

Iron deficiency and congestive heart failure

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Iron deficiency is a common and sometimes overlooked factor in patients with congestive heart failure (CHF), and is associated with a poor prognosis. Research indicates that testing CHF patients for iron deficiency, and supplementing with iron when appropriate, could increase functional capacity, improve quality of life, decrease the number of CHF-related hospitalizations, and possibly decrease mortality.

Iron is a component of hemoglobin, which delivers oxygen to the tissues. In addition, iron is a cofactor for the enzyme cytochrome oxidase, which plays a role in mitochondrial ATP production via the electron-transport chain. ATP is essential for the pumping action of the heart; therefore, iron deficiency could exacerbate heart failure whether or not the patient is anemic. Patients with CHF are prone to iron deficiency for a number of reasons. CHF may be associated with poor appetite, which can lead to multiple nutritional deficiencies. In addition, gastric acid plays a role in iron absorption, and a large proportion of CHF patients have hypochlorhydria,¹ either due to their age and their disease, or to the use of proton pump inhibitors or other acid-blocking drugs. Many patients with CHF also have bowel wall edema (secondary to the backup of fluid from the heart), which can impair nutrient absorption. Moreover, some patients with CHF have impaired delivery of iron to their metabolically active cells, even though their iron stores are normal or even increased. This is known as functional iron deficiency (as opposed to absolute iron deficiency).

Patients with CHF are considered to have absolute iron deficiency if their serum ferritin level is below 100 µg/L. This cut-off level is well above that used to diagnose iron deficiency in healthy individuals. The higher value takes into account the fact that CHF is associated with chronic inflammation, and that serum ferritin levels rise in response to inflammation. CHF patients are thought to have functional (as opposed to absolute) iron deficiency if their serum ferritin level is between 100 and 300 µg/L (which is frequently seen in patients with chronic inflammatory diseases) and their transferrin saturation is below 20%. Blood tests for iron deficiency are not as reliable as bone marrow biopsy, but the blood tests are generally preferred in clinical practice because they are noninvasive.

In a prospective cohort study of 1,506 patients with chronic CHF, 753 patients had absolute or functional iron deficiency according to the above definition. During a median follow-up period of 1.92 years, 29.2% of the patients died. Iron deficiency was a strong predictor of mortality ($p = 0.001$). In multivariable analysis, iron deficiency (but not anemia) remained a strong and independent predictor of mortality (hazard ratio = 1.42; $p = 0.002$).² Similar findings were reported in another study.³

In a double-blind trial,⁴ 459 patients with chronic CHF (New York Heart Association [NYHA] class II or III), a left ventricular ejection fraction (LVEF) of 40% or less for NYHA class II, or 45% or less for NYHA class III, and iron deficiency as defined above were randomly assigned to receive intravenous iron (200 mg per dose, as ferric carboxymaltose) or placebo (saline). The total iron dose required for repletion was calculated at baseline, according to Ganzoni's formula.⁵ The dosing frequency was weekly until iron repletion was achieved and then every 4 weeks (starting at week 8 or week 12, depending on the time required for repletion). At baseline, in the group that received iron, the mean serum ferritin level was 53 µg/L and the mean transferrin saturation was 17.7%. At 24 weeks, the proportion of patients who reported being much or moderately improved was significantly higher in the iron group

than in the placebo group (50% vs. 28%; $p < 0.001$). At 24 weeks, the proportion of patients in NYHA class I or II was significantly higher in the iron group than in the placebo group (47% vs. 30%; $p < 0.001$). Significant improvements were seen in the iron group compared with the placebo group for distance walked in 6 minutes and health-related quality of life. The beneficial effect of iron was similar in patients with and without anemia. The death rate was nonsignificantly lower by 38% in the iron group than in the placebo group. No serious side effects were seen.

In another double-blind trial, 304 patients with CHF and iron deficiency according to the above definition were randomly assigned to receive intravenous iron (as ferric carboxymaltose) or placebo (saline) over a 52-week period. Iron was given in dosages based on body weight and initial hemoglobin levels, with the aim of correcting iron deficiency and subsequently maintaining iron sufficiency. Compared with placebo, iron supplementation resulted in sustained improvement in functional capacity, symptoms, and quality of life; these differences were statistically significant from week 24 until the end of the study. The frequency of hospitalization for worsening heart failure was significantly lower by 61% ($p < 0.01$) and the death rate was nonsignificantly lower by 14% in the iron group than in the placebo group.⁶

The clinical trials discussed above used intravenous iron, because oral iron preparations are sometimes poorly absorbed and frequently cause gastrointestinal side effects. In contrast, intravenous iron is generally well tolerated, although anaphylactic reactions have occurred on rare occasions. However, intravenous iron is substantially more expensive than oral supplements, and is also not widely available in some places. Oral iron does improve iron status in CHF patients, but it may not be as effective as intravenous therapy. A retrospective study was conducted on 105 patients with CHF and iron deficiency (as defined above) who had received oral iron at a mean daily dose of 130 mg (range, 65-150 mg). After a median treatment period of 164 days, the median value for serum ferritin increased from 39 $\mu\text{g/L}$ to 75 $\mu\text{g/L}$, transferrin saturation increased from 10% to 21%, and hemoglobin increased from 10.4 g/dl to 11.6 g/dl ($p < 0.0001$ for all). When compared with the changes in CHF patients who received intravenous iron in one of the trials cited above, the increases in transferrin saturation were similar, but the increases in ferritin levels were markedly greater with intravenous iron (mean for oral iron: 40 $\mu\text{g/L}$ at baseline, increased to 72 $\mu\text{g/L}$; mean for intravenous iron: 53 $\mu\text{g/L}$ at baseline, increased to 312 $\mu\text{g/L}$).⁷

Iron supplementation of non-deficient patients is not risk-free. Because it is a pro-oxidant, iron may increase oxidative stress, which could exacerbate various chronic illnesses. In addition, iron overload can impair blood glucose control. However, when administered according to the laboratory guidelines described in this article, patients with CHF could benefit greatly, with minimal risk of serious side effects.

¹ Furbetta D, et al. Behavior of hydrochloric acid secretion in cardiopathies. *JAMA*. 1951;146:1615.

² Klip IT, et al. Iron deficiency in chronic heart failure: An international pooled analysis. *Am Heart J*. 2013;165:575-582.e3.

³ Jankowska EA, et al. Iron deficiency: an ominous sign in patients with systolic chronic heart failure. *Eur Heart J*. 2010;31:1872-1880.

⁴ Anker SD, et al. Ferric carboxymaltose in patients with heart failure and iron deficiency. *N Engl J Med*. 2009;361:2436-2448.

⁵ http://www.al-nasir.com/www/PharmCalc/mob_exec_calc.php?ID=ganzoni

⁶ Ponikowski P, et al. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency. *Eur Heart J.* 2015;36:657-668.

⁷ Niehaus ED, et al. Repletion of iron stores with the use of oral iron supplementation in patients with systolic heart failure. *J Card Fail.* 2015;21:694-697.