EDITORIAL

# Anemia and Iron Deficiency — New Therapeutic Targets in Heart Failure?

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Anemia ranges in prevalence from below 10% among patients with mild heart failure symptoms to over 40% for patients with advanced disease.[1] Its prevalence is similar among patients who have systolic dysfunction and among patients who have heart failure with preserved systolic function.[2,3] Anemia has been associated with older age, diabetes mellitus, chronic renal dysfunction, more advanced heart failure symptoms, lower peak exercise capacity, and worse health-related quality-of-life metrics.[3] Anemia has also been shown to be a powerful predictor of rehospitalization rates and survival in chronic heart failure.

A complex interaction between impaired cardiac performance, activation of neurohormonal and inflammatory responses, renal dysfunction, drug effects, and bone marrow hyporesponsiveness appears to contribute to the development of anemia.[4,5] In a minority of cases, the cause of anemia may be dilutional rather than a true decrease in red-cell mass. The erythropoietin level is typically increased in proportion to the severity of heart failure but to a lesser degree than expected for the severity of anemia, suggesting blunted erythropoietin production. Levels of circulating proinflammatory cytokines (e.g., tumor necrosis factor $\alpha$ [TNF-$\alpha$], interleukin-1, interleukin-6, and C-reactive protein) are inversely related to the hemoglobin level.[1] Interleukin-6 and TNF-$\alpha$ inhibit renal erythropoietin production by activating the GATA binding protein GATA2 and nuclear factor-$\kappa$B and also inhibit proliferation of bone marrow erythroid progenitor cells.[1] Interleukin-6 stimulates the production of hepcidin in the liver, which blocks duodenal iron absorption and down-regulates the expression of ferroprotein, which in turn prevents the release of iron from total body stores.[4]

Iron deficiency is another potential cause of anemia, as poor nutrition is often present in association with heart failure and may curtail the absorption of dietary iron. Gastrointestinal malabsorption, long-term aspirin use, and uremic gastritis may also precipitate iron-deficiency anemia. The prevalence of iron deficiency has been reported to range from 5 to 21%.[1]

Since anemia is closely associated with poor clinical outcomes, it seems logical to consider whether correcting anemia may improve functional capacity and survival. Iron is essential not only for erythropoiesis but also for several bioenergetic processes in skeletal muscle. Chronic iron deficiency may, by itself, reduce exercise capacity and cause ultrastructural alterations in cardiomyocytes.[6] It has therefore been postulated that iron supplementation may be beneficial in patients who have iron deficiency and heart failure regardless of whether anemia is present. Two small, placebo-controlled trials of intravenous iron therapy in patients with heart failure have been reported previously. In the first, 40 patients with anemia received treatment with intravenous iron or saline infusion for 5 weeks. In the intravenous-iron group as compared with the saline-infusion group, the mean hemoglobin level increased by 1.4 g per deciliter, and there was a significant improvement in the Minnesota Living with Heart Failure score, decreased levels of C-reactive protein and N-terminal pro–brain natriuretic peptide, and an increased left ventricular ejection fraction and distance on the 6-minute walk test.[7] In the FERRIC-HF (Ferric Iron Sucrose in Heart Failure) trial (ClinicalTrials.gov number,

NCT00125996), 35 patients with iron deficiency received intravenous iron, aimed at improving the ferritin level, or saline infusion.[8] Intravenous-iron loading decreased the New York Heart Association (NYHA) functional class and improved the patient's global assessment score. The peak oxygen uptake rose significantly in patients who had anemia but not in patients who did not have anemia.

The FAIR-HF (Ferinject Assessment in Patients with Iron Deficiency and Chronic Heart Failure) trial, reported on by Anker and colleagues in this issue of the *Journal*,[9] is a multicenter trial that evaluated the efficacy of intravenous-iron infusion on symptoms and submaximal exercise capacity in a cohort of patients with mild or moderate heart failure due to left ventricular systolic dysfunction (NCT00520780). The trial enrolled 459 patients with NYHA functional class II or III symptoms, a depressed left ventricular ejection fraction, and documented iron deficiency. According to a randomized, placebo-controlled design, patients were assigned to receive 200 mg of intravenous iron or infused saline weekly until their iron stores were replete. Then, intravenous iron or placebo infusions were continued every 4 weeks up to week 24. The primary end points were the self-reported Patient Global Assessment and the NYHA functional class at week 24. Secondary end points included the distance on the 6-minute walk test and health-related quality-of-life validated surveys at weeks 4, 12, and 24.

The two groups of patients were well matched regarding the baseline characteristics: overall, 82% had NYHA class III symptoms; the mean left ventricular ejection fraction was 32%; the mean serum ferritin level was 52 $\mu$g per liter in the ferric carboxymaltose group and 60 $\mu$g per liter in the placebo group; and 50% of patients had anemia. Ferric carboxymaltose therapy rapidly increased ferritin levels to be within the normal range; a modest increase in the serum hemoglobin level was seen in patients who had anemia (mean [±SE] increase, 9.1±2.2 g per liter; $P<0.001$) but not in patients who did not have anemia. The administration of intravenous iron, as compared with placebo, convincingly improved the self-reported Patient Global Assessment (odds ratio, 2.5) and the NYHA functional class (odds ratio, 2.4). For the self-reported Patient Global Assessment, 50% of the treated patients reported that they were much or moderately improved, as compared with only 28% of the control patients. The degree of improvement in both end points was similar in patients with anemia and those without anemia. Furthermore, significant improvement in the secondary end points, including an increase of more than 30 m in the 6-minute walk distance, was also observed. There was also a nonsignificant trend toward fewer hospitalizations for cardiovascular reasons (hazard ratio, 0.53; 95% confidence interval, 0.25 to 1.09; $P=0.08$).

Like any well-done clinical trial, this study has several limitations and raises a number of unanswered questions. First, the dropout rate was higher than might be expected for a relatively short-term trial (8.6% of patients assigned to receive the active treatment and 12.9% of those assigned to receive placebo). Second, the trial's primary end points, particularly the NYHA class, were relatively subjective and less convincing than physiological variables such as submaximal or maximal exercise capacity. Furthermore, the number of patients with mild symptoms (NYHA class II) was too small to show a statistical benefit. Whether ferric carboxymaltose therapy is useful in patients with mild or advanced heart failure symptoms remains unknown. Why patients with anemia did not have a greater symptomatic benefit than patients without anemia also remains puzzling. Whether oral iron replacement might provide a similar benefit at a lesser expense remains unknown. Finally, whether correction of iron deficiency can favorably improve the long-term release of biomarkers and proinflammatory cytokines, improve ventricular remodeling, decrease hospitalizations for heart failure, and improve survival will require additional study.

Nonetheless, this trial suggests a new avenue for therapeutic exploration. Improvement in the quality of life is increasingly important to patients with heart failure, and the approach taken in this study may have merit in patients with moderately symptomatic heart failure and documented iron deficiency. Additional controlled trials will help to better select the patients most likely to benefit, clarify the optimal route and duration of iron replacement, and provide insight into possible mechanisms of the benefit.

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