REVIEW ARTICLE

Anemia in heart failure

Should we supplement iron in patients with chronic heart failure?

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KEY WORDS

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ABSTRACT

Anemia has been identified as an independent prognostic factor of both morbidity and mortality for patients with congestive heart failure (CHF). The association between anemia and adverse outcomes has raised the hypothesis that anemia correction might lead to an improvement in the prognosis of patients with CHF. Nevertheless, data from large randomized trials about the effect of anemia correction on patient outcome are still lacking. Numerous clinical studies, randomized and nonrandomized, have evaluated the efficacy of erythropoietin or iron supplementation for treating anemia in patients with CHF, and their effect on patient symptoms and functional status. The superiority of any of these approaches has not been established yet. This review will discuss different treatment options for anemic patients with CHF, with emphasis on the correction of iron deficiency.

Introduction Epidemiological data confirm a discouraging perspective for the impact of congestive heart failure (CHF) on patient morbidity and mortality, as well as health care costs.[1] In addition to optimal management of the heart failure (HF) syndrome, there is a clear need for prevention and modification of all comorbidities that could possibly improve the prognosis. Anemia is a potentially treatable comorbidity with severe prognostic implications.

Prevalence and significance of anemia in congestive heart failure The prevalence of anemia ranges from 10% to >50%, depending on the population studied, the severity of HF and the diagnostic criteria used.[2-11] Patients in the New York Heart Association (NYHA) functional class IV, refractory to medical treatment, are more likely to be anemic. The prevalence of anemia in this patient group approaches 80%, while the reported prevalence in patients in the NYHA functional class I or II was less than 10%.[12]

Population aging, the intensification of treatment with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), and the simultaneous increase in the prevalence of renal failure could account for the continuous rise in the prevalence of anemia in CHF.[4,13]

Several studies have documented that the presence or development of anemia is correlated with increased mortality and morbidity and with higher hospitalization rates, irrespectively of age, gender, diabetes, and the NYHA functional class.[5,6,14] Within the range from 25 to 37, each 1% decrease in hematocrit is associated with an 11% higher risk of death.[6] Interestingly, in Val-HeFT (Valsartan Heart Failure Trial),[15] increased risk of death was found not only in lower hemoglobin (Hb) percentiles but in the upper ones as well, suggesting a U-shaped relationship.

Severe anemia results in the activation of the sympathetic and renin-angiotensin systems, similarly to CHF, potentially leading to exacerbation of these maladaptive responses.[16-19] Whether this is the case with less severe anemia remains unclear. Anemia is more common in patients with renal failure. The risk of death in anemic patients with CHF and chronic kidney disease (CKD) is increased compared with anemic patients with normal renal function.[20,13,9]

Despite all the compelling evidence about the association of anemia with prognosis in HF, whether anemia is just a marker of the severity of disease or directly affects prognosis and adverse outcomes has not been clarified yet.

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Anemia etiology in congestive heart failure The etiology of anemia in HF is multifactorial. Hematinic deficiencies,[21] reduced iron uptake, poor nutrition, use of acetylsalicylic acid and oral anticoagulation, malabsorption and cardiac cachexia,[22] iron entrapment in the reticuloendothelial system, blockage of duodenal absorption and prevention of iron release from body stores,[23-26] chronic renal function impairment,[27-29] water retention,[30,31] ACE inhibitors and ARBs[32-34] contribute to the development of anemia in CHF patients. We measured the iron content in the bone marrow aspirates of 37 anemic patients suffering from end-stage HF.[35] Iron deficiency anemia was documented by this rigorous method in 27 patients (73%), 2 patients (5.4%) had dilutional anemia, and 1 patient (2.7%) had drug-induced anemia. No specific cause was found in 7 patients (18.9%), who were considered to have "anemia of chronic disease".

In the majority of these patients, a clear cause of iron deficiency (such as gastrointestinal blood loss) was not identified. Chronic inflammation can lead to inefficient iron handling and entrapment in the reticuloendothelial system.[25] As a result, less iron is available for hematopoiesis. Therefore, although iron deficiency may represent a key pathophysiologic mechanism for anemia development in HF, chronic disease seems to be the underlying cause even in the majority of those cases. Irrespective of specific etiology, iron deficiency represents a potentially important therapeutic target.

Treatment options Since anemia is an independent risk factor for adverse outcomes in HF, it is reasonable to assume that correction of anemia should improve the prognosis of patients. However, this has not been proved in adequately powered trials yet.

Several studies, both randomized and nonrandomized, have implemented different treatment strategies and investigated the impact of anemia correction on the functional status of patients with CHF. The treatment strategies are: 1) erythropoietin-stimulating agents (ESA), 2) iron supplementation, and 3) both of them.

