Iron Repletion in Heart Failure Patients

Donald Silverberg, Adrian Iaina, Dov Wexler, Doron Schwartz

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There is increasing interest in the role of iron deficiency in causing or worsening congestive heart failure (CHF). A potential role for iron deficiency in playing a causal role in CHF is suggested by the fact that iron deficiency is common in CHF with or without anemia. In a recent study of 546 patients with stable systolic heart failure, if iron deficiency was defined as ferritin <100 μg/L, or as ferritin 100 to 300 μg/L and percent transferrin saturation of <20%, it was found in 37% of CHF patients; 32% did not have anemia, and 57% did have anemia (anemia defined as a hemoglobin [Hb] level of <12 g/dL in women and <13 g/dL in men).1 Iron deficiency was more prevalent in women, in those with more advanced CHF as measured by New York Heart Association class, those with higher N-terminal pro β-type natriuretic peptide levels (a sign of more severe CHF), and those with higher C-reactive protein levels (a sign of increased inflammation). After a mean duration of 731 days, in multivariable models, iron deficiency, but not anemia, was related to increased risk of death or heart transplantation, the adjusted hazard ratio being 1.58 (P<0.01).

In a study of anemic CHF patients, approximately half had serum iron levels below normal, and the great majority also had elevated soluble transferrin receptor (a dependable measure of iron deficiency).2 In another study of anemia in severe CHF, markedly reduced iron stores in the bone marrow were found in 73% of the cases.2,3 Thus, absolute iron deficiency (defined as a serum ferritin <100 μg/L and % transferrin saturation <20%) or functional iron deficiency (defined as a serum ferritin ≥100 μg/L and percentage transferrin saturation <20%) are commonly seen in CHF patients with anemia or even without anemia.

Iron is indispensable for life, serving as a metal cofactor for many enzymes, either nonheme iron-containing proteins or hemoproteins. Hemoproteins are involved in many crucial biological functions, including oxygen binding (hemoglobins), oxygen metabolism (oxidases, peroxidase, catalases, etc), and electron transfer (cytochromes). Many nonheme iron-containing proteins catalyze key reactions involved in energy metabolism and DNA synthesis. In addition, iron-containing proteins are required for the metabolism of collagen, tyrosine, and catecholamines.4 However, Naito et al5 found that iron deficiency in Dahl salt-sensitive rats improved survival, prevented hypertension, CHF, vascular hypertrophy, left ventricular hypertrophy, and proteinuria, inhibited oxidative stress, fibrosis, and inflammation, and maintained the molecular signaling pathway. In contrast, a previous study in Sprague-Dawley rats by the same group found just the opposite, that iron deficiency actually caused diastolic dysfunction and heart failure with pulmonary congestion, left ventricular hypertrophy and dilation, cardiac fibrosis, reduction in erythropoietin levels, worsening of the molecular signaling pathways (as measured by cardiac STAT3 phosphorylation), and an increase in the inflammatory cytokine tumor necrosis factor-α and proteinuria.6 The reason for the discrepancy in the results of the 2 studies is not clear but is probably related to the different types of rats used. In another recent animal study, iron deficiency in rat hearts caused mitochondrial ultrastructural aberrations, irregular sarcomere organization, and release of cytochrome C.7 Thus, the effects of iron deficiency in different animal models are contradictory.

