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MODERN ASPECTS OF IRON DEFICIENCY IN CHRONIC HEART FAILURE

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Abstract
The constant growth and development of the medical industry cannot prevent the continuous growth of patients with (CHF). The high morbidity and mortality from CHF has not been eliminated even today, despite the existence of countless drugs; guidelines and recommendations for the guaranteed and optimal use of upgrades, which are based on the principles of evidence-based medicine [1,6,11]. Globally industrialized countries have their own analytical epidemiological data of CHF 0.37-2.49% in the general population, among patients older than 65 years, the frequency of CHF exceeds 3.66-13.85%. Western European countries and the USA provided the following data on the prevalence of CHF in the population: 0.18-0.56 %, an indicator that doubles annually [2,6,41]. The research data of the EPOCH-CHF (epidemiological Examination of patients with CHF in real practice) indicate the frequency of CHF with functional classes I-IV (FC) according to the classification of the New York Heart Association (NYHA) in the Russian Federation 10.87% in women and 6.49% in men (on average 8.97%) [3.39-41].

Keywords: chronic heart failure, chronic kidney disease, anemia of chronic disease/diseases, iron deficiency, erythropoietin, iron deficiency anemia.

Introduction

The effect of anemia on the prognosis in patients with CHF. Data from various studies suggest that Hb concentration and hematocrit index (Ht) are predictors of survival in patients with CHF [5,8,11,12,20]. ACD increases the risk of mortality and repeated hospitalizations in acute CHF and CHF in the presence of left ventricular (LV) dysfunction [4-8]; and also increases the risk of death from 19.67% to 49.95%.

In LV systolic dysfunction, a direct relationship is also found [10,12,15]. In these curves, the dependence of mortality on Hb concentration does not show a clear linear dependent relationship. But the risk of death significantly increases at the lowest Hb values [12,16,21]. Val-HeFT studies have established the same risk ratio in the upper two quartiles with Hb 13.75-14.76 g/dl and > 14.74 g/dl, whereas an increased risk of death was noted in quartiles < 39.89-49.87 g/l) leads to the development of congestive HF [28.30]. Non - hemodynamic mechanisms include: stimulation of erythropoiesis; increased release of oxygen from oxyhemoglobin. Renal hypoxia resulting from ACD leads to an increase in the production of erythropoietin (EPO) by the cells of the juxtaglomerular apparatus, which subsequently stimulates the bone marrow [22,30]; further, the reaction to hypoxia directly stimulates blood stem cells [27,33]. As a result of anemia, the concentration of 2,3-diphosphoglycerate in erythrocytes increases, which increases the return of oxygen to tissues (a shift of the curve to the right, dissociated by oxyhemoglobin), this is partially compensated by a decrease in oxygen blood capacity. EPO is synthesized by peritubular fibroblasts, which are located in the cortical and cerebral layers of the kidneys [31,36]. Low partial pressure of oxygen leads to stimulation of the production of a hypoxia-inducing factor-1 of peritubular fibroblasts, causing transcription of the EPO gene. The kidneys are very sensitive to hypoxia, which reduces renal blood flow and glomerular filtration rate (GFR). With CHF, renal blood flow decreases [34] and kidney dysfunction is often observed [7,28]. Although structural changes in the kidneys, which could lead to a decrease in EPO production, do not develop as often.

Thus, by reducing renal blood flow, you can achieve: stimulate tubulointerstitial cells and EPO hyperproduction. Indeed, the data of a number of authors indicate an increase in the level of EPO and the severity of HF, respectively [32,36]. Further in a vicious circle, the duration of stimulation of tubulointerstitial cells leads to depletion, and leads to a decrease in the production of EPO. ACD in CHF acts as a consequence of relative resistance to EPO (the level of EPO is twofold:normal or elevated) under conditions of oxygen deficiency (hypoxia) and cytokine expression increase.

