analyzer LIAISON® (Diasorin, Germany, Italy).

d) Determination of NTproBNP level in blood was carried out by antibody immobilization using the "Biomedica" reagent (Austria) on automatic analyzers by enzyme immunoassay method.

e) Determination of pathological cytokine levels IL-1, IL-6, and TNF-α in the plasma of patients with chronic heart failure and anemia was performed by ELISA using the "Vector-best" biotest kits (Russia).

f) Determination of creatinine level and investigation of glomerular filtration rate (GFR) were performed by the Popper method based on the Jaffe reaction, and GFR was calculated using the Cockcroft–Gault formula.

g) Doppler echocardiographic study of the heart with assessment of systolic and diastolic functions of the left ventricular myocardium was performed on the "Vivid-3" device by General Electric Healthcare (USA). Analysis of three-dimensional image recordings on videotape was performed on a GE analyzer (USA).

h) The 6-minute walk test was conducted, modified according to the method of Yu.N. Belenkov, and clinical status was assessed using the SHOKS scale according to V.Yu. Mareev.

Statistical Processing of the Study Material

Modern methods of mathematical and statistical analysis ensuring comprehensive processing of the obtained data were applied in the study. The research combines descriptive and analytical approaches: it was conducted at a clinical base using prospective data, covering selected patient groups and evaluating indicators within a specific period, which classifies it as a clinical type of scientific research. For analysis of quantitative and qualitative indicators, contemporary biostatistical methods were used. To compare and assess the likelihood of differences between values of groups with a small number of variants, we applied the nonparametric Wilcoxon U-rank test, while for intragroup indicators, the Mann-Whitney test was used. For comparative analysis of medians, mean values, and standard deviations, nonparametric criteria were applied—the Kruskal-Wallis χ^2 test.

Statistical data processing was performed using modern software tools, including MS Excel 2019 and IBM SPSS Statistics 26, which ensured high accuracy of calculations, modeling of dependencies, and reliability of the obtained results. Descriptive statistics are presented as mean values (M), medians, and 1st and 3rd quartiles.

Key conclusions defended:

1. Progressive chronic heart failure (CHF) is characterized by a decrease in hemoglobin (Hb) concentration and hematocrit (Ht). In patients with ischemic CHF, anemia may develop both in the context of iron deficiency (ID) and with various erythropoietin dysfunctions.

2. Patients with CHF and anemia demonstrate different erythropoietin responses: decreased, normal, or increased plasma concentrations (hypo-, normo-, and hyper-erythropoietinemia). Both low and excessive EPO levels are markers of more severe clinical CHF course, aggravating its manifestations and contributing to

refractory heart failure with severe cardiovascular complications and worsening kidney function, reflected by increased plasma creatinine and decreased glomerular filtration rate (GFR), corresponding to CHF functional class.

3. Patients with CHF and anemia, as well as iron deficiency, show significantly higher NTproBNP levels and increased cytokine inflammatory response compared to patients without anemia.

4. The presence of anemia, iron deficiency, and EPO dysfunction in patients with different CHF severity (both NYHA I–II and III–IV classes) leads to worsening of systolic and diastolic left ventricular function. Simultaneously, there is a decline in 6-minute walk test performance, reflecting reduced physical endurance.

5. Therapy with only standard drugs (basic therapy) in patients with CHF and anemia does not significantly affect erythropoietin levels in blood or transferrin saturation. The presence of anemia reduces the effectiveness of traditional drug treatment.

6. Combined therapy including both basic drugs and methoxy polyethylene glycol-epoetin beta (MPEG-EPO beta) in patients with CHF and anemia with hypoerythropoietinemia contributes to an increase in hemoglobin, hematocrit, and erythropoietin levels. There is also a decrease in NTproBNP, IL-1, IL-6, TNF-α, creatinine levels, regression of left ventricular hypertrophy, and increase in left ventricular ejection fraction (LVEF).

7. Intravenous administration of iron in the form of ferric (III) hydroxide saccharate complex as part of combined therapy with basic treatment in patients with CHF and anemia leads to a significant increase in hemoglobin, plasma ferritin, and transferrin saturation.

8. Triple combined therapy—basic drugs with MPEG-EPO beta and intravenous ferric (III) hydroxide saccharate complex—in patients with CHF, anemia, iron deficiency, and hypoerythropoietinemia exerts a comprehensive positive effect by increasing hemoglobin, hematocrit, ferritin, and erythropoietin levels; reducing NTproBNP, IL-1, IL-6, and TNF-α; increasing LVEF; and improving exercise tolerance.

Scientific novelty of the study:

- A comprehensive characterization of anemia in patients with ischemic CHF was provided, focusing on ferritin, transferrin saturation (TSAT), and erythropoietin plasma levels. Anemia in ischemic CHF can be accompanied by iron deficiency or not, and with various erythropoietin dysfunctions.
- Correlations between hemoglobin, ferritin, TSAT, erythropoietin, NT pro BNP (N-terminal pro-brain natriuretic peptide), and cytokine levels during therapy stages were analyzed, revealing associations with systolic and diastolic left ventricular myocardial function parameters.
- The severity of CHF with anemia was assessed considering iron deficiency and erythropoietin concentration. Iron deficiency significantly increases NT pro BNP levels and intensifies inflammatory cytokine responses.
- The importance of erythropoietin-producing kidney function was determined; a relationship was found between plasma erythropoietin levels and leukotriene concentration during therapy. EPO level increase during treatment correlated with a decrease in cytokine-induced inflammation in anemic CHF patients.
- CHF patients with anemia were stratified based on erythropoietin plasma levels into normo-, hyper-, and hypo-erythropoietinemic groups.
- The necessity of an individualized therapeutic approach for CHF patients with anemia was emphasized, requiring mandatory erythropoietin level determination and assessment of iron deficiency before anemia correction.
- A comprehensive pharmacological scheme for anemia correction in CHF patients was proposed, including standard basic therapy (ACE inhibitors, β-blockers, angiotensin II receptor blockers, mineralocorticoid receptor antagonists, digoxin, diuretics) combined with the new erythropoietin drug methoxy polyethylene glycol-epoetin beta (MPEG-EPO beta) and intravenous ferric (III) polysaccharide complex.

- A comparative analysis of different therapeutic approaches for CHF patients with anemia was performed for the first time:
  a) Basic therapy without anemia correction
  b) Basic therapy combined with MPEG-EPO beta
  c) Basic therapy combined with intravenous ferric (III) polysaccharide complex
  d) Triple combination: basic therapy + MPEG-EPO beta + intravenous ferric (III) polysaccharide complex
- Practical recommendations for the combined treatment approach in CHF patients with anemia were formulated, depending on anemia severity, iron deficiency, transferrin saturation, and erythropoietin levels.

Scientific and practical significance of the study

1. An improved comprehensive diagnostic system was developed and implemented in clinical practice to identify systolic and diastolic left ventricular myocardial dysfunction, as well as laboratory abnormalities related to anemia, iron deficiency, and EPO deficiency in patients with chronic heart failure.

2. Optimal pharmacological correction methods for these disorders in anemic CHF patients were developed. These schemes involve the use of standard basic pharmacotherapy (ACE inhibitors, β-blockers, angiotensin II receptor blockers, mineralocorticoid receptor antagonists, diuretics, digoxin) combined with methoxy polyethylene glycol-epoetin beta (MPEG-EPO beta) and intravenous ferric (III) polysaccharide complex.

3. The results provide a basis for a personalized therapeutic approach for CHF patients with anemia, allowing the selection of the most effective treatment strategy based on clinical, functional, and laboratory data.

Approbation of the work and practical implementation

The results obtained during the conducted study were integrated into the educational activities of the Department of Cardiology at the Azerbaijan State Institute for Advanced Medical Studies named after A. Aliyev and are used within the framework of the educational and methodological training of specialists. The

practical recommendations developed based on the study, concerning comprehensive therapy for patients with chronic heart failure (CHF) and anemic syndrome, which include the use of methoxy polyethylene glycol-epoetin beta (MPEG-EPO beta), intravenous administration of ferric (III) polysaccharide complex, as well as their combined use, have been implemented in the clinical practice of the cardiology department of City Clinical Hospital №3 in Baku and the D. Abdullayev Scientific Research Institute of Cardiology.

The main provisions of the dissertation were presented at the ESC Heart Failure conference in Nice in 2009; in 2010 at a similar conference in Berlin; in 2011 at the Türk Kardioloji Derneği Congress in Istanbul; in 2012 at the ESC Heart Failure meeting in Belgrade and at the annual European Society of Cardiology Congress in Munich. In 2013, the dissertation findings were reported at the ESC Heart Failure conference in Lisbon, at the European Society of Cardiology Congress in Amsterdam, and at the Türk Kardioloji Derneği forum in Istanbul.

In 2014, discussions continued at the World Congress of Cardiology in Melbourne and at the European Society of Hypertension meeting in Athens. In 2015, the report was presented at the ESC Euroimaging Congress in Seville; in 2016 at the ESC Heart Failure conference in Florence; and in 2018 in Vienna at the same specialized forum.

Later, in 2023, the dissertation provisions were presented in Athens at the ACC "ACC Middle East & Eastern Mediterranean 2023" conference, held from November 3 to 5. Subsequently, on November 27–28, 2024, the report was presented in Nalchik at the XIV Scientific and Educational Conference of Cardiologists and Therapists of the Caucasus, and on May 23–24, 2025, in Ivano-Frankivsk at the International Scientific and Practical Conference "Current Issues of Medicine, Pharmacology, Therapy, and Rehabilitation."

The preliminary discussion of the dissertation was held at the meeting of the Academic Council of the Azerbaijan State Institute for Advanced Medical Studies named after A. Aliyev with the participation of staff from the D. Abdullayev Scientific Research Institute of Cardiology (Protocol No. 11, June 25, 2024).

At Azerbaijan Medical University, a scientific seminar under the Dissertation Council ED 2.27 was held (Protocol No. 4, February 11, 2025).

Institution where the dissertation was conducted

The dissertation was completed at the Department of Cardiology of the Azerbaijan State Institute for Advanced Medical Studies named after A. Aliyev, based on the cardiology department of City Clinical Hospital №3, the D. Abdullayev Scientific Research Institute of Cardiology, and the private clinic named after N. Tusi.

Publications related to the dissertation topic

A total of 67 publications on the dissertation topic have been published in journals recommended by the HAC of the Azerbaijan Republic for dissertation defense. The results of the dissertation work were published in 34 articles (including 9 international and 25 local publications) and 33 abstracts (23 of which were international).

Volume and Structure of the Dissertation.

The dissertation is presented in A4 format in Times New Roman font size 14 with 15 line spacing it consists of 391 pages 409616 characters the dissertation includes 71 tables and 62 figures the work consists of an introduction 21934 characters a literature review chapter I 97992 characters description of materials and methods of research chapter II 38677 characters results and their discussion chapter III 30775 characters chapter IV 29386 characters chapter V 35616 characters chapter VI 31024 characters chapter VII 38747 characters conclusion 77432 characters findings 5923 characters practical recommendations 2110 characters the list of references includes 404 sources of which 9 are in Azerbaijani 59 in Russian and 336 in English. Total number of characters — with the description of clinical cases from medical histories.

