Intravenous Iron Therapy in Heart Failure

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KEYWORDS

• Anemia • Intravenous (IV) iron • Iron deficiency • Heart failure • Peak oxygen consumption
• Ferrous carboxymaltose

KEY POINTS

- Iron deficiency is prevalent in heart failure and a marker of worse outcomes with respect to mortality, hospitalization, and quality of life.
- Repletion of iron with intravenous formulations, particularly ferrous carboxymaltose, has shown significant improvements in quality of life and rate of hospitalization in recent clinical trials.
- Repletion of iron with oral formulations has not resulted in significant improvements in outcomes, likely related to concerns with iron absorption in the gut.

INTRODUCTION

Anemia has long been acknowledged as a common comorbidity in patients with heart failure (HF) with reduced ejection fraction. There have been a number of studies that have shown that anemia is an independent predictor of mortality in patients with HF,[1–4] and anemia has been associated with reduced exercise capacity[5,6] and worse New York Heart Association (NYHA) class.[7] In addition, there is evidence that iron deficiency alone is related to poor functional capacity in patients with HF.[8] In particular, iron deficiency is more prevalent in the more advanced stages of HF (NYHA classes III and IV), in women, and in patients with higher levels of proinflammatory markers.

Recently, iron deficiency anemia has been evaluated as a potential target for therapeutic intervention in HF, with some notable results. Intravenous iron infusions have been found to significantly reduce HF hospitalizations and symptom burden in patients with HF in multiple recent studies. This article will focus on the evaluation and management of iron deficiency anemia, particularly in reference to management with intravenous (IV) iron repletion.

ANEMIA AND IRON DEFICIENCY IN HEART FAILURE

The World Health Organization defines anemia as a hemoglobin less than 13.0 g/dL in male individuals and hemoglobin less than 12.0 g/dL in nonpregnant female individuals, and is usually either due to red blood cell (RBC) destruction or inadequate RBC production. Of the multiple potential etiologies of anemia, iron deficiency is the most common in all patient groups and particularly in patients with HF.[9,10] Iron deficiency also may be present without clinical evidence of anemia.

THE PATHOPHYSIOLOGY OF IRON DEFICIENCY IN HEART FAILURE

The importance of iron in oxidative metabolism and other processes like fatty acid oxidation may explain why iron deficiency, even without anemia,

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can have consequences in the patient with HF[11,12] at the cellular level. The mitochondrial respiratory chain can be suppressed in states involving low cellular iron reserves, leading to reduced ATP production, and thus impairment in exercise capacity and increasing fatigue.[13,14]

The reduction in oxygen carrying capacity of blood reduces delivery of oxygen to organs, which, when coupled with reduced cardiac output in HF, results in a significant overall increase in relative oxygen extraction by tissues, requiring a higher cardiac output and more rapid circulatory time to keep up with demand.[15]

MECHANISMS OF IRON DEFICIENCY AND ANEMIA

The Role of Hepcidin

Regulation of iron absorption, storage, and distribution is a tightly controlled process in which hepcidin plays a central role. Hepcidin is a peptide hormone produced in the liver and released via the action of interleukin (IL)-6. It is considered the "master regulator" of systemic iron metabolism.[16] Hepcidin inhibits the protein ferroportin, which is found in the gastrointestinal tract, macrophages, and hepatocytes. Effectively, hepcidin functions to block duodenal iron absorption and recycling through the mononuclear phagocytic system,[16,17] thus inducing a "trapping" of iron within macrophages.[18] This results in decreased iron delivery to the bone marrow.

In HF, hepcidin is initially upregulated (likely related to the release of IL-6), resulting in the development of iron deficiency.[19] In the later stages of HF and with progression of disease, hepcidin is downregulated, possibly as an attempt to reverse prior iron deficiency.[19] In patients with chronic kidney disease (and in many cases cardiorenal syndrome), worsening glomerular filtration rate may also result in decreased hepcidin clearance in the kidneys,[20] further impacting iron deficiency. There is evidence that erythropoietin therapy in renal failure can suppress hepcidin levels,[20] but anemia resolves only after addition of iron therapy in iron-deficient individuals.

Diagnosing Iron Deficiency

The most well-accepted definition of iron deficiency is transferrin saturation (TSAT) <20% and ferritin less than 100 ng/mL.[18,21] Although both these indices are low in absolute iron deficiency, in states of functional iron deficiency whereby iron is sequestered within stores due to a proinflammatory state and elevated hepcidin levels, TSAT will remain low but ferritin levels may rise above 100 ng/mL.[18] This reflects "anemia of chronic disease," which occurs frequently in HF.

Therapeutic Interventions

A number of randomized clinical trials have now been performed to better define the role of iron replacement therapy in HF. Starting with the Ferinject Assessment in Patients with Iron Deficiency and Chronic Heart Failure (FAIR-HF) trial,[22] we have seen improvements in functional capacity and possibly a reduction in HF hospitalizations. FAIR-HF was the first major randomized controlled trial to evaluate the effects of IV iron (ferric carboxymaltose) in patients with chronic HF and iron deficiency, regardless of evidence of anemia. Patients were NYHA class II-III with ejection fraction (EF) $\leq$45%, and randomized 2:1 to IV iron versus placebo. By 24 weeks, significant improvements in HF symptoms using NYHA class and the Patient Global Assessment (PGA) were found in patients treated with IV iron repletion. Six-minute walk test (6MWT), Kansas City Cardiomyopathy Questionnaire (KCCQ), and European Quality of Life–Five Dimensions (EQ-5D) scores also improved. The intervention showed benefit on "softer" endpoints, but more convincing evidence with regard to hospitalization and survival was needed.

In 2015, the CONFIRM-HF study[24] assessed the use of ferric carboxymaltose on the functional status of patients with EF $\leq$45% with signs/symptoms of HF (**Table 1** for inclusion/exclusion criteria). The primary endpoint of 6MWT was significantly improved, but importantly, this study showed a decrease in hospitalizations related to worsening HF in patients treated with IV iron versus placebo (**Fig. 1**). Although this was not a prespecified endpoint of the study, this result was notable. Serum ferritin, TSAT, and hemoglobin levels increased significantly (P<.001) between the groups by week 24, and there was a persistent effect up to week 52, without an increase in adverse events. This finding further extended the known effect of IV iron therapy up to 12 months with an objective measure of patient functionality using the 6MWT. In addition, subgroup analyses showed significant improvements specifically in patients with renal dysfunction and diabetes, with a larger treatment effect observed than most in these populations. This benefit deserves further study.

To further assess the effect of IV iron (ferric carboxymaltose [FCM]) on exercise capacity in patients with symptomatic chronic HF and iron deficiency, the EFFECT-HF[25] trial was undertaken. The investigators used cardiopulmonary stress testing as an objective measure of exercise