Iron Repletion in Heart Failure Patients

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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 $<100 \mu g/L$, or as ferritin 100 to 300 $\mu g/L$ 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). 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 $\beta$-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 majority also had elevated soluble transferrin receptor (a dependable measure of iron deficiency). In another study of anemia in severe CHF, markedly reduced iron stores in the bone marrow were found in 73% of the cases.

Thus, absolute iron deficiency (defined as a serum ferritin $<100 \mu g/L$ and percent transferrin saturation $<20\%$) or functional iron deficiency (defined as a serum ferritin $\geq 100 \mu g/L$ 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. However, Naito et al 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-$\alpha$ and proteinuria. 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. Thus, the effects of iron deficiency in different animal models are contradictory.

There are many causes of iron deficiency in CHF, 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-$\alpha$ and interleukin-6. They can cause 4 hematologic abnormalities: (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. Six studies where IV iron was used in iron-deficient CHF patients have been performed, but only 2 were placebo-controlled, double-blind studies. In 1 of these 2 studies, a small, single-center study, 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 β-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)\(^{10}\), 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 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**

D.Si. has received honoraria from Amgen and Vifor International for lectures.

**References**

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