RESEARCH RESULTS AND DISCUSSION

This study was conducted over five years (2009-2013) at the A. Aliyev State Institute of Advanced Medical Studies at the City Clinical Hospital No. 3.

Table presents data for patients with CHF without anemia, i.e. the control group.

Analysis of the presented results showed that in patients with CHF with anemia, compared to patients with CHF without anemia, there is a decrease in Hb by 24.4% ($p<0.001$)) and Ht by 27.9% ($p<0.001$)) in CHF I-II FC, as well as Hb by 28.7% ($p<0.001$)) and Ht by 32.7% ($p<0.001$) in CHF III-IV FC.

Compared with the control group, some patients with CHF with anemia showed ID, i.e. a decrease in the iron level by 5.3% ($p = 0.708$) and ferritin by 69.0% ($p < 0.001$)) in CHF I-II FC, as well as in CHF III-IV FC - by 28.1% ($p = 0.128$) and ferritin by 61.3% ($p = 0.06$)). The level of plasma EPO in patients with CHF with anemia showed hypoerythropoietinemia in some cases - a decrease by 74.9% or 4 times ($p = 0.003$) and 78.2% or 4.6 times ($p = 0.005$), in other cases hypererythropoietinemia - an increase by 3 times ($p = 0.977$). In patients with CHF with anemia, the level of NT pro BNP in the blood increased by 79.7%. ($p<0.001$)) Analysis of the level of PC showed that in patients with CHF with anemia, the increase in IL-1 was greatest by 2.7 times in CHF I-IIFC ($p=0.021$), and in patients with CHF III-IV FC it increased by 2.8 times ($p=0.117$), and the level of IL-6 was higher by 76.6% ($p=0.117$). The level of plasma TNF-α increased by 19.9% ($p=0.196$) and 3.7 times ($p=0.042$), respectively.

Compared with the control group, patients with CHF with anemia had an increase in creatinine by 33.5% ($p = 0.014$) and 54.8% ($p = 0.008$), respectively. SCF was reduced by 32.8% ($p = 0.002$) and 36.0% ($p = 0.011$), respectively, indicating a progressive deterioration in renal function due to renal hypoperfusion.

Anemia in patients with CHF was often accompanied by hypotension, as a result of which the prescription of such essential basic line drugs as perindopril, ramipril, bisoprolol, metaprolol succinate,with their exceptional cardioprotective properties became simply impossible, or was prescribed in very small doses.

Table. Laboratory and functional parameters of patients with CHF without anemia

Indicators	CHF I-II FC (n=22)		p0	CHF III-IV FC (n=12)		p0
	Before treatment	After treatment		Before treatment	After treatment	
Hb, g/l	(126,4) 128,0 120,0 – 130,0	(126,4) 128,0 120,0 – 130,0	1,000	(125,3) 127,0 120,0 – 130,0	(125,3) 127,0 120,0- 130,0	1,000
Ht, %	(53,6) 54,0 50,0 – 60,0	(53,9) 54,0 50,-60,0	0,317	(55,0) 56,0 51,0 – 58,0	(55,5) 56,0 53,0-58,0	0,317
Iron, µmol/ml	(15,8) 14,8 13,3 – 18,4	(16,4) 14,9 13,5-18,5	0,042*	(17,2) 17,1 14,9 – 20,3	(17,5) 17,1 14,9-20,6	0,068
Ferritin, ng/ml	(138,2) 106,5 104,0 – 171,0	(139,1)106, 0 103,0-171,0	0,340	(163,3) 104,0 91,9 – 175,5	(164,7)103, 5 91,9-184,0	0,414
CT # < 20% / ≥ 20%	1 (4,5%) / 21 (95,5%)	1 (4,5%) / 21 (95,5%)	1,000	1 (8,3%) / 11 (97,1%)	1 (8,3%) / 11 (97,1%)	1,000
EPO, ME/ml	(12,0) 7,6 2,2 – 11,8	(12,0) 7,6 2,3 – 11,8	0,498	(17,4) 13,0 7,5 – 21,5	(16,8) 13,0 5,1-21,5	0,180
NTproBNP, pgmol/l	(1406,3) 1426,6 527,0 – 1885,7	(729,9)502, 4 395,1- 1034,5	0,001*	(2015,6) 2259,0 1567,0 – 2554,6	(899,4) 898,4 563,0- 1195,6	0,005*
IL-1, pg/ml	(3,7) 0,7 0,0 – 1,6	(2,3) 0,7 0,0-1,6	0,180	(3,5) 1,5 0,4 – 4,3	(3,3) 1,4 0,4-4,5	0,715
IL-6, pg/ml	(42,2) 9,3 0,9 – 38,2	(31,5) 8,0 0,9-26,1	0,092	(16,0) 15,3 4,8 – 24,8	(13,7) 12,4 4.8-18,3	0,128
TNF-α, pg/ml	(21,7) 3,1 1,2 – 11,9	(17,9) 3,1 0,5-11,9	0,223	(3,8) 2,7 0,7 – 4,1	(3,2) 2,5 0,3-4,1	0,180
crea, mkmol/l	(107,4) 104,5 88,4 - 115	(102,0) 99,8 88,4-110,0	0,014*	(90,2) 86,2 80,2 – 104,0	(88,4)86,2 80,2-98,5	0,197
GFR, ml/min	(81,6) 80,1 59,5 – 97,9	(83,5)79,2 59,5-97,9	0,131	(87,9) 86,6 64,0 – 105,6	(88,4)84,2 67,1-105,6	0,345
EDV, ml	(229,0) 259,5 202,0 – 261,0	(228,3) 255,5	0,076	(233,1) 253,5	(230,0)252, 5	0,154

		242,0-257,0		208,0 – 257,5	199,0-259,0	
ESV, ml	(163,1) 188,0 178,0 – 190,0	(144,8)136,5 155,0-168,0	<0,001*	(159,3) 180,0 139,6 - 183,0	(147,0)160,0 134,0-165,5	0,005*
LVEF, %	(44,6) 41,0 38,0 – 47,0	(46,3) 42,5 41,0-47,0	0,003*	(35,5) 33,0 31,0 – 37,2	(38,0) 36,1 34,7-40,0	0,005*
MMLV, r	(260,1) 258,0 212,0 – 302,6	(226,3)226,0 180,0-265,3	<0,001*	(291,6) 264,7 209,6 – 350,0	(250,8)218,9 180,4-313,0	0,003*
LV sm	(4,2) 4,2 3,8 – 4,3	(4,0)3,9 3,8-4,1	0,001*	(4,2) 4,2 3,9 – 4,5	(4,1) 4,1 4,0-4,2	0,105
RV, sm	(3,0) 3,0 3,0 – 3,2	(2,9) 2,8 2,7-3,1	0,004*	(3,0) 3,0 2,7 – 3,1	(3,0) 2,8 2,6-3,0	0,200
Ve/Va	(0,97) 0,80 0,70 – 1,00	(1,07)0,84 0,70-1,30	0,396	(0,96) 0,80 0,60 – 1,14	(1,23) 1,00 0,70-2,00	0,033*
IVRT, ms	(116,9) 113,5 113,0 – 116,0	(113,0)111,0 104,0-112,0	0,001*	(114,6) 114,5 111,5 – 121,0	(114,3)114,0 107,0-120,0	0,357
6-minute walk test, m	(318,5) 294,0 254,0 – 392,0	(369,5)361,0 314,0-430,0	<0,001*	(313,0) 316,0 219,0 – 404,0	(364,3)379,0 275,0-443,0	0,003*
SHOKS	(7,0) 7,0 6,0 – 8,0	(3,0)3,0 3,0-4,0	<0,001*	(9,8) 10,0 8,5 – 11,0	(4,4)4,0 3,5-5,0	0,002*

Note: The cells of the tables indicate (M) Me; Q1 – Q3 statistically significant difference:

p0 – between indicators before and after treatment (according to the Wilcoxon W-criterion)

* - the "0" hypothesis is rejected

- in the CT line, the number of patients is indicated

ARNI and sodium-glucose cotransporter inhibitors type 2 (IGC-2) were not used. It is for this reason that doctors often content themselves with prescribing digoxin to patients with CHF III-IVFC.

For this reason, the treatment of this category of patients should focus on the correction of the anemic syndrome. Thus, in particular, in patients of group IV, compared with the control group, before the therapy there was a decrease in iron levels by 23.7% ($p<0.05$) and ferritin by 65.7% ($p<0.001$) and 61.3% ($p<0.05$). Hypererythropoietinemia was observed in 33 (18.96%) patients with CHF with anemia. The level of plasma EPO in them was 85.8±11.2 IU/ml ($p<0.001$) in women, and 118.4±23.7 IU/ml ($p<0.05$) in men. This category of patients is represented as patients with CHF III-IV FC and anemia with hypererythropoietinemia, and these were patients with PC, who had concomitant type 2 diabetes. Hypererythropoietinemia in patients with CHF with anemic syndrome was associated with sharp cytokine aggression, in particular, an increase in TNF-α and IL-6. The key indicator in patients with hypererythropoietinemia was a significant increase in the level of NT pro BNP in the blood plasma. It is obvious that renal hypoperfusion in patients with CHF can lead to a decrease in the EPO level and thus contribute to the development of anemia. However, the EPO level, as our results show, is not always reduced in patients with CHF, and the EPO level correlates with the NT pro BNP level. At the same time, an increased EPO level is associated with an unfavorable prognosis. Thus, the presence of hypererythropoietinemia indicates a severe course of the disease and contributes to the development of severe clinical symptoms of the disease and refractory heart failure.