There are many causes of iron deficiency in CHF,8 including reduced iron intake due to anorexia, or gastrointestinal blood loss caused by gastrointestinal bleeding from diaphragmatic hernias, ulcers, gastritis, tumors, platelet inhibitors, and anticoagulants. It has also been found that proton pump inhibitors such as omeprazole, which are widely used, also reduce iron absorption. In addition, CHF can cause intestinal cell dysfunction with reduced iron absorption because of bowel edema and other factors. Erythropoietin (EPO) and its derivatives use up iron to form Hb, and this can cause iron deficiency. Elevated cytokines can also cause abnormalities in EPO and iron metabolism (Figure 1). These are elaborated in CHF, especially tumor necrosis factor-α and interleukin-6. They can cause 4 hematologic abnormalities:8 (1) reduced EPO production in the kidney, leading to inappropriately low levels in the blood for the degree of anemia present; (2) bone marrow damage leading to reduced erythropoietic response of the bone marrow to EPO; (3) increased hepcidin secretion from the liver, which can cause failure of iron absorption from the gut; as well as (4) hepcidin-induced trapping of iron in iron stores in the macrophages and hepatocytes. The latter 2 result in reduced iron levels in the blood, and therefore reduced iron supply to the bone marrow and rest of the body.

Correction of the iron deficiency in men with intravenous (IV) iron alone in several studies seems to improve the CHF, independent of whether anemia is present.8 Six studies where IV iron was used in iron-deficient CHF patients have been performed,8 but only 2 were placebo-controlled, double-blind studies.9,10 In 1 of these 2 studies, a small, single-center study,9 40 patients received either IV iron as iron sucrose (Venofer, Vifor Int Zurich) at 200 mg a week for 5 weeks, or a placebo infusion. At 6-month follow-up, there was significant improvement in the treated compared with the control...
group in Hb levels, New York Heart Association class, left ventricular ejection fraction, 6-minute walk test, hospitalization rate, Minnesota Living with Heart Failure Questionnaire quality of life score, creatinine clearance, C-reactive protein, and N-terminal pro B-type natriuretic peptide, as well as slowing of heart rate and lower diuretic requirements.

In the other double-blind, placebo-controlled study, a large, multicenter study (FAIR-HF study\(^8\)), patients were randomly assigned to several doses of IV ferric carboxymaltose (Vifor Int Zurich) versus matching placebo control. A total of 459 subjects with chronic left ventricular systolic dysfunction were studied for 26 weeks. The use of IV iron was associated with significant improvements in Hb, New York Heart Association functional class, 6-minute walk distance, the patient global assessment scale, Kansas City quality of life scale, and renal function only in the treated group. In subgroup analysis, the magnitude of the treatment effect did not differ in subjects with or without anemia (defined as a Hb ≤12 g/dL). The treatment effects on patient global assessment scale and New York Heart Association were also not related to age, presence of diabetes, or even to the initial severity of the CHF, renal function, or serum ferritin levels. The fact that improvement was similar in the treated group in both anemic and nonanemic groups suggests that part of the effect of the IV iron was because of its direct effect on body tissues irrespective of hemoglobin.

These studies suggest that the iron deficiency of many CHF patients can be improved by IV iron. Conversely, in another controlled study of anemia treatment in CHF,\(^3\) the use of oral iron in anemic CHF patients for 1 year was not associated with any increase in Hb or improvement in any CHF parameters. Clearly, a large mortality-driven, placebo-controlled study is needed to confirm the effects of IV iron in CHF.

In patients with CHF and iron deficiency who do not reach the target Hb (usually about 11 to 12 g/dL),\(^8\) after correction of the iron deficiency with IV iron, and in whom other causes of anemia have been ruled out, then EPO or its derivatives should be started. The use of EPO or its derivatives along with oral or IV iron has shown promising results in CHF but await confirmation in long-term controlled studies. The prior correction of iron deficiency will allow for lower doses of EPO to be used, cause a more rapid increase in Hb than if EPO were used alone, increase the chances of attaining the target Hb, reduce the price of anemia treatment compared with use of EPO without previous correction of the iron deficiency, and will help prevent the vascular complications that have been associated with high-dose EPO therapy.\(^8\)

**Conclusion**

There is growing evidence that iron deficiency is common in heart failure and may be an important contributor to worsening of the condition. Its correction with IV iron in several studies appeared to improve the anemia, as well as cardiac, renal, and patient function (Figure 2). If further studies bear this out, this treatment could be an important new addition to the therapy of heart failure.

**Disclosures**

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**References**


