REVIEW

Iron Deficiency in Patients With Congestive Heart Failure

Maria Stampa, MD
Department of Cardiology, Evagelismos Hospital, Athens, Greece

A large percentage of patients with chronic heart failure (HF) have anemia, defined as hemoglobin (Hb) of <12 g/dl, hovering around 30% in non-hospitalized HF patients and about 50% of hospitalized patients.[1,2] The presence of anemia is an independent risk factor, associated with increased rates of mortality, HF hospitalization and morbidity. The cause of anemia in HF is multifactorial with 63.8% of patients having at least two factors that cause anemia. Chronic kidney insufficiency, iron deficiency, vitamin B12 deficiency, hemodilution, chronic diseases, and cachexia are the most common causes.[3]

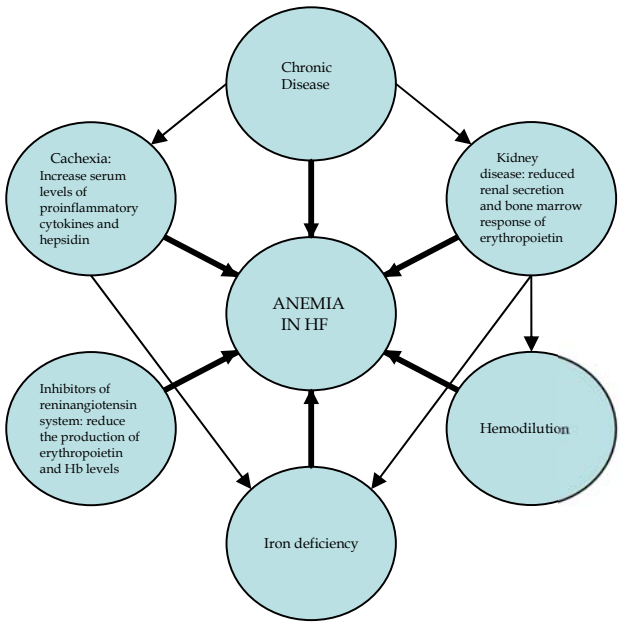

FIGURE 1. CAUSES OF ANEMIA IN HEART FAILURE

Iron deficiency with or without anemia is common in patients with HF, relates to disease severity, and is a strong and independent predictor of outcome.[4] Iron deficiency is defined as a ferritin level < 100µg/L or ferritin level 100-299 µg/L with a transferrin saturation < 20%.[4] Anemic patients were more often iron deficient than non anemic patients. There are two types of iron deficiency, the absolute and the functional iron deficiency (Fig. 2).

In absolute iron deficiency there is a reduction in transferrin saturation (%TSat) and in serum ferritin and this is associated with reduced total body iron stores often related to iron mechanisms and erythropoesis.[5,6]

FIG 2

ABSOLUTE	FUNCTIONAL
Serum ferritin < 100 ng/Dl TSat < 20%	Abnormality of supply & demand Serum ferritin normal or ↑ TSat < 20%
• Poor dietary iron intake • Reduced GI absorption, duodenal transport or food absorption • Drug interaction • GI blood loss • Menorrhagia	• Poor iron stores nonresponding to demand of erythropoiesis • Chronic inflammation process blocking the use of stored iron

Commonest causes comprise low dietary iron, poor gastrointestinal (GI) absorption, impaired GI absorption and GI blood loss, drug interaction (e.g. omeprazole), reduced absorption of food and menorrhagia . In functional iron deficiency, %TSat is reduced but serum ferritin is normal or elevated and body stores are normal or elevated. This reflects insufficient iron supply to meet the requirement despite normal or abundant body iron stores, because iron is trapped inside the cells of the reticulo-endothelial system and is not disposable for cellular metabolism.[5,6] It is believed to be mainly caused by proinflammatory activation which causes hepsidin overproduction.[7] One study conducted by Nanas et al. used the criterion of bone marrow iron staining to determine the prevalence of iron deficiency in patients with HF. They found that 73% of patients with advanced HF and anemia had depleted iron stores. [8] Iron plays a key role in oxygen uptake, transport, and storage, in the oxidative metabolism of the skeletal muscle and erythropoiesis. If we consider anemia of chronic HF as anemia of chronic disease, then there will be increased uptake and retention of iron in the cells of the reticuloendothelial system. This is achieved by the expression of divalent metal transporter 1 (DMT 1), which is up-regulated by cytokines. Divalent metal transporter 1 mediates iron transport into the intestinal mucosal cells and into the activated macrophages, but the export of iron from these cells is inhibited by down-regulation of the expression of ferroportin by means of an increase in hepsidin. Hepsidin is a peptide synthesized by the liver in response to an increase in transferrin saturation, microbial infection, or inflammation. [14-16] This protein also inhibits iron absorption from the gut, and hepsidin levels seem to reflect iron load and response to erythropoietin (EPO) rather than inflammation and EPO resistance. Thus, this implies normal or increased ferritin with low serum iron, low transferrin, low transferrin saturation and thus poor availability of iron in the bone marrow. In a recent study of 546 patients, iron deficiency (absolute or