Analysis of the obtained data of the study of NTproBNP in patients with CHF with anemia in patients of groups II, III, IV before treatment compared with the control group showed an increase in the level of NTproBNP by 44.4% ($p = 0.013$), by 61.4% ($p = 0.002$), by 79.7% ($p < 0.001$), respectively. Thus, on the one hand, an increase in the class of CHF with anemia was accompanied by an increase in the level of plasma NTproBNP, as a predictor of the severity of CHF, on the other hand, the results of our studies emphasize the factor of anemia contributing to a higher increase in NTproBNP than in patients with CHF without anemia. Thus, in patients of groups II, III, IV, before treatment, compared with the control group, an increase in

the level of NT pro BNP was noted by 44.4% ($p<0.05$), by 61.4% ($p<0.001$), by 79.7% ($p<0.001$). Moreover, in patients with CHF FC I-II with anemia, the increase in the NTproBNP level occurred to a greater extent than in patients with CHF FC III-IV. Thus, the presence of anemic syndrome in patients with CHF is accompanied by a sharp increase in the plasma level of NTproBNP, which causes a reliable increase in PC in patients with CHF in all the examined groups. An increase in the FC of CHF is also accompanied by even greater cytokine aggression. Comparison of the obtained results of patients with CHF with anemia showed that their anemia negatively affects the PC levels in the blood. A decrease in the level of IL-6 in the blood of patients in group I by 76.5% ($p = 0.002$) and 70.5% ($p = 0.002$), respectively, was reliable, and in the remaining groups, a decrease in this indicator in patients with CHF with anemia compared to the indicators of the control group was unreliable, as in the works of other clinicians. However, in patients with CHF III-IV FC with anemia of groups II and III, an insignificant increase in the level of IL-6 in the blood plasma was observed, and in patients with group IV, the level of IL-6 in the blood remained within the normal range, but its changes in the level in group IV were insignificant. Thus, in patients with CHF without anemia, there is a significant sharp increase in the level of IL-6 in the blood compared to patients with CHF with anemia. And in patients with CHF with anemia, compared with the control group, there is a significant increase in the blood of TNF-α. ($p = 0.042$) by 3.7 times, IL-1 by 2.6 times, and IL-6 in patients with ID by 76.6% ($p = 0.849$). Interpretation of the results of the TNF-α level in the blood plasma of patients with CHF and anemia gives grounds to establish a reliable increase in its level only in patients of group IV by 19.9% ($p<0.05$). Thus, the presence of anemia and ID in patients with CHF causes activation of the PC, while the greatest activation of the TNF-α level in the blood plasma is observed. Moreover, a sharp activation of the TNF-α level was noted to a greater extent in severe patients with CHF. In our studies, in patients with CHF III-IV FC with anemia, as well as according to the data of other clinicians, the observed aggression of the PC was

accompanied by EPO resistance and a high increase in NT pro BNP. The results of the study of creatinine levels in patients with CHF in all examined groups showed that the creatinine level in patients with CHF anemia in all examined groups compared to the control group was increased by 33.5% ($p<0.001$) and 54.8% ($p<0.05$), respectively, and the SCF was reduced by 32.8% ($p<0.001$) and 36.0% ($p<0.01$), respectively, which indicates a progressive deterioration in renal function due to renal hypoperfusion. In patients with CHF with anemia, compared to the control group, there is a deterioration in systolic and diastolic function of the LV myocardium. LVEF decreased by 15.8% ($p = 0.030$). Analysis of the parameters of diastolic function of the LV myocardium in patients with CHF with anemia in all examined groups showed their reliable deterioration. Diastolic function of the LV myocardium in patients with CHF FC I-II is impaired according to the pseudo-normal type, and in patients with CHF FC III-IV - according to the restrictive type. Thus, the presence of anemia in CHF worsens the parameters of diastolic function of the LV myocardium - an increase in Ve / Va by 46.6% ($p = 0.004$), and in severe patients by 2.3 times ($p = 0.007$). IVRT was increased by 4.2% ($p=0.121$) and 7.7% ($p=0.133$), respectively. Contradictory literature data on the effect of anemia, DI and EPO deficiency on the severity of CHF allowed our data to coincide with the statements of clinicians on the decrease in systolic function of the LV myocardium only in severe patients and diastolic function of the myocardium in all patients with CHF. In patients with CHF with anemia, compared with CHF without anemia, there is a reliable decrease in the 6-minute walk test in severe patients by 47.4% ($p<0.001$). The results obtained compared with the control group demonstrated a picture of decreased tolerance to physical activity in the presence of anemia.

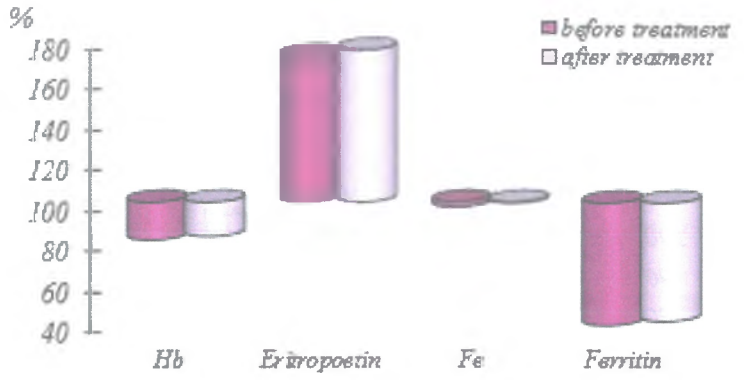
The presence of ID and EPO deficiency further reduced exercise tolerance. Therefore, in managing such patients, key attention should be given to the timely diagnosis and treatment of anemic syndrome. The earlier anemia correction is initiated—especially in patients with CHF of NYHA functional class I–II—the

higher the chances of a favorable treatment outcome. For example, in patients of group IV compared to the control group before treatment, a decrease in iron level by 23.7% ($p=0.588$) and in ferritin by 65.7% ($p<0.001$) and 61.3% ($p=0.006$), respectively, was observed.

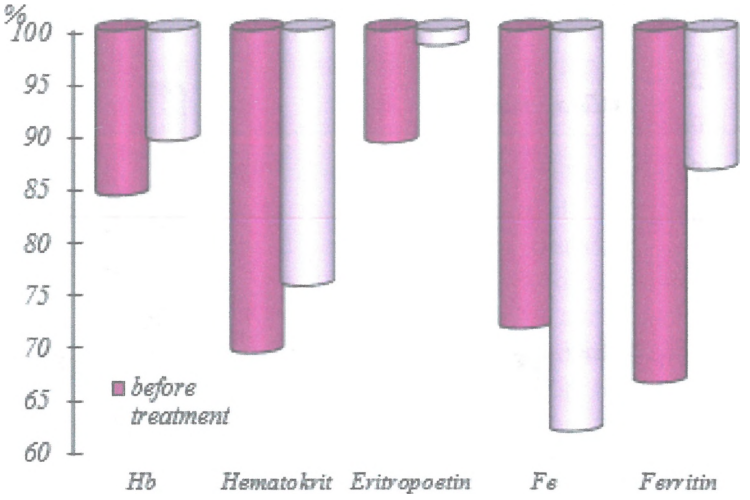
The study of the influence of basic therapy of CHF on the anemia factor is of great interest whether this factor worsens or, on the contrary, improves (graphs 2–5). The obtained results show that in patients with CHF of NYHA class I–II with anemia against the background of basic therapy there was a significant but slight increase in Hb level by 2.1% ($p=0.019$), the increase in Ht during basic therapy was significant ($p<0.001$) by 8.2%. Compared with the control group there was a significant decrease in Hb and Ht ($p<0.001$). It should be noted that in patients with CHF with anemia of group I before treatment iron deficiency was observed at a ferritin level of 42.9 ng/ml and TSAT <20% and after treatment iron deficiency remained. The increase in ferritin levels was significant ($p<0.001$) but treatment did not affect the correction of iron deficiency since it increased only to 58.5 ng/ml. The level of EPO in plasma during treatment remained within normal values ($p=0.925$), compared with the control group the EPO level was increased but still within the normal range. The NT pro BNP level during treatment was decreased ($p=0.040$) by 37.2%, compared with the control group it was non significantly increased. During treatment there was a non significant decrease in IL-1 ($p=0.179$), IL-6 ($p=0.081$), while the decrease in TNF-α level was significant ($p=0.038$) by 36.6%. Compared with the control group there was a significant decrease in IL-6 level by 5.4 times ($p=0.015$) and a non significant decrease in TNF-α. Renal function in patients with CHF I–II FC with anemia of group I was represented by a slight decrease in plasma creatinine level ($p=0.429$) and an increase in GFR ($p=0.347$). Compared with the control group their creatinine level was increased by 10.3% ($p=0.010$) and GFR decreased by 29.4% ($p<0.001$). The 6MWT index was significantly increased by 10.3% ($p<0.001$), and the SHOKS score was significantly reduced from 8.5 points to 4.2 points ($p<0.001$). Compared with the 6MWT of the control group it was

non significantly increased. A decrease in NYHA class was observed, with 2 patients moving from class II to class I. Parameters of systolic function EDV and ESV were significantly decreased ($p<0.001$), LVEF significantly increased by 2.3% ($p<0.001$). LVM decreased ($p<0.001$). IVRT decreased by 2.7% ($p<0.001$). Compared with the control group there was a non significant decrease in LVEF, an increase in LVM and RV size. EDV was decreased by 28.7% ($p<0.001$) and ESV by 37.7% ($p<0.001$). LA size was significantly increased by 4.5% ($p=0.012$). Parameters of LV diastolic function compared with the control group showed a non significant decrease in IVRT and a significant increase in the Ve/Va index by 25.6% ($p=0.043$). In patients with CHF of NYHA class III–IV with anemia against the background of basic therapy there was also a slight but significant increase in Hb by 6.1% ($p=0.042$), Ht by 10.1% ($p=0.027$), a decrease in iron levels ($p=0.345$), an increase in ferritin ($p=0.018$) and EPO ($p=0.398$) within the normal range. The decrease in NT pro BNP level was non significant ($p=0.176$). Compared with the control group patients with CHF III–IV FC with anemia showed a decrease in Hb by 10.4% ($p=0.010$) and Ht by 24.1% ($p=0.002$), a decrease in ferritin level by 13.1% ($p=0.612$), a decrease in EPO level to normal values and a non significant decrease in NT pro BNP.

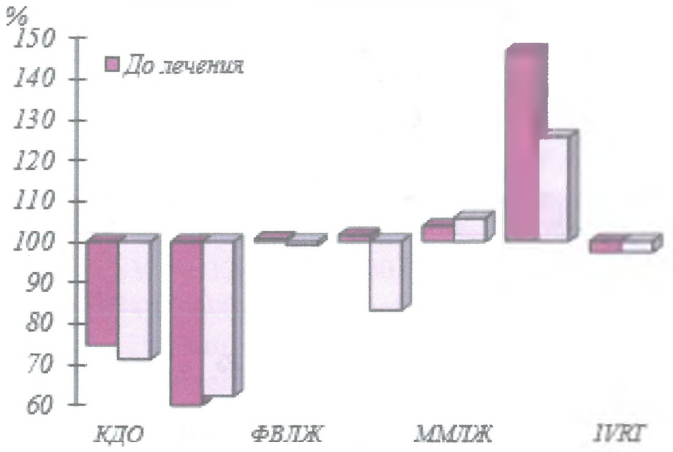
Against the background of the conducted treatment, an insignificant decrease in IL-1 ($p=0.893$) and IL-6 ($p=0.249$) was observed, while TNF-α decreased 1.6-fold ($p=0.043$). Compared to the control group, a reduction in IL-6 levels by 8.3-fold was noted ($p=0.001$). A slight improvement in renal function was observed: serum creatinine decreased by 1.2% ($p=0.018$) and eGFR increased ($p=0.866$). Analysis of left ventricular (LV) systolic function showed that in all patients with chronic heart failure (CHF) and anemia of NYHA class III–IV, treatment with baseline drugs led to a decrease in end-diastolic volume (EDV, $p=0.027$), end-systolic volume (ESV, $p=0.027$), right ventricular size (RV, $p=0.317$), left atrium (LA, $p=0.458$), and LV mass (LVM) decreased significantly ($p=0.017$).