Predictors of anemia in CHF. One of the leading causes of anemia in CHF, together with neurohormonal factors and proinflammatory cytokines, which lead to the development of ACD; as a consequence of iron deficiency (J), reduced EPO production and suppressed bone marrow function, it is hypototic that renal dysfunction makes a certain contribution to the development of the latter. The study of patients with anemia in 20.97% of cases consisted of persons with J, in 7.96% — with a deficiency of various hematopoietic factors (vitamin B12 and folic acid inclusive), in 12.93% — other identified causes of anemia (CRF is also included in them), in 57.91% of cases, no specific causes of anemia were identified in patients. And the latter are designated as ACD [27,39]. It is necessary to emphasize the fact that in patients with CHF, absolute or relative J is accompanied both in the presence of CRF and without it. Although reduced kidney function is associated with a developed EPO deficiency found in CKD.

There are important causes of anemia in patients with CHF:

–Activation of renin-angiotensin-aldosterone systems (RAAS). With CHF, a decrease in oxygen partial pressure (PO2); slowing of renal blood flow; increased angiotensin II (AT II); and increased sodium reabsorption in the renal tubules of the proximal order, which is directly related to the activation of RAAS, stimulating the production of EPO. The response to peripheral vasodilation and decreased blood pressure, which develops due to tissue hypoxia, increases the tone of the sympathetic nervous system compensatorily, and renal blood flow worsens [29,40]. Angiotensin converting enzyme (ACE) inhibitors and AT II receptor antagonists (ARA) represent the gold standard in the treatment of CHF, lead to a

decrease in EPO secretion [17,40-41] and also have the ability to increase the degree of the natural hematopoietic inhibitor AsSDKP [38,41]. In connection with the above, when using ACE inhibitors, EPO is required at higher doses.

–Pro-inflammatory cytokines, namely tumor necrosis factor alpha (TNFa), the expression of all cytokines increases with CHF and CKD, contribute to a decrease in erythropoiesis and resistance to EPO [39,41]. TNFa, interleukin 6 (IL-6), including pro-inflammatory cytokines [19,40], CRP in quantitative ratio increases with CHF [24,35], inhibiting the production of EPO- reduces the level of Hb, respectively [18,23]. All these pro-inflammatory cytokines inhibit the proliferation of cells that are precursors of a number of erythroids [36,41]. IL-6 is considered a stimulant producing acute-phase hepcidin protein in the liver. Hepcidin blocks the absorption of iron in the small intestine, and at the same time the transport of iron in macrophages, enterocytes. [21,45]. The close relationship of TNF and Hb levels in patients with CHF was demonstrated, this confirms a significant association of anemia in individuals with CHF with an immune-inflammatory degree [21,37]. Thus, in ACD, a change in the inflammatory status is considered an influential component [39,40].

– Iron deficiency or iron deficiency state [5,18]

– Hemodilution is the cause of a decrease in Hb in patients with 49.98% of cases with a pronounced reduced contractility of the heart [21,35]. True anemia was diagnosed in only 50% of patients, others had hemodilution, which were proven by labeled I3II albumin. Both hemodilution and true anemia are associated with a poor prognosis, but hemodilution worsens the survival rate [21,27,38].

–Malabsorption — in this process, absorption through the intestinal mucosa is disrupted against the background of chronic hypoxia. In total, in a small number of patients with CHF, there is a deficiency of B12 and folic acid levels directly related to malabsorption [37-39].

– Kidney dysfunction with advanced proteinuria.

–The use of medications included in the standard therapy of patients with CHF, including: ACE, ARA and acetylsalicylic acid (ASA).

–Concomitant diseases: Diabetes mellitus (DM).