Erythropoietin-stimulating agents Erythropoietin (EPO) is produced by the kidney in response to hypoxia. It stimulates the bone marrow, promotes survival and proliferation of erythroid precursor cells and inhibits their apoptosis, thus increasing the production of erythrocytes. In addition, EPO has a cardioprotective role, independently of its erythropoietic action.[36,37] EPO is considered the treatment of choice for anemia of chronic disease.[25] Therefore, it appears to be a promising agent for the treatment of anemia in HF.

In small-scale trials, both randomized and nonrandomized, anemia correction with ESA resulted in the improvement in the NYHA class, significant increase of ejection fraction, marked fall in the doses of oral and intravenous diuretics used, significant reduction in the hospitalization rate, improvement in the quality of life in the Minnesota Living with Heart Failure Questionnaire score, increase in peak oxygen consumption (peak $V0_2$), and improvement in plasma B-type natriuretic peptide (BNP) levels and renal function.[38-42]

However, less favorable results have also been reported. Only a trend for symptomatic improvement and fewer hospitalizations was observed in a study of patients with symptomatic CHF and anemia treated with darbepoetin-α (STAMINA-HeFT [Study of Anemia in Heart Failure-Heart Failure Trial]).[43] Darbepoetin-α treatment did not significantly improve exercise duration, NYHA class, or the quality of life score compared with placebo. A nonsignificant trend towards a lower risk of all-cause mortality was also observed.[43] In another study, patients receiving darbepoetin-α compared with placebo had an improvement in the self-reported Patient Global Assessment of Change score but no differences in the Kansas City Cardiomyopathy and Minnessota Living with Heart Failure Questionnaire scores. A trend towards increased exercise time was observed but no change in peak $V0_2$.[44] Van Velduishen et al.[45] demonstrated no statistically significant improvement in a 6-minute walking distance test, Patient Global Assessment, NYHA class, ejection fraction, and Minnessota Living with Heart Failure Questionnaire scores in the group of patients treated with darbepoetin-α, compared with placebo. In the same study, 6 of the 110 patients in the darbepoetin-α group died, although these deaths were not considered as related to the treatment.

In the STAMINA-HeFT study[43] (darbepoetin-α vs. placebo), adverse events were similar in both groups. Nevertheless, one should always take into account the potential adverse effects of EPO, namely an increase in blood pressure (possibly via increased viscosity and reduced nitric oxide availability), increase in vascular cytosolic calcium, anti-fibrinolytic activity that could lead to vascular thrombosis, seizures, and increase in endothelial activation.[16,18,19,46-48] In addition, the optimal dose regimen of EPO for HF patients has not been standardized.

The studies suggesting that treatment of anemia with ESA might lower morbidity in HF are limited by small sample sizes. The potential benefits of this intervention need to be reevaluated in larger, adequately selected group of patients, in powered, randomized studies. The large-scale RED-HF™ trial (Reduction of Events with Darbepoetin Alfa in Heart Failure) that will enroll 3400 patients in 60 countries[49] is designed to evaluate the effect of darbepoetin-α on mortality and morbidity in patients with CHF and anemia.

Iron supplementation alone Since iron deficiency has been recognized as a significant cause of anemia in CHF, it is reasonable to assume that iron supplementation alone would be an effective therapeutic alternative for correction of anemia. In

one of our studies,[35] iron deficiency, confirmed by bone marrow aspiration, was identified as the most common cause of anemia in end-stage CHF patients.

In a prospective, open-label, noncontrolled study, Bolger et al.[50] demonstrated that intravenous iron was a simple, safe, and effective therapy that increased Hb, improved exercise capacity, and reduced symptoms in 16 anemic patients with CHF.

Similarly, in a single-blinded randomized controlled study by Okonko et al.,[51] which enrolled 35 patients with CHF and anemia, intravenous iron resulted in an increase in exercise tolerance (peak VO_2), paralleled by the improvement of symptoms and amelioration of patients' functional state.

In a placebo-controlled study that involved 40 HF patients, renal failure, and anemia, Toblli et al.[52] reported that intravenous iron treatment resulted in an increase in ejection fraction, decrease in NYHA class, improvement of renal function and of plasma N-terminal proBNP levels, reduction of hospitalizations, increase of exercise tolerance, and improvement of the Minnessota Living with Heart Failure Questionnaire scores.