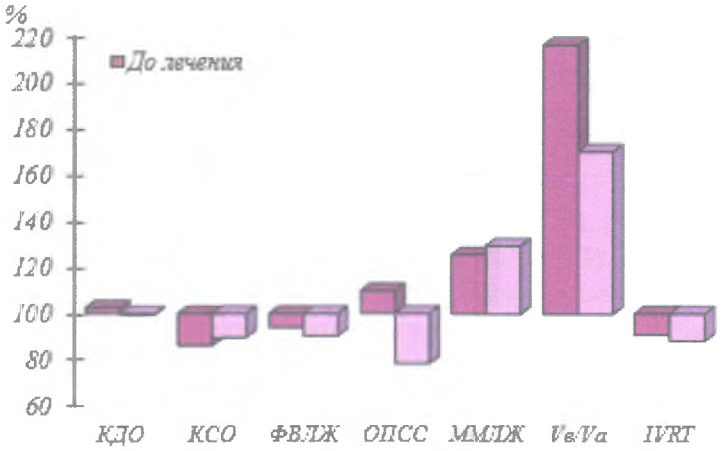
Graph. 2. Blood parameters before and after treatment in patients of group I – CHF I-II (control – 100%)



Graph 3. Blood parameters before and after treatment in patients of group I – CHF III-IV (control – 100%).



Graph. 4. Echocardiography indicators before and after treatment in patients of group I – CHF I-II (control – 100%).



Graph. 5. Echocardiography indicators before and after treatment in patients of group I – CHF III-IV (control – 100%).

However, the increase in LV ejection fraction (LVEF) by 3.0% ($p=0.059$) was not statistically significant.

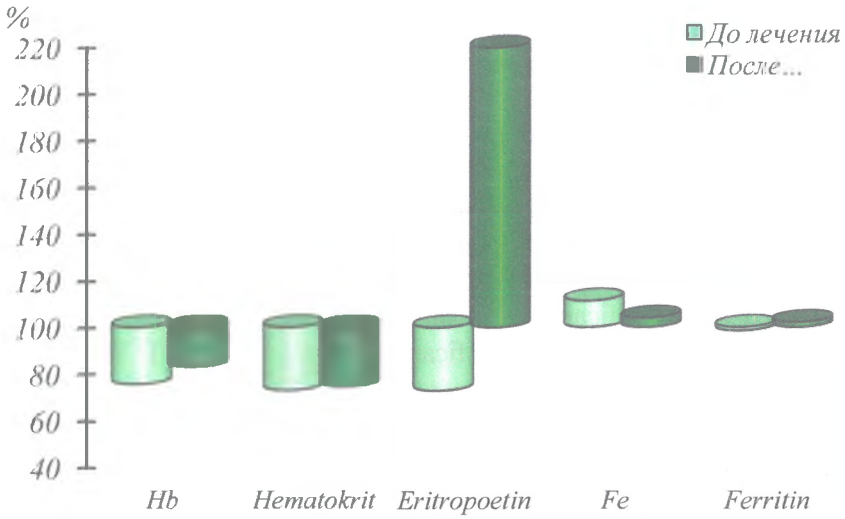
Analysis of LV diastolic function showed that in patients with CHF NYHA III–IV and anemia, baseline therapy led to a statistically non-significant decrease in the Ve/Va ratio ($p=0.458$) and a slight decrease in IVRT by 2.7% ($p=0.017$). Compared to the Doppler-ECHO parameters of the control group, there was a non-significant decrease in LVEF, an increase in LVM, and enlargement of the LA. RV size decreased by 19.8% ($p=0.002$). Volume parameters (EDV and ESV) decreased non-significantly. LV diastolic function compared with the control group showed a significant decrease in IVRT by 11.5% ($p=0.003$) and a non-significant increase in the Ve/Va index.

The 6-minute walk test (6-MWT) results increased slightly and significantly by 17.3% ($p=0.018$), while the shock index (SHOKS) decreased from 11.3 points to 5.9 points ($p=0.017$). Analysis of 6-MWT compared with the control group showed a non-significant decrease in the distance walked in patients with CHF NYHA III–IV and anemia. A reduction in NYHA class was observed in patients with CHF and anemia, with two patients improving from class II to class I.

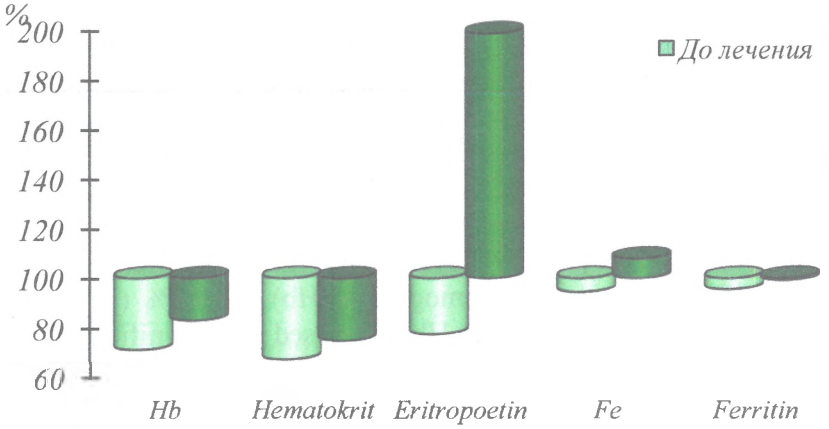
As seen from the results, baseline drugs in patients with CHF and anemia do not significantly affect hematopoietic parameters. The effectiveness of baseline therapy decreases in CHF with anemia due to anemia itself, decreased ferritin, reduced transferrin saturation, i.e., the development of iron deficiency and EPO dysfunction.

The results for patients with CHF and anemia with hypoerythropoietinemia in group II are presented in graphs 6–9. In patients with CHF NYHA I–II and anemia (group II), treatment led to a significant increase in hemoglobin (Hb) by 9.7% ($p<0.001$), while compared with group I, Hb decreased non-significantly by 0.6% ($p=0.386$). In patients with CHF NYHA III–IV, Hb increased by 16.6% ($p=0.005$), but compared with group I, Hb decreased by 7.2% ($p=0.006$).

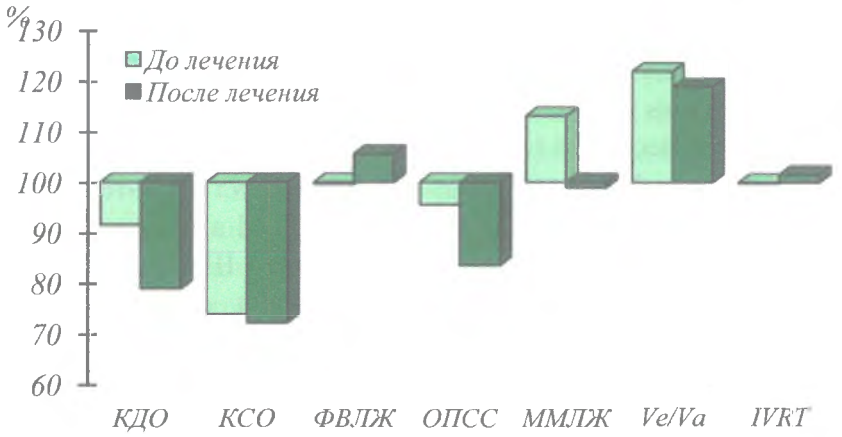
At the same time, compared with the control group, Hb levels in CHF NYHA I–II patients decreased significantly by 17% ($p<0.001$), and in CHF NYHA III–IV patients by 16.9% ($p=0.010$).



Graph. 6. Blood parameters before and after treatment in patients of group II – CHF I-II receiving basic therapy with erythropoietin MEB (control – 100%).



Graph. 7. Blood parameters before and after treatment in patients of group II – CHF III-IV receiving basic therapy with erythropoietin MEB (control – 100%).



Graph. 8. Echocardiography indicators before and after treatment in patients of group II – CHF I-II receiving basic therapy with erythropoietin MEB (control – 100%).

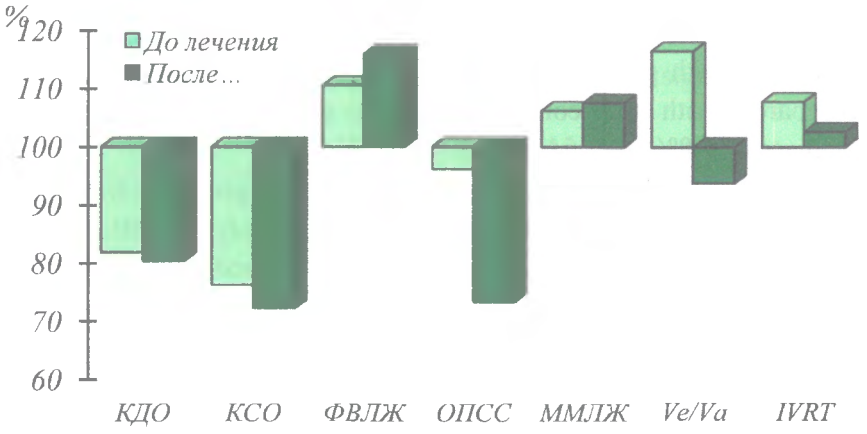


Fig. 9. Echocardiography indicators before and after treatment in patients of group II – CHF III-IV FC receiving basic therapy with erythropoietin MEB (control – 100%).

In patients with CHF NYHA I–II with anemia, hematocrit (Ht) increased by 2.6% (p=0.242), compared with group I (p=0.032), while in patients with CHF NYHA III–IV, Ht increased by 12.4% (p=0.007) but decreased by 1.3% compared with group I (p=0.598). Compared with the control group, Ht in CHF NYHA I–II patients decreased significantly by 25.4% (p<0.001), and a similar decrease of 25.1% (p<0.001) was observed in CHF NYHA III–IV patients.

Analysis of serum iron showed a slight decrease of 3% (p=0.957) in CHF NYHA I–II patients of group II, while in CHF NYHA III–IV patients, iron increased by 16% (p=0.285). Compared with the control group, iron increased by 4% (p=0.529). Ferritin levels showed a non-significant increase of 4.3% (p=0.122), consistent with the absence of iron deficiency in this category. In CHF NYHA I–II patients of group II, ferritin increased 2.4-fold compared with group I, as these patients had iron deficiency (p=0.003). Compared with the control group, ferritin decreased slightly by 0.8% (p=0.823). In CHF NYHA III–IV patients with anemia, ferritin increased non-significantly by 4.7% (p=0.475); compared with group I, ferritin increased by 14.2% (p=0.899), and compared with the control group, it showed a non-significant increase of 7.8% (p=0.544).