When analyzing the NHANES III (National Health And Nutrition Examination Survey III) studies, the risk of developing ACD in patients with DM and CRF was 2 times higher compared to patients at the identical stage of CRF without DM [34,41]. The prevalence of J in CHF in studies by various authors varies from 4.97% to 20.66%, which is most likely due to the use of diagnostic criteria and insufficient examinations to clarify the characteristics of anemia (i.e., the saturation of transferrin dissolving transferrin or ferritin receptors is determined) [9,14,39,41]. It was detected in 42.90% of patients with J (serum iron level < 7.95 mmol/l or ferritin < 29.95 mg/L), ACD was diagnosed in only 6.3% of patients [23,34]. Inversely proportional to this, iron with a low content in the bone marrow was diagnosed in 72.85% with normal values of serum iron, ferritin and EPO. But in this case, the average volume of the erythrocyte is at the level of the normal lower limits of the norm, i.e. microcytic anemia has not been diagnosed in any patient. The latter is caused by the release of iron from the bone marrow into other depots of the reticuloendothelial system (RES), here iron is unavailable for erythropoiesis with normal or elevated serum iron and ferritin, and this is characteristic of ACD [29,33]. 148 patients with a stable course of CHF were studied, anemia was detected in 42.67% [5,19], but at the same time J was observed in 4.97% of patients; 24.58% have anemia due to CRF, 4.97% — B12 and folate deficiency anemia, 5.95% — beta-thalassemia, 59.47% are designated as ACD, which is due to activation of

proinflammatory cytokines, a decrease in EPO production, and/or errors in the use of iron, although its content is sufficient in the reticular-endothelial system [21,33]. Thus, ACD is the most common form of anemia in CHF.

KRAS syndrom. Anemia is a frequent comorbid condition in patients with CHF and CRF. It is known that anemia of any etiology causes congestive CHF, associated with reduced LV contractility and renal function. This process allows you to combine the combination of anemia, CHF and CPN with a BEAUTIFUL term that attracts the attention of medical communities and organizations. Publications of clinical and experimental data have confirmed a close relationship between anemia, CRF and congestive HF. In this situation, they aggravate the course of each other, thus creating a “vicious circle" of the disease progressing. In published studies, among 12065 patients hospitalized in Canada for the period from 1993 to 2001, decompensated CHF, anemia was detected in 16.97%; patients with CKD prevailed among patients with ACD [28.39]. A study was conducted that studied patients undergoing hemodialysis, a decrease in Hb levels by 1 g/dl led to an increased risk of LV dilation by 41.95%, the development of HF by 17.85% and mortality by 13.85% [38.41]. Multivariate analysis showed that a reduced Hb level by 1 g/dl in patients with a transplanted kidney increased the risk of congestive HF by 23.87% [34].

Treatment of anemia. It is possible to reduce the risk of cardiovascular complications (CVD) and mortality after correction of ACD. However, the current standard of therapy for patients with CHF does not recommend ACD therapy, i.e. recommendations for correcting anemia in HF. Their confirmation of a significant improvement in the quality of life of patients with CHF when taking EPO drugs was found in numerous studies: the progression of renal dysfunction slows down [24,39], association with HF and even improves renal function and cardiac activity – slightly increased ejection fraction (EF), decreased LVH, and the frequency of angina attacks; questions about the safety of therapy ACD remained unresolved. At the present time, the method of ACD therapy is available. Blood transfusion, as a method of correcting Hb, of historical interest, is used in post-hemorrhagic conditions, although this is associated with an increased risk and indicates a temporary effect, as a result of which it is not recommended as an effective prolonged treatment[38,40]. The commonly used classes of drugs currently used in the treatment of anemia are considered to be iron preparations: per os and intravenous (IV); EPO preparations, including their combination. The value of the CRS syndrome was first evaluated and confirmed in randomized trials [40.41], the lower the level of Hb indicators, the higher the Cr indicator. It is necessary to note the effect of epoetin alfa and intravenous iron preparation, which significantly improves LV LV, FC according to NYHA, the functional ability of the body and kidney condition, reduces the need for vitamin D and the number of hospitalizations - repeated, which are associated with decompensation of CHF.