FAIR-HF (Ferinject® Assessment in Patients With IRon Deficiency and Chronic Heart Failure)[53] was a randomized, placebo-controlled study of intravenous iron supplementation in 459 patients with iron deficiency, with and without anemia. Intravenous administration of ferric carboxymaltose improved the Patient's Global Assessment, NYHA class, and 6-minute walking test distance, with no difference in the magnitude of the improvement between anemic and nonanemic patients. There were no differences in the outcomes between the treatment groups, although these were not the primary endpoints of the trial.

It is important to emphasize that the criteria for the diagnosis of iron deficiency anemia differed considerably between all the above studies.

In Bolger's study,[50] patients were required to have Hb ≤12 g/dl and iron deficiency was defined as ferritin ≤400 ng/ml. Benefits from iron supplementation in the Patient's Global Assessment, Minnessota Living with Heart Failure Questionnaire scores, and a 6-minute walking test had a linear correlation with Hb changes. Patients with a greater response were those with more severely depleted iron stores. Patients with gastrointestinal disease did not have lower iron, ferritin, or transferrin saturation values and demonstrated a similar response to intravenous iron supplementation compared to respective patients without gastrointestinal pathology.[50]

In the Ferric-HF (Ferric Iron Sucrose in Heart Failure) trial, Okonko et al.[51] used different criteria to determine iron deficiency. Patients with Hb <12.5 g/dl (anemic group) or 12.5 to 14.5 g/dl (nonanemic group) were enrolled, and iron deficiency was defined as ferritin <100 ng/ml or 100 to 300 ng/ml with transferrin saturation (TSAT) <20%. In this way, Okonko et al.[51] introduced the concept of iron deficiency without anemia. Again, improvement in all endpoints was more obvious in the anemic group of patients.

Toblli et al.[52] defined iron deficiency as ferritin <100 ng/ml and/or TSAT ≤20%, while anemia was defined as the serum value of Hb <12.5 g/dl for men and <11.5 g/dl for women.

FAIR-HF enrolled 459 patients, both anemic and nonanemic (Hb: 9.5–13.5 g/dl) with iron deficiency defined as ferritin <100 ng/ml or ferritin between 100 and 300 ng/ml with TSAT <20%. Interestingly, in this study, the degree of improvement in all endpoints was similar in both anemic and nonanemic patients, suggesting that iron deficiency might represent a significant comorbidity in CHF, even without anemia. These findings strengthen the assumption that either absolute or relative iron deficiency (entrapment of iron in the reticuloendothelial system, blockage of duodenal absorption, prevention of iron release from body stores as seen in anemia of chronic disease) is common in HF. This could lead to an alternative therapeutic approach in HF patients, where iron administration will be the first line of treatment and ESA will have a role when a compensatory increased rate of hematopoiesis is needed.

In the FAIR-HF trial, 83% of the patients enrolled were in the NYHA class III, suggesting that the results of this study may be applied mainly to patients with more severe CHF. The number of NYHA II patients was too small for meaningful statistical comparisons. It is not known whether the favorable results of iron supplementation can be expected in less severely sick populations.

A large, multicenter, randomized study (IRON-HF) is currently underway and is expected to provide further evidence concerning the efficacy and safety of iron supplementation in CHF. In this trial, anemic CHF patients with low TSAT, low iron levels, and low to moderately elevated ferritin levels will receive either iron intravenously, once weekly for 5 weeks, or iron orally 3 times weekly for 8 weeks or placebo. Maximal exercise capacity at 3 months will be the primary endpoint of the study.[54]

Erythropoietin-stimulating agents in conjunction with iron supplementation In one of our studies, 25 consecutive patients with end-stage CHF and iron deficiency anemia, documented by bone marrow aspiration, were randomized to treatment either with the combination of subcutaneous darbepoetin-α and intravenous iron once weekly or with intravenous iron alone once weekly.[55] There were no adverse events related to the study drug administration. A significant rise in the Hb values was noted, starting as early as 2 weeks after treatment initiation, at a similar rate in both groups. It was clear that both the time course and the degree of anemia correction did not differ between the 2 groups, suggesting that in this patient population the combination of darbepoetin with iron does not confer additional benefits compared with iron alone.

Discussion It still remains unclear whether increasing Hb values improves the long-term prognosis of anemic patients with CHF. The potential benefits from ESA or iron administration on rates of hospitalization, functional capacity, and HF symptoms have been addressed in several small-scale studies. However, clear indications about treatment initiation and optimal regimen (ESA, iron, or both) currently do not exist.