In CHF NYHA I–II and III–IV patients of group II, transferrin saturation (TSAT) remained >20% after therapy (p=1.000). In CHF NYHA I–II patients, plasma EPO levels increased almost threefold after treatment (p<0.001) and were also elevated compared with group I (p=0.063). Compared with the control group, plasma EPO increased 2.2-fold (p=0.007). In CHF NYHA III–IV patients with anemia, EPO increased significantly 2.5-fold (p=0.041), was higher than in group I (p=0.554), and increased 2-fold compared with the control group (p=0.184) and group I (p=0.139).

It should be noted that in all CHF patients with anemia and hypoerythropoietinemia, TSAT remained >20% (p=1.000). In CHF NYHA I–II patients of group II, NT-proBNP decreased by 48.4%

($p<0.001$) and compared with group I, it increased slightly ($p=0.460$). Compared with the control group, patients in group II showed a trend toward decreased plasma NT-proBNP ($p=0.443$). In CHF NYHA III–IV patients of group II, NT-proBNP decreased significantly by 49.1% ($p=0.005$) and decreased compared with group I ($p=0.612$).

Following therapy, TNF-α in CHF NYHA I–II patients of group II decreased significantly by 67.2% (3.1-fold, $p<0.001$) and compared with group I, the decrease was non-significant ($p=0.922$). Compared with the control group, TNF-α decreased by 25.3% ($p=0.184$). In CHF NYHA III–IV patients with anemia, TNF-α decreased significantly by 59% ($p=0.034$) and was non-significantly lower than in group I ($p=0.499$).

IL-6 decreased by 69.5% in CHF NYHA I–II patients of group II ($p<0.001$), decreased 2.1-fold compared with group I ($p=0.025$), and decreased 61.8% compared with the control group ($p=0.528$). In CHF NYHA III–IV patients with anemia, IL-6 decreased 3.2-fold ($p=0.028$). Compared with group I, IL-6 appeared to increase 3.3-fold ($p=0.076$), but the value remained within normal limits. Compared with the control group, IL-6 decreased significantly by 60.6% ($p=0.021$).

IL-1 decreased by 31.5% in CHF NYHA I–II patients of group II ($p=1.000$) and 3.4-fold compared with group I ($p=0.820$). Compared with the control group and group I, IL-1 activation decreased by 25% ($p=0.045$). In CHF NYHA III–IV patients with anemia, IL-1 decreased by 30% ($p=0.091$), non-significantly higher than in group I ($p=0.735$), and compared with the control group, IL-1 decreased 1.6-fold ($p=0.236$).

Overall, the positive dynamics in patients with CHF and anemia showed suppression of cytokine aggression when MEB (multicomponent erythropoietin-based therapy) was included in combined therapy.

Creatinine decreased significantly in CHF NYHA I–II patients by 23.7% ($p=0.002$), while eGFR increased by 24.5% ($p=0.002$),

which was higher than in group I (p=0.021). Compared with the control group, creatinine remained 7.2% higher (p=0.286), and eGFR remained 16.4% lower (p=0.112). In CHF NYHA III–IV patients with anemia, creatinine decreased by 21% (p=0.005), but compared with the control group, remained 24.8% higher (p=0.021) and decreased 12.2% compared with group I (p=0.075). eGFR increased by 14.9% (p=0.007) and was higher than in group I, but remained 26.9% lower than the control group (p=0.057).

6-MWT increased significantly in CHF NYHA I–II patients with anemia by 25.1% (p<0.001) and in CHF NYHA III–IV by 38.3% (p=0.017). Compared with the control group, 6-MWT values were lower but non-significant. Compared with group I, CHF NYHA III–IV patients with anemia showed a non-significant increase of 21.5% (p=0.151).

Analysis of LV systolic and diastolic function in CHF NYHA I–II patients with anemia and hypoerythropoietinemia showed significant decreases in LV systolic parameters such as stroke volume, LV end-diastolic and end-systolic volumes, LV mass, wall thickness, myocardial performance index, with a significant increase in LVEF and ΔS%. LVEF increased by 10.1% (p<0.001), and LV mass decreased by 23.9% (p<0.001). Compared with the control group, LVEF increased by 15.9% and 28.4% compared with group I, but non-significantly. Overall, LVEF increased by 12.1%. Myocardial output decreased significantly by 24.6% (p=0.002), and ΔS% increased by 31% (p=0.004). LV mass decreased by 12.9% (p=0.012). IVRT decreased significantly (p<0.001) by 1.7%, while Ve/Va increased non-significantly (p=0.252).

In CHF NYHA III–IV patients with anemia and hypoerythropoietinemia, systolic LV parameters including ESV (p=0.006), LA (p=0.003), RV (p=0.011), and LV mass (p=0.012) decreased significantly, and LVEF increased (p=0.012), with LVEF increasing by 12.1% (p<0.001). Compared with the control group, LVEF increased 15.9% and compared with group I by 28.4%, but non-significantly.

The results indicate that the presence of anemia at early stages of CHF should be carefully considered when initiating therapy, as MEB therapy showed significant positive dynamics in LV systolic and diastolic function. Diastolic function showed a significant increase in Ve/Va by 3.3% ($p=1.000$) and a decrease in IVRT by 5.1% ($p=0.002$). In CHF NYHA III–IV patients with anemia, Ve/Va decreased by 6.2% compared with group I ($p=0.042$) and also decreased non-significantly compared with the control group. IVRT in group II increased significantly by 2.6% ($p<0.001$) compared with the control group and by 15.8% compared with group I ($p=1.000$).

SHOKS decreased in CHF NYHA I–II patients with anemia and hypoerythropoietinemia from 7.8 to 2.5 points ($p<0.001$), and in CHF NYHA III–IV patients from 11 to 3.8 points. NYHA class decreased in 9 patients from II to I, in 1 patient from III to I, and in 5 patients from III to II. Diuretic dose and number were reduced.

Adding MEB to baseline therapy in CHF patients with anemia did not lead to iron-deficiency states. The data confirm erythropoietin dysfunction in CHF patients with anemia, which causes the development of anemic syndrome. In these patients, MEB is necessary to correct plasma EPO levels.

Laboratory and functional results in CHF NYHA I–II patients with anemia and iron deficiency (group III) are shown in graphs 10–13. In CHF patients with anemia and iron deficiency, as well as normal or hyper-erythropoietinemia, administration of intravenous iron (saccharated iron III) with baseline drugs led to a significant increase in Hb by 5.2% ($p=0.001$), Ht by 5.9% ($p=0.004$), plasma ferritin 2.1-fold ($p<0.001$), and TSAT >20% ($p=0.001$), with a non-significant decrease in EPO within the normal range (-7.5 ± 1.6 IU/mL, $p=0.108$). Iron levels increased slightly ($p=0.879$).

Compared with group I, Hb increase was non-significant ($p=0.449$), Ht decrease was non-significant ($p=0.240$), ferritin increased significantly 2.5-fold ($p=0.001$), and TSAT remained

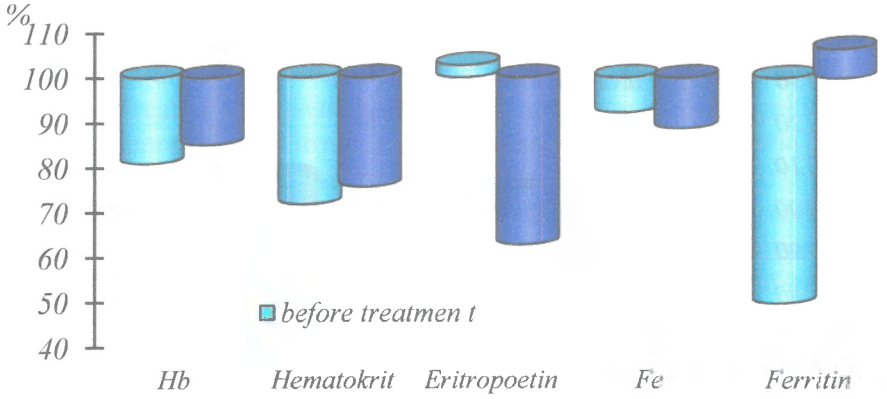
>20% (p=0.025). Compared with the control group, Hb decreased by 14.9% (p<0.001), Ht by 24% (p<0.001), ferritin by 6% (p=0.966), and EPO was 37.1% lower (p=0.388).

In CHF NYHA I–II patients, NT-proBNP decreased significantly by 27.8% (p=0.001); compared with group I, it decreased by 92.7% (p=0.001), and compared with the control group, decreased 2.2-fold (p=0.001). IL-1 decreased by 36.7% (p=0.100), compared with group I decreased (p=0.608), and compared with the control group increased 2.7-fold (p=0.038). IL-6 increased non-significantly (p=0.253), but compared with group I increased 4.7-fold (p=0.001), and compared with the control group decreased by 12.9%. TNF-α in plasma was non-significantly increased (p=0.867), 2.1-fold higher than in group I (p=0.024), and decreased slightly compared with the control group (1.2-fold, p=0.332).

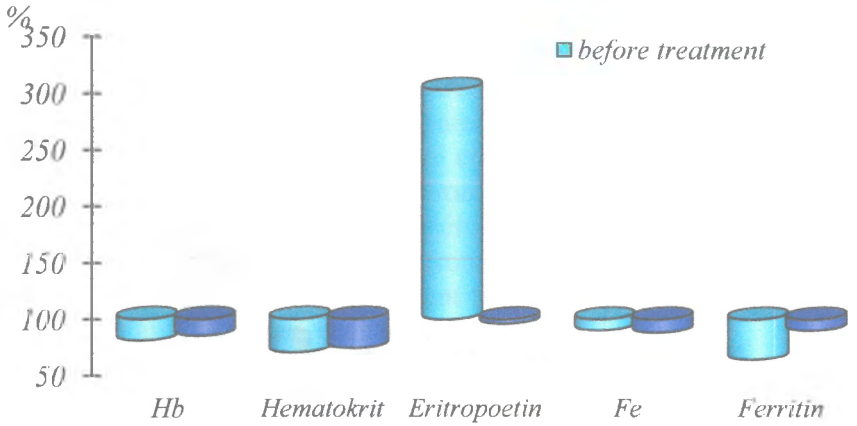
Creatinine decreased significantly by 13.1% (p=0.002) in CHF NYHA I–II patients with anemia, decreased by 4.9% compared with group I (p=0.001), and was 4.9% higher than in the control group (p=0.462). eGFR increased significantly by 9.7% (p=0.006); compared with the control group, it remained 24.5% lower (p=0.005), and compared with group I increased by 6.3% (p=0.650).

In CHF NYHA III–IV patients with anemia and iron deficiency, Hb increased by 5.2% (p=0.030), Ht by 6.1% (p=0.039), plasma ferritin 1.4-fold (p=0.071), TSAT >20% (p=0.008), and EPO decreased non-significantly to normal range (p=0.349). Iron was within normal limits (p=0.948). Compared with group I, Hb increased by 14.2% (p=0.855), Ht by 25.1% (p=0.854), ferritin 1.4-fold (p=0.071), and TSAT >20% (p=0.576).