Discussion

In the modern world, the development of medicine requires the use of new terms in order to designate and indicate the essence of the whole pathophysiological chain cascade. In this connection, anemia is determined to be a predictor of chronic heart failure (CHF). In recent scientific papers, this anemia is called anemia of chronic disease (ACD) .The latter, in turn, affects the course and prognosis of both the underlying pathology and complications, in particular CHF. There are a huge number of links that affect anemia in CHF. But the leading link is still absolute or relative erythropoietin deficiency, which are

caused by: the effect of proinflammatory cytokines, endothelial and renal dysfunction. A lot of randomized controlled trials (RCTs) have been carried out, which proved that when correcting even moderate anemia in CHF, the prognosis improves. I.e., tolerance to stress (physical, emotional) increases; the functional class of CHF according to NYHA decreases, the quality of life improves, structural and functional indicators (qualitative and quantitative) of the heart; the need for diuretic drugs decreases; and the number of hospitalizations. But no study indicates the nature and effect of correcting anemia on the following indicators: long-term survival of patients; hemoglobin level.

Epidemiological features of anemia in CHF. Polymorbidity or multimorbidity, due to a combination of pathologies with ACD, contribute to the progression and complication of the course of CHF. That is why, by identifying and developing the therapeutic principles of anemia in a timely manner, we will be able to solve the problems that are considered relevant at the moment.

The RCT of the prevalence of anemia varies due to the diversity of its diagnostic criteria and the heterogeneity of the populations covered [3-4,8]. Accordingly, the prevalence varies from 3.97% to 60.86% of cases [7]. Using WHO recommendations for the diagnosis of anemia, a reduced hemoglobin (Hb) level < 13 g/dl in men; and < 12 g/dl in women was taken as a basis [6,8]. In this regard, anemia was diagnosed in 48.97% of patients with severe CHF [9,12]. ANCHOR data (Anemia in Chronic Heart Failure Outcomes and Resource Utilization) indicate the spread of anemia in CHF in 41.89% of cases [7.10]. While no newly detected ACD was established in 9.64% in the data of studies of SOLVD (Studies Of Left Ventricular Dysfunction) [11]; in 16.91% of patients in Val-HeFT (Vasodilator-Heart Failure) [12] and in 14.28% of patients in COMET (CarvedilolOrMetoprolol European Trial) [13]. Similar statistical data on the prevalence of anemia were established in the authors' studies, taking into account the preserved and reduced LV function [11-14,17]. According to which, risk groups for the development of ACD have been identified. The incidence of ACD increases in women with a combination of multimorbid conditions: chronic kidney disease (CKD) and diabetes mellitus (DM) [5,7]. It is in them that anemia spreads in 30.6-61.8%, in outpatient patients in the absence of multimorbidity, anemia is common in patients in 4.7-22.8% [3.7]. Patients with ACD have much more severe FC CHF according to NYHA; high creatinine (Cr), and vice versa low body mass index (BMI). Also, these patients have poor exercise tolerance (FN); low quality of life (QOL); high need for diuretics (D); increased content of pro-inflammatory cytokines; C-reactive protein (CRP) [15,19-22,27].

Conclusion

Anemia, being a frequent concomitant pathology in patients with CHF, is associated with a worse long-term prognosis. Despite the fact that the cause of anemia in CHF is not completely clear, undoubtedly a role in its development belongs to renal dysfunction, neurohormonal shifts and the expression of proinflammatory cytokines. A certain number of large studies have conducted the treatment of anemia with recombinant EPO, together with intravenous administration of iron iron preparation in patients with CHF. The results obtained were favorable. Despite this, the level of Hb, which requires correction of anemia and its target values; not harmful to patients with CHF, require further research. The urgency of the problem regarding safety is due to an increase in the number of patients with CHF, high frequency indicators, kidney dysfunction associated with this pathology and an increased risk of CVD in the treatment of ACD: EPO drugs of this contingent of patients, as well as a progressive cancer process in patients receiving chemotherapy. European recommendations in the therapy of anemia in CHF have

established the importance of correcting it in CHF. Also, among the potentially necessary methods, therapy with EPO drugs, together with iron preparations, is considered [12,41].