The follow-up period after anemia correction should be long enough to allow any positive effect on the heart to be exerted and be clinically detected. Hb and hematocrit values should be maintained within the normal range during follow-up. We should keep in mind that pharmaceutical agents, interventions such as revascularization and device therapies need a period of 3 to 6 months to induce reverse remodeling and affect the outcomes.[56-58] The effectiveness of iron supplementation therapy should be evaluated at least after a follow-up period of similar duration, after anemia correction.

At this stage, it is reasonable to assume that severely symptomatic CHF patients or severely anemic patients with HF are suitable candidates for anemia correction. If the decision to start treatment is made, the applied regimen should be the most appropriate for adequate, but also rapid and safe correction of anemia.

Based on the assumption that iron deficiency (either absolute or relative) is frequently present in CHF patients, iron supplementation alone is an attractive option. In CKD, even when it is not clear which of the above-mentioned conditions predominates, weekly intravenous iron administrations are recommended, up to 8 to 10 doses.[59] If there is no erythropoetic response, an inflammatory blockage of iron availability is the most likely underlying mechanism of iron deficiency, and, in this case, coadministration of ESA may be tried. Parenteral iron administration in all relevant studies in CHF populations was proved safe, since no serious adverse events were reported. Nevertheless, parenteral iron therapy can be associated with hypersensitivity reactions and systemic adverse effects. Iron has been found to promote the formation of reacting oxygen species, inhibit host defenses, and serve as an essential nutrient for tumor cell growth.[60] Whether anemia correction could be also achieved by oral administration of iron still remains unclear. A number of studies have documented the failure of oral iron supplements to maintain adequate iron stores in EPO-treated hemodialysis patients,[61] suggesting that oral administration of iron might fail to establish a positive iron balance, although a small percentage of hemodialysis patients have been reported to respond favorably to oral iron administration.[59] However, HF patients might be different from CKD patients, and the option of oral iron supplementation should be further investigated. The identification of oral iron administration responders among the HF population would be of significant clinical interest.

Iron is an essential element present in a variety of molecular systems, playing an important role not only in oxygen transport and storage but also in cell growth and proliferation.[61] It was therefore reasonable to hypothesize that iron deficiency without anemia could be a legitimate target for treatment. In the experimental studies, iron deficiency was related to diastolic HF, left ventricular hypertrophy and dilation, fibrosis and cellular dysfunction.[62-63] Silverberg[4] reported that thrombocytosis enhanced by iron deficiency can lead to thrombosis, atherosclerosis, and increased mortality. Several studies have demonstrated protective effects of intravenous iron supplementation in EPO-treated CKD patients via reduction of platelet counts,[64] whereas iron depletion in this setting was associated with increased mortality.[65]

Until evidence-based indications from the large-scale randomized trials become available, treatment should be based on an etiological approach. Although the underlying pathophysiology seems to be that of anemia in chronic disease, thorough diagnostic evaluation should be performed in order to identify other mechanisms of anemia and appropriate treatment should be applied. Taking into consideration the above studies, one could consider a therapeutic approach for HF-related anemia where iron administration alone is the first-line treatment, and the combination with ESA is reserved for cases with inadequate response or when increased erythropoetic rate is needed, as in coexisting renal failure. Clearly, more clinical studies are needed, carefully designed with a sufficiently long follow-up period after anemia correction and including HF patients in lower NYHA classes, where the potential benefit from treating anemia, or iron deficiency without anemia, is still not known.

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ARTYKUŁ POGLĄDOWY

Niedokrwistość w niewydolności serca

Czy powinniśmy stosować suplementację żelaza u chorych z przewlekłą niewydolnością serca?

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SŁOWA KLUCZOWE

anemia, erytropoetyna, niedobór żelaza, zastoinowa niewydolność serca

STRESZCZENIE

Niedokrwistość jest niezależnym czynnikiem rokowniczym powikłań i zgonu u chorych z zastoinową niewydolnością serca (ZNS). Związek niedokrwistości z niekorzystnym przebiegiem choroby stał się podstawą hipotezy, że leczenie niedokrwistości może poprawić rokowanie u chorych z ZNS. Wciąż jednak nie ma danych z dużych badań z randomizacją na temat wpływu leczenia niedokrwistości na losy kliniczne tych chorych. W wielu badaniach klinicznych, z randomizacją i bez, oceniano skuteczność erytropoetyny lub suplementacji żelaza w leczeniu niedokrwistości u chorych z ZNS oraz wpływ na dolegliwości i stan czynnościowy chorych. Dotychczas nie wykazano wyższości żadnej z tych metod. W tym artykule przeglądowym omawiamy różne opcje terapeutyczne dla chorych z niedokrwistością i ZNS, ze szczególnym uwzględnieniem korekcji niedoboru żelaza.

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