Compared with Group I, there was an increase of 3.9% (p=0.672), while compared with the control group, it decreased by 9.7% (p=0.539). The blood EPO level was elevated, indicating that this group included patients with hypererythropoietinemia. During treatment, it increased by 69.3% (p=0.349).

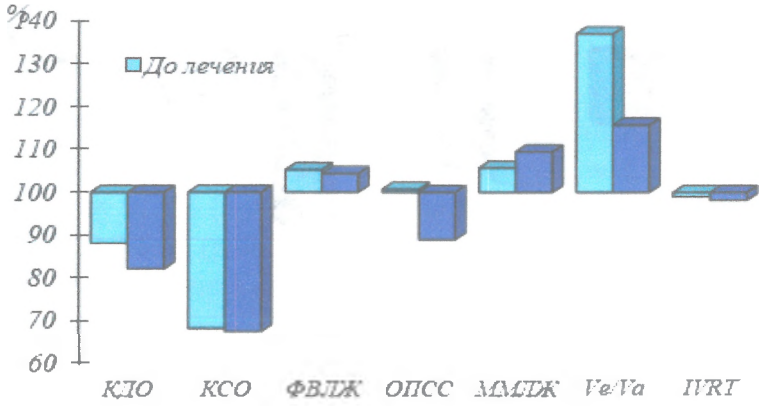


Graph. 10. Blood parameters before and after treatment in patients of group III – CHF I-II (receiving basic therapy with intravenous administration of iron saccharate III (control – 100%).

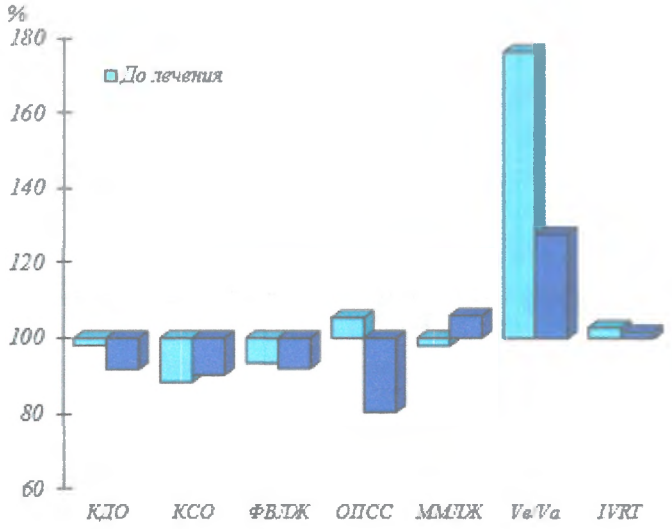


Graph. 11. Blood parameters before and after treatment in patients of group III – CHF III-IV (receiving basic therapy with intravenous administration of iron sucrose III (control – 100%).

Analysis of NT-proBNP levels in patients with CHF III–IV FC showed that plasma NT-proBNP decreased by 23.2% (p=0.035) during treatment. When compared with Group I, NT-proBNP increased 2.2-fold (p=0.006), since the baseline NT-proBNP level in



Graph. 12. Echocardiography indicators before and after treatment in patients of group III with CHF I-II FC (receiving basic therapy with intravenous administration of iron sucrose III (control – 100%).



Graph. 13. Echocardiography indicators before and after treatment in patients of group III – CHF III-IV FC (receiving basic therapy with intravenous administration of iron sucrose III (control – 100%).

Group I was lower; compared with the control and Group I, it decreased 2.1-fold ($p=0.002$). In patients with CHF III–IV FC and anemia, treatment caused IL-1 levels to decrease by 34% ($p=0.088$), but compared with Group I, it increased 1.6-fold ($p=0.904$), and compared with the control group, it increased 1.9-fold ($p=0.038$).

IL-6 levels decreased by 16.8% ($p=0.309$) during treatment; compared with Group I, they were 14.2-fold higher ($p=0.849$) and 1.7-fold higher than in the control group ($p=0.002$). TNF-α in plasma decreased by 1.1% ($p=0.408$); compared with Group I, it increased 1.2-fold ($p=0.762$) and compared with the control group, 2-fold ($p=0.065$).

In patients with CHF and anemia III–IV FC, creatinine levels decreased significantly by 13.8% ($p=0.038$); compared with Group I, it decreased by 18.7% ($p=0.004$), and compared with the control group, it increased by 15.6% ($p=0.062$). GFR increased by 8.3% ($p=0.125$) during treatment; compared with the control group, it decreased by 28.4% ($p=0.007$), and compared with Group I, it increased by 8.6% ($p=0.628$).

The 6-MWT test increased by 21.6% ($p<0.001$) in patients with CHF and anemia III–IV FC. Compared with the control group, it was 9.0% lower ($p=0.236$), and compared with Group I, it was 13% higher ($p=0.303$). NYHA functional class decreased: in CHF I–II FC with anemia, SHOKS decreased from 6.6 to 2.1 points ($p<0.001$), and in CHF III–IV FC with anemia, from 10.9 to 3.6 points ($p<0.001$). One patient improved from II FC to I FC, three patients from III FC to II FC, and one patient from IV FC to III FC. Diuretic dose and number were also reduced.

Systolic function parameters of the left ventricle (LV) in CHF I–II FC patients with anemia III group showed significant improvement after treatment: LVEF increased by 3.1% ($p<0.001$), LV mass decreased by 9.9% ($p<0.001$), RV size decreased by 1% ($p=0.005$), and LA size decreased by 2.3% ($p<0.001$). Compared with Group I and the control group, LVEF increased by 5.3% ($p=0.242$) and 4.4% ($p=0.175$), LV mass increased by 5.9% ($p=0.208$) and decreased by 18.2% ($p=0.627$).

After treatment, the Ve/Va ratio decreased by 6.9% ($p=0.458$); compared with the control group, it increased by 15.7% ($p=0.180$), and compared with Group I, it decreased by 7.9% ($p=0.309$). IVRT

significantly decreased by 4.1% ($p<0.001$); compared with the control and Group I, it decreased by 1.8% ($p=0.906$) and increased by 0.9% ($p=0.511$), respectively.

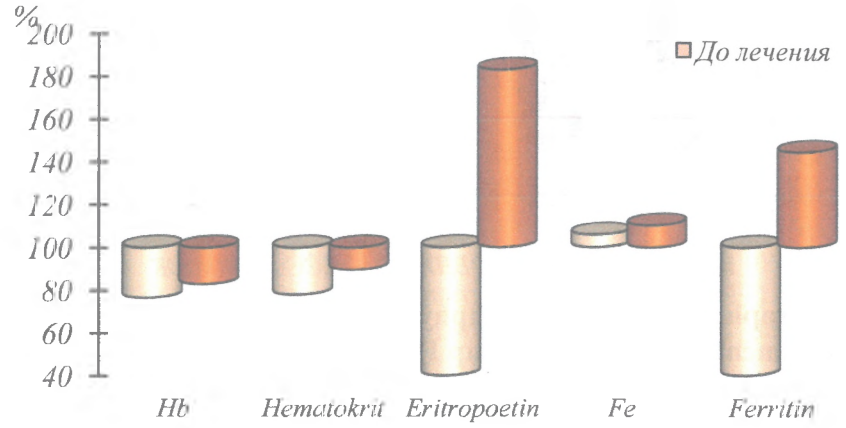
Systolic and diastolic LV function in CHF III–IV FC patients with anemia III group after treatment showed significant improvement: LVEF increased by 5.3% ($p<0.001$), LV mass decreased by 7.0% ($p<0.001$), RV size decreased by 4.0% ($p=0.005$), and LA size decreased by 3.2% ($p<0.001$). Compared with the control group, LVEF decreased by 8.1% ($p=0.026$), LV mass increased by 5.9% ($p=0.290$). Compared with Group I, LVEF increased by 1.8% ($p=0.626$), LV mass decreased by 18.2% ($p=0.146$).

Diastolic function: Ve/Va ratio decreased non-significantly by 7.4% ($p=0.732$). Compared with the control and Group I, Ve/Va increased by 27.7% ($p=0.149$) and 1.3-fold ($p=0.145$), respectively. IVRT decreased slightly by 1.5% ($p=0.733$); compared with Group I, it significantly increased by 14.8% ($p<0.001$) and compared with the control group, increased by 1.6% ($p=0.671$).

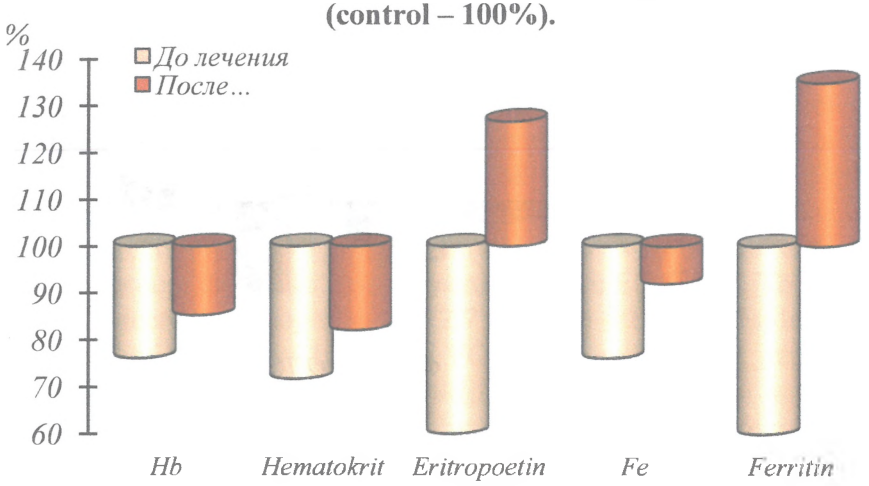
The results of patients with CHF and anemia group IV are presented in graphs 14-17. In patients with CHF and anemia of group IV in CHF FC I-II, against the background of the conducted therapy, there is a reliable increase in the Hb level by 8.4% ($p<0.001$), Ht by 15.4% ($p<0.001$), iron level by 8.1% ($p<0.001$), ferritin level in the blood by 4.2 times ($p<0.001$), CT>20%, EPO in the blood by 7.3 times ($p<0.001$) and a decrease in the NTproBNP level in the blood plasma by 54.2% ($p<0.001$), the IL-1 level in the blood plasma by 85.6%, the IL-6 level in the blood plasma by 78.2% ($p<0.01$), and the TNF-α level in the blood plasma by 91.7%. Compared with patients in group I of patients with CHF with anemia and the control group, there was also an increase in the level of Hb by 0,6% ($p=0.944$) and Ht by 11,8% ($p=0.002$) and decresed by 10,4% ($p=0.002$).

Compared with patients of group I of patients with CHF with anemia and the control group, there was also an increase in the level of iron and ferritin ($p<0.001$) and ($p<0.001$), CT>20%. Compared with patients of group I of patients with CHF with anemia and the control group, there was also an increase in the level of EPO ($p=0.018$). Compared with patients of the control group, there was a increase in the level of NT pro BNP by 1,6 times ($p=0.003$).