References

1. McMurray JJ, Steward J. Epidemiolodgy, aetiolodgy, and prognosis of heart failure. Heart 2000; 83: 596-602.
2. Rickenbacher P. Herzinsuffizienz: Epidemiologie, Patophysiologie. Swiss Med Forum 2001; 1/2: 4-9.
3. Арутюнов Г. П., Кафарская Л. И., Савелов Н. А и др. Хроническая сердечная недостаточность: структурные и микробиологические изменения в толстой кишке. Тер архив 2007; 2: 31-7.
4. Komajda M. Prevalence of anemia in patients with chronic heart failure and their clinical characteristics. J Card Fail 2004; 10: S1-4.
5. Anand IS. Pathogenesis of anemia in cardiorenal disease. Rev Cardiovasc Med 2005;
6(Suppl 3): S13-21. 6. Tang Y-D, Katz SD. The prevalence of anemia in chronic heart failure and its impact on clinical outcomes. Heart Fail Rev 2008; 13: 387-92.
7. Tang Y-D, Katz SD. Anemia in chronic heart failure: prevalence, etiologie, clinical correlates, and treatment optiones. Circulation 2006; 113: 2454-61.
8. Dallman PR. Iron Nutrition in Health and Disease. Eastleigh, UK: John Libbey & Co., 1996.
9. Felker GM, Gattis WA, Leimberger JD, et al. Usefulness of anemia as a predictor of death and rehospitalizacion in patients with decompensated heart failure. Am J Cardiol 2003; 92: 625-8.
10. Go AS, Yang J, Ackerson LM, et al. Hemoglobin level, chronic kidney disease, and the risks of death and hospitalizacion in adults with chronic heart failure. Circulation 2006; 113: 2713-23.
11. Ishani A, Weinhandl E, Zhao Z, et al. Angiotensin-converting enzyme inhibitor as a risk factor for the development of anemia, and the impact of incident anemia on mortality in patients with left ventricular dysfunction. JACC 2005; 45: 391-9.
12. Anand IS, Kuskowski MA, Rector TS, et al. Anemia and change in hemoglobin over time related to mortality and morbidity in patients with chronic heart failure: results from Val-HeFT. Circulation 2005; 112: 1121-7.
13. Komajda M, Anker SD, Charlesworth A, et al. The impact of new onset anaemia on morbidity and mortality in chronic heart failure: results from COMET. Eur Heart J 2006; 27: 1440-6.
14. Nair D, Shlipak MG, Angeja B, et al. Association of anemia with diastolic dysfunction among patients with coronary artery disease in the Heart and Soul Study. Am J Cardiol 2005; 95: 332-6. 15. Felker GM, Shaw LK, Stough WG, O'Connor CM. Anemia in patients with heart failure and preserved systolic function. Am Heart J 2006; 151: 457-62.
16. Berry C, Norrie J, Hogg K, et al. The prevalence, nature, and importance of hematologic abnormalities in heart failure. Am Heart J 2006; 151: 1313-21.
17. O'Meara E, Clayton T, McEntegart MB, et al. Clinical correlates and consequences of anemia in a broad spectrum of patients with heart failure: results of the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) Program. Circulation 2006; 113: 986-94.
18. Anand IS, Rector T, Deswal A, et al. Relationship between proinflammatory cytokines and anemia in heart failure. Eur Heart J 2006; 27 (Suppl 1): 485.