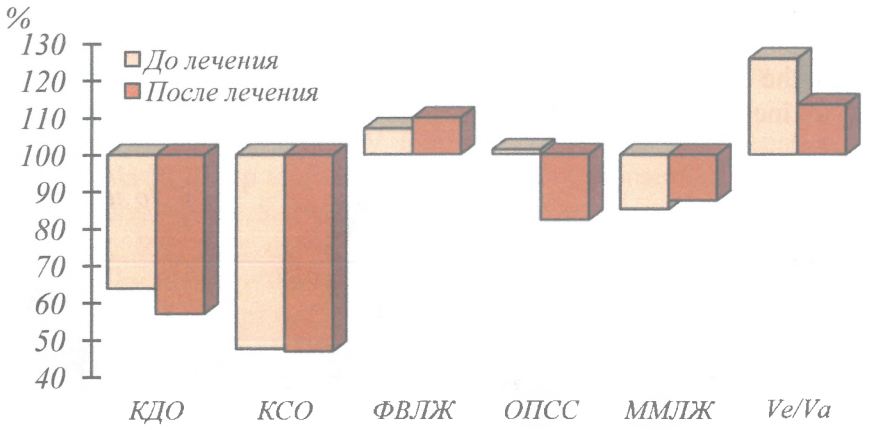
Compared with patients of group I of patients with CHF with anemia and the control group, there was also a decrease in the level of cytokine aggression, IL-6 by 1,8 times and 8,6 times($p<0.001$).



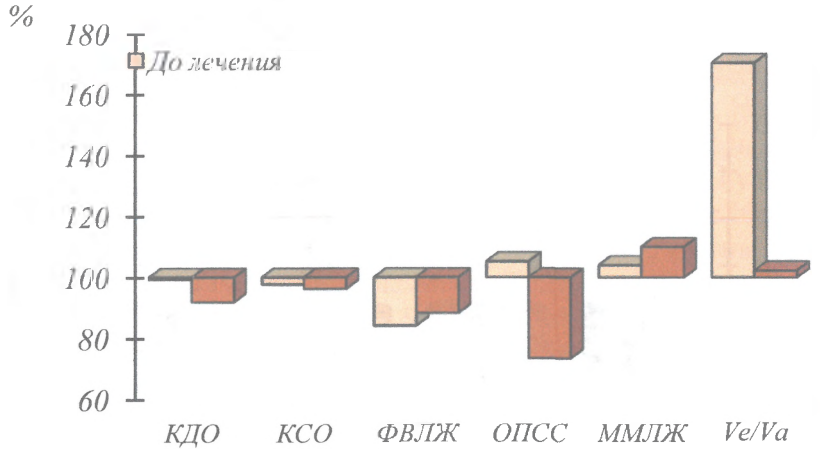
Graph. 14. Blood parameters before and after treatment in patients of group IV – CHF I-II (receiving basic therapy with MEB and intravenous administration of iron sucrose III) (control – 100%).



Graph. 15. Blood parameters before and after treatment in patients of group IV – CHF III-IV (receiving basic therapy with MEB and intravenous administration of iron sucrose III) (control – 100%).



Graph. 16. Echocardiography indicators before and after treatment in patients of group IV with CHF I-II FC (receiving basic therapy with MEB and intravenous administration of iron sucrose III) (control – 100%).



Graph. 17. Echocardiography parameters before and after treatment in patients of group IV – CHF III-IV FC (receiving basic therapy with MEB and intravenous administration of iron sucrose III) (control – 100%).

During treatment, there was a decrease in creatinine level by 12% (p=0.012), an increase in SCF by 7.4% (p=0.002), and an increase in SCF was also observed compared to group I by 29,7% (p <0.001). Analysis of the parameters of systolic and diastolic function of the LV myocardium in patients with CHF FC I-II with anemia of group IV revealed a significant decrease in EDV, ESV (p<0.001), LVM by 10.6% (p<0.001), a decrease in the size of the LA by 2.8% (p<0.001), and the RV. LVEF was increased by 6.7% (p<0.001), compared to group I, yf was also increased by 11% (p=0.028). LV diastolic myocardial function indices IVRT did not change during treatment, Ve/Va slightly decreased. 6-MTX increased by 21.6% (p<0.001) during treatment, compared to group I (p=0.017) and the control group (p=0.011) it was also increased. SHOKS decreased from 6.5 points to 2.2 points (p<0.001).

In patients with CHF III-IV functional class with anemia and ID, with hypoerythropoietinemia, there was an increase in Hb by 12% (p=0.003) during treatment, compared with the control group (p= 0.004). Also, an increase in Ht by 15.4% (p=0.003), compared with the control group (p <0.001). An increase in the iron level by 22.7% was observed (p= 0.004). An increase in the level of ferritin in the blood during treatment by 3.5 times (p=0.003), compared with the control group (p=0.023). CT increased during treatment by more than 20% (p= 0.001), compared with patients of group I by more than 20% (p=0.021). An increase in the level of EPO in the blood during treatment by 5.6 times (p= 0.004). was reliable, compared with patients of group I of patients with CHF with anemia and the control group, there was also an increase in the EPO level. The level of IL-1 decreased insignificantly 2,7 times (p = 0.050), the level of IL-6 in patients with CHF III-IV FC with anemia during treatment significantly decreased by 43.7% (p = 0.014), compared with the indicator of the control group it was also reduced 2,5 times (p = 0.029). The dynamics of TNF-α demonstrated a reliable decrease in its level in the blood during treatment by 67.0% (p = 0.008), compared with patients of group I, a decrease in its level was observed 2,3 times (p = 0.030). The level of creatinine in patients with CHF III-IV FC with anemia of group IV significantly decreased

by 11.7% (p = 0.012) after treatment, and compared with group I it was also reduced 15,4% (p = 0.026). The increase in SCF during treatment was non-significant by 15.8% (p=0.012), compared to the indicator in Group I, there was a significant increase of 29.7% (p<0.001) and 35.5% (p=0.021) (p<0.05), respectively.

The results of the dynamics of the parameters of systolic function of the LV myocardium in patients with CHF I-IIFC with anemia group IV against the background of the conducted therapy showed an insignificant decrease in the echocardiography parameters such as RV, EDV, ESR, LA. The increase in LVEF was insignificant. In addition, in patients with CHF I-II with anemia group IV against the background of therapy there is an insignificant increase in Ve, a decrease in Va and Ve / Va. The IVRT indicator did not change. The obtained results of the dynamics of the parameters of systolic function of the LV myocardium in patients with CHF III-IV FC with anemia group IV against the background of therapy established a significant decrease in the echocardiography parameters such as EDV 8,7%, ESV 9,0% (p = 0.003). LVMM was reduced by 9.0% (p = 0.004). RV, LMM, LA. LVEF was significantly increased by 12.2% (p = 0.003). (p<0.001). The sizes of the left atrium were reduced after treatment by 4.6% (p=0.011) and the right ventricle by 3.3% (p=0.026). Analysis of the diastolic function indices revealed an insignificant decrease in Ve/Va by 23.2% (p=0.028) and an increase in IVRT by 5.5% (p=0.009) in patients with CHF III-IVFC and anemia of group IV against the background of the therapy, but a reduce compared to the index of control group. The 6-minute walk test index in patients with CHF III-IVFC was significantly increased by 21.6% (p<0.001) and by 64.9% (p<0.001). There is also an increase in exercise tolerance by 64.9% (p<0.001), a decrease in NYHA class from FC II to FC I in 10 patients, from FC III to FC II in 3 patients, as well as the dose and number of prescribed diuretics. A decrease in the SHOKS from 10.9 points to 3.6 points (p<0.001) was found.

The main objective of this study was to provide correct correction of anemic syndrome, reducing the effectiveness of basic drugs and aggravating the course of CHF. Therapy with basic drugs

in patients with CHF with anemia does not affect the levels of ferritin, EPO in blood plasma, ST. The anemic factor was accompanied by inhibition of the decrease in the level of plasma NTproBNP and cytokine aggression during treatment with basic drugs. Positive dynamics of the parameters of systolic function of the LV myocardium were unreliable. The presence of anemia in CHF increases the severity of diastolic dysfunction of the LV myocardium. We approached this problem taking into account the levels of ferritin, ST, EPO in the blood, which is absent in the literature. Treatment tactics in the literature were aimed directly at correcting anemia without taking into account such important indicators as the levels of ferritin, ST and EPO in combination. There are data in the literature on the use of therapy for CHF with anemia directly with erythropoietins, iron III polysaccharide complex IVIP or their combination. At the same time, there are few data in the literature on the combined therapy of patients with CHF with anemia with basic drugs with MEB, with iron III polysaccharide complex, due to the poor study of MEB. In contrast to the literature data, and even to what we believe to be approved guidelines, our results contain positive, new data on the use of ESS in the form of MEB. Of the erythropoietin-stimulating agents, short-acting drugs or darbopoietin-α were used.

However, to correct anemia in CHF, it is necessary to constantly activate erythropoietin receptors, which is achieved due to MEB, resembling physiological erythropoiesis. It cannot be said that the encouraging results of therapy for patients with CHF with anemia concern only IVIP. But what if there is an EPO deficiency or hypoerythropoietinemia? This fact is inevitable and cannot be ignored. The innovative feature of our work was the use of MEB, which, unlike other erythropoietin drugs, in particular from the drug darbopoietin-α, α-epoetin, β-epoetin used in European studies, does not contribute to arterial hypertension, thrombosis. There was no thrombocytosis in the blood test and negative changes in the coagulogram. Thus, without limiting ourselves to the guidelines, it is necessary to conduct further studies on the use of IVIP and ESS. We have conducted our studies on the use of the new EES-MEB. It is

possible that funds are needed, due to the high cost of the MEB, to conduct large, randomized studies.