19. Opasich C, Cazzola M, Scelsi L, et al. Blunted erythropoietin production and defective iron supply for erythropoiesis as major causes of anaemia in patients with chronic heart failure. Eur Heart J 2005; 26: 2232-7.
20. Anand I, McMurray JJ, Whitmore J, et al. Anemia and its relationship to clinical outcome in heart failure. Circulation 2004; 110: 149-54.
21. Al-Ahmad A, Rand WM, Manjunath G, et al. Reduced kidney function and anemia as risk factors for mortality in patients with left ventricular dysfunction. JACC 2001; 38: 955-62.
22. Horwich TB, Fonarow GC, Hamilton MA, et al. Anemia is associated with worse symptoms, greater impairment in functional capacity and a significant increase in mortality in patients with advanced heart failure. JACC 2002; 39: 1780-6.
23. Ghali JK, Anand IS, Abraham WT, et al. Randomized doubleblind trial of darbepoetin alfa in patients with symptomatic heart failure and anemia. Circulation 2008; 117: 526-35.
24. Sharma R, Francis DP, Pitt B, et al. Haemoglobin predicts survival in patients with chronic heart failure: a substudy of the ELITE II trial. Eur Heart J 2004; 25: 1021-8.
25. Datta BN, Silver MD. Cardiomegaly in chronic anemia in rats and man experimental study including ultrastructural, histometric, and stereologic observations. Lab Invest 1975; 32: 503-14. 26. Olivetti G, Quaini F, Lagrasta C et al. Myocyte cellular hypertrophy and hyperplasia contribute to ventricular wall remodeling in anemia- induced cardiac hypertrophy in rats. Am J Pathol 1992; 141: 227-39.
27. Levin A. The treatment of anemia in chronic kidney disease understandings in 2006. Curr Opin Nephrol Hypertens 2007; 16: 267-71.
28. Collins AJ. The hemoglobin link to adverse outcomes. Adv Stud Med 2003; 3: S194-7.
29. National Kidney Foundation. K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification. Am J Kidney Dis 2002; 39(Suppl.1): S17-31.
30. Metivier F, Marchais SJ, Guerin AP, et al. Pathophysiology of anaemia: focus on the heart and blood vessels. Nephrol. Dial Transplant 2000; 15(Suppl. 3): 14-8.
31. Физиология человека. Под ред. Р. Шмидта и Г. Тевса. В 3 томах. М.: Мир 1996; 2: 313 с. 32. Takenaga K, Fukuma N, Seino Y, Takano T. A 69-year-old woman with congestive heart failure caused by myocardial ischemia and severe anemia. J Cardiology 2000; 36(3): 197-9.
33. Davie NJ, Crossno JT, Frid MG, et al. Hypoxia-induced pulmonary artery adventitial remodeling and neovascularization: potential contribution of circulating progenitor cells (R1). Am J Physiol Lung Cell Mol Physiology 2003; [E pub a head of print].
34. Bauer C, Kurtz A. Oxygen sensing in the kidney and its relation to erythropoietin production. Annu Rev Physiol 1989; 51: 845-56.
35. Anand IS, Ferrari R, Kalra GS, et al. Edema of cardiac origin. Studies of body water and sodium, renal function, hemodynamic indexes, and plasma hormones in untreated congestive cardiac failure. Circulation 1989; 80: 299-305.
36. McClellan WM, Flanders WD, Langston RD, et al. Anemia and renal insufficiency are independent risk factors for death among patients with congestive heart failure admitted to community hospitals: a population-based study. J Am Soc Nephrol 2002;13:1928-36.
37. Volpe M, Tritto C, Testa U et al. Blood levels of erythropoietin in congestive heart failure and correlation with clinical, hemodynamic, and hormonal profiles. Am J Cardiol 1994; 74: 468-73. 38. van

der Meer P, Voors AA, Lipsic E, et al. Prognostic value of plasma erythropoietin on mortality in patients with chronic heart failure. JACC 2004; 44: 63-7.

39. Ezekowitz JA, McAlister FA, Armstrong PW. Anemia is common in heart failure and is associated with poor outcomes: insights from a cohort of 12,065 patients with new-onset heart failure. Circulation 2003; 107: 223-5.

40. Mrug M, Stopka T, Julian BA, et al. Angiotensin II stimulates proliferation of normal early erythroid progenitors. J Clin Invest 1997; 100: 2310-4.

41. Albitar S, Genin R, Fen-Chong M, et al. High dose enalapril impairs the response to erythropoietin treatment in haemodialysis patients. Nephrol Dial Transplant 1998; 13: 1206-10. 42. van der Meer P, Lipsic E, Westenbrink BD, et al. Levels of hematopoiesis inhibitor N-acetyl-seryl-aspartyl-lysyl-proline partially explain the occurrence of anemia in heart failure. Circulation 2005; 112: 1743-7.