CONCLUSIONS

1. As chronic heart failure (CHF) progresses with anemia, hemoglobin (Hb) levels decrease by 24.4% ($p<0.001$) in CHF functional class I–II (NYHA I–II) and by 28.7% ($p<0.001$) in CHF III–IV. Hematocrit (Ht) decreases by 27.9% ($p<0.001$) and 32.7% ($p<0.001$), respectively. Anemia is accompanied by iron deficiency (ID) (a reduction in ferritin by 69.2% at transferrin saturation [TSAT] <20% and 61.3% at TSAT <20%, respectively), as well as without ID. There are also signs of deteriorating renal function: creatinine increases, and glomerular filtration rate (GFR) decreases by 32.8% ($p=0.002$) and 36.0% ($p=0.011$), respectively. Exercise tolerance declines with worsening NYHA class (CHF III–IV) by 47.4% ($p<0.001$). (10,15,16,22,24)
2. In patients with CHF and anemia, erythropoietic activity varies: normal erythropoietin levels are found in 36.2%, with ID 30,5%; hypoerythropoietinemia by 44.9%, with ID - 25,2% and hypererythropoietinemia by 18.9%, with ID - 6,8%. Hypererythropoietinemia was observed in severe patients with CHF III–IV FC with post-infarction cardiosclerosis and concomitant type 2 diabetes mellitus. (20,25,34)
3. Patients with CHF and anemia show a relatively sharp increase in NT-proBNP levels by 79.7% ($p<0.001$), with the highest increase in patients with ID and TSAT <20%. (21,41,43,46,47)
4. CHF patients with anemia show increased inflammatory activity, evidenced by elevated plasma concentrations of IL-6 and TNF-α. TNF-α is particularly increased in severe CHF III–IV FC by 3.7 times ($p=0.042$) and IL-6 in patients with ID with TSAT <20% - 76.6%. (30,36,37,39,44,50)
5. In CHF I–II with anemia, left ventricular (LV) systolic function remains comparable to controls. In CHF III–IV, LV ejection fraction (LVEF) decreases by 15.8% ($p=0.030$). Diastolic

function also changes: in I–II, pseudonormal pattern prevails (Ve/Va increases by 46.6%, p=0.004), and in III–IV, restrictive pattern dominates (Ve/Va increases 2.2 times, p=0.007). (53,54,55,60,61)

6. In CHF I–II with anemia, positive correlations were found between Hb and ferritin (ρ=0.282), TSAT (ρ=0.282), Ht (ρ=0.515), Ve/Va (ρ=0.220), and GFR (ρ=0.291), and between TSAT and LV myocardial mass (ρ=0.167). Negative correlations were found between Hb and NT-proBNP (ρ=-0.230), EPO and IL-6 (ρ=-0.195), TSAT and IL-1 (ρ=-0.165), and Ve/Va (ρ=-0.168). In CHF III–IV, positive correlations were observed between Hb and GFR (ρ=0.292), Ve/Va (ρ=0.328), and negative correlations between Hb and TNF-α (ρ=-0.276), TSAT and NT-proBNP (ρ=-0.383), Ve/Va (ρ=-0.321), and Ht and creatinine (ρ=-0.447). (61,66)
7. The effectiveness of basic therapy in CHF with anemia is reduced by anemia, ID, and EPO dysfunction. No significant improvement was observed in LV systolic and diastolic functions: LVEF increased by 2.3% (p<0.001), IVRT decreased by 3.3% (p<0.001) in CHF I–II. In CHF III–IV, LVEF increased by 3% (p=0.059), IVRT decreased by 3.1% (p=0.017). Renal function worsened (GFR decreased by 1.2%, p<0.01) and exercise tolerance improved slightly. (53,55,60,61)
8. In CHF I-II FC and III-IVFC patients with anemia and hypoerythropoietinemia, the use of combined therapy with basic drugs and MEB led to an increase in Hb by 9.7% (p<0.001) and 16.6% (p=0.005), respectively, Ht by 2.6% and 12.4% (p=0.007), an increase in EPO levels by 3 times (p<0.001) and 2.5 times (p=0.041), a reduction in NT-proBNP by 2 times (p<0.001) and 2 times (p=0.005), interleukin-6 (IL-6) by 2.5 times and 3.2 times (p=0.028), TNF-α by 3.1 times (p<0.001) and 2.4 times (p=0.034), creatinine by 23.7% (p=0.002) and 13.8% (p=0.005), and an increase in GFR by 24.5% (p=0.002) and 14.9% (p=0.007). 6-MWT increased by 25.1% (p<0.001) and 38.3% (p=0.002). SHOKS score decreased from 7.8 points to 2.5 points (p<0.001) and from 11 points to 3.8 points (p=0.002). LVH

regressed by 23.9% ($p<0.001$) and 12.9% ($p=0.012$), LVEF increased by 10.2% ($p<0.001$) and 12.1% ($p=0.002$), and IVRT decreased by 1.7% and 5.1% ($p=0.002$) (18,19,20,22,26,28,29, 31,32,35,45,54,55,58,63).

9. In CHF I-II FC and III-IVFC patients with anemia and iID, the use of combined therapy with basic drugs and intravenous iron (III) saccharate led to a significant increase in hemoglobin (Hb) by 5.2% ($p=0.001$) and 5.2% ($p=0.030$), hematocrit (Ht) by 5.9% ($p=0.004$) and 6.1% ($p=0.039$), plasma ferritin by 2.1 times ($p<0.001$) and 40.7%, transferrin saturation (TS) >20% ($p=0.001$); a decrease in NT-proBNP by 27.8% ($p=0.002$) and 23.2% ($p=0.035$), IL-1 by 36.7% ($p=0.100$) and 34% ($p=0.088$), creatinine by 13.1% ($p=0.002$) and 13.8% ($p=0.038$); and an increase in GFR by 9.7% ($p=0.006$) and 8.3%. LVH regressed by 9.9% ($p<0.001$) and 7% ($p<0.001$), LVEF increased by 3.1% ($p<0.001$) and 5.3% ($p<0.001$), and isovolumic relaxation time (IVRT) decreased by 4.1% ($p<0.001$). 6-MWT improved by 16.6% ($p<0.001$) and 21.6% ($p<0.001$). The SHOKS score decreased from 6.6 points to 2.1 points and from 10.9 points to 3.6 points ($p<0.001$) (33, 38, 40, 42, 53, 55, 57, 65, 66).
10. In CHF I-II FC and III-IV FC patients with anemia, ID, and hypoerythropoietinemia, combined therapy with basic drugs including MEB and intravenous iron (III) saccharate led to a significant increase in the target Hb level by 8.4% ($p<0.001$) and 12.0% ($p=0.003$), Ht by 15.4% ($p<0.001$) and 15.4% ($p=0.003$), ferritin by 4.2 times ($p<0.001$) and 3.5 times ($p=0.003$), ST >20% ($p<0.001$), EPO by 7.3 times ($p<0.001$) and 5.6 times ($p<0.001$); a decrease in NT-proBNP by 54.2% ($p<0.001$) and 33.0% ($p=0.004$), IL-1 by 6.9 times ($p<0.001$) and 2.7 times ($p=0.050$), IL-6 by 4.6 times ($p<0.001$) and 1.8 times ($p=0.014$), TNF-α by 12 times ($p<0.001$) and 3 times ($p=0.008$), creatinine by 12.0% ($p<0.001$) and 11.7% ($p<0.001$), and an increase in GFR by 7.4% ($p=0.002$) and 15.7% ($p=0.012$). Physical exercise tolerance increased by 21.6% ($p<0.001$) and 64.9% ($p<0.001$). The SHOKS score decreased from 6.5 points to 2.2 points ($p<0.001$) and from 10.9 points to 3.6 points ($p<0.001$). MMLVLV

decreased by 10.6% ($p<0.001$) and 9.0% ($p=0.004$). Systolic function of the left ventricle improved, with LVEF increasing by 6.7% ($p<0.001$) and 12.2% ($p<0.003$). Diastolic function improved, as indicated by a reduction in Ve/Va by 23.2% ($p=0.028$). (49, 55, 59, 61).

11. Correction of anemia in patients with CHF should be performed taking into account individual parameters, in particular plasma ferritin levels, transferrin saturation (ST), and erythropoietin levels. (53, 54, 55, 61, 65).

PRACTICAL RECOMMENDATIONS

1. Regardless of functional class or phenotype, patients with chronic heart failure (CHF) require therapeutic interventions aimed at correcting anemia. The greatest effectiveness of anemia correction is observed in patients at early stages of the disease, which is due to less severe systemic alterations and higher compensatory capacity of the body.
2. Patients with CHF and anemia are more likely to develop heart failure that is refractory to standard therapy. In such cases, anemia correction should be differentiated based on plasma levels of ferritin, transferrin saturation, and erythropoietin, enabling the selection of the most rational and pathogenetically justified treatment approach.
3. When selecting baseline therapy in patients with CHF complicated by anemia, it is important to consider the potential impact of prescribed medications on renal erythropoietin production, as certain drugs may suppress erythropoietic activity and exacerbate the impairment of oxygen transport function in the blood.
4. In patients with CHF, anemia, and hypoerythropoietinemia without iron deficiency, treatment with methoxy polyethylene glycol-epoetin beta (MPG-EPO beta) at a dose of 0.60 mcg/kg (50 IU) subcutaneously once a month for six months is recommended. The treatment regimen should be individualized based on the patient's current hemoglobin level. Notably,

combined therapy with MPG-EPO beta in CHF patients with anemia is not associated with the development of iron deficiency.

5. In patients with CHF who have anemia and iron deficiency in the presence of normal or elevated erythropoietin levels (normo- or hypererythropoietinemia), intravenous administration of iron (III) polysaccharide complex is recommended. The preparation should be administered at a dose of 200 mg intravenously twice a week for five weeks, which helps replenish iron stores and improve erythropoiesis.
6. For patients with CHF and anemia who present with both iron deficiency and reduced erythropoietin production (hypoerythropoietinemia), a combined therapeutic approach is advisable. It is recommended to administer MPG-EPO beta at 0.60 mcg/kg (50 IU) subcutaneously once a month for 6 months (with dose adjustments based on hemoglobin levels), in combination with intravenous iron (III) polysaccharide complex at 200 mg twice weekly for 5 weeks.

LIST OF SCIENTIFIC WORKS PUBLISHED ON THE TOPIC OF THE DISSERTATION

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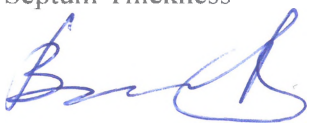
List of Abbreviations

ACEI – Angiotensin-Converting Enzyme Inhibitors
ACD – Anemia of Chronic Disease
AH – Arterial Hypertension
ARB – Angiotensin II Receptor Blockers
BB – Beta-Blockers
BP – Blood Pressure
CVD – Cardiovascular Diseases
CO – Cardiac Output
DM – Diabetes Mellitus
ECHO – Echocardiography
EPO – Erythropoietin
ESC – European Society of Cardiology
FC – Functional Class
GFR – Glomerular Filtration Rate
Hb – Hemoglobin
Ht – Hematocrit
HR – Heart Rate
IDA – Iron Deficiency Anemia
IL – Interleukin
IVRT – Isovolumic Relaxation Time
LA – Left Atrium
LVEF – Left Ventricular Ejection Fraction
LV – Left Ventricle
LVM – Left Ventricular Mass
ME-B – Methoxypolyethylene Glycol-Epoetin Beta
NTproBNP – N-terminal Pro–Brain Natriuretic Peptide
PC– plasma cytokines
PWLV – Posterior Wall Thickness of LV
RAAS – Renin-Angiotensin-Aldosterone System
RV – Right Ventricle
SNS – Sympathetic Nervous System
SV – Stroke Volume
TPR – Total Peripheral Resistance
TNF-alpha – Tumor Necrosis Factor Alpha

ST –Saturation of transferrin
Va (A peak) – Late Diastolic Filling Velocity
Ve (E peak) – Early Diastolic Filling Velocity
Ve/Va – Ratio of Early to Late Diastolic Filling Velocities
6MWT – Six-Minute Walk Test
CHF – Chronic Heart Failure
PW – Posterior Wall Thickness
IVS – Interventricular Septum Thickness



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