functional) was found in 37% of patients, but not anemia; it was related to an increased risk of death or heart transplantation, reinforcing its importance as an independent predictor of unfavorable outcome.

Iron deficiency is an emerging problem in chronic HF, associated with disease severity; higher New York Heart Association (NYHA) functional class and higher NT-proBNP level, lower mean corpuscular volume levels, decreased renal function, decreased exercise capacity (shorter distance covered during the 6-minute walking test, lower peak-oxygen consumption during cardiopulmonary exercise testing), and lower quality of life. [4] Iron deficiency causes dysfunction of myocardium and skeletal muscles because these organs have high energy demands, and their function is depending on intact iron metabolism. As already mentioned, iron deficiency is a strong and independent predictor of outcome and its correction is very important for improvement of cardiac function and functional capacity, to help prevent the progression of renal failure, markedly reduce hospitalization and diuretic doses, and improve self-assessed quality of life. [9] Therefore, it is important to study the iron metabolism of patients with chronic HF, whether iron deficiency is absolute or functional, and start treatment with intravenous (IV) iron. On the other hand, one might think that oral iron could possibly achieve similar results but the answer for the oral use is most likely negative for a variety of reasons. Absorption of oral iron preparations in the anemia of chronic disease is blocked by hepsidin,[12] these preparations are not well tolerated, mostly due to GI side effects, and drug interactions may occur, such as with proton pump inhibitors.[13]

The effect of iron on the heart may by related not only to improved oxygenation owing to increased Hb, but also directly to its effects on the mitochondrial and other cellular elements that require iron, and not necessarily related to the correction of the anemia per se. [10] Seven studies refer to the result of effect of IV iron supplementation in patients with chronic HF. Two of these include both anemic and non-anemic patients. The first study by Bolger et al. including 16 patients with stable HF, NYHA class II-III, left ventricular ejection fraction (LVEF) of 26$\pm$13%, showed that IV iron therapy without co-administration of EPO was simple and safe, improved exercise capacity, decreased symptoms and increased Hb in anemic patients with chronic HF.[18] In the double-blind, randomized, placebo-controlled study by Toblli et al. it was shown that therapy with IV iron and without EPO in patients with chronic HF and moderate chronic renal failure, reduced plasma NT-proBNP and inflammatory markers and produced improvement in LVEF, NYHA class, exercise tolerance and renal function.[19] The Ferric Iron Sucrose in Heart Failure (FERRIC-HF) study showed that 16 weeks of IV iron therapy in anemic and non anemic HF patients with iron deficiency, improved exercise tolerance and symptoms and the benefits were more evident in non anemic patients with iron deficiency.[10] In one study by Drakos et al. the administration of IV iron with erythropoietin in HF patients with anemia and iron deficiency, measured by bone marrow aspiration, increased Hb about the same as did erythropoietin alone.[20] In the study of Usmanov et al. it was demonstrated that in patients with optimally-treated chronic HF, NYHA class III-IV, Hb<11g/dL and chronic kidney insufficiency, treatment with IV with iron for 26 weeks, produced a significant increase in Hb in anemic patients and in a large proportion improved cardiac remodeling, assessed by echocardiography, and NYHA class but not in those patients with NYHA class IV.[21] Comin-Colet et al. reported that long-term combined therapy with IV iron and EPO in elderly patients with advanced HF, mild-to-moderate renal dysfunction, and anemia, corrected Hb and creatinine levels, improved symptoms, reduced plasma NT-pro-BNP and cardiovascular hospitalizations.[22] The FAIR-HF study was a randomized double-blind placebo-controlled multicenter trial, which included the greatest number of patients. Randomized patients with reduced left ventricular ejection fraction, with or without anemia and iron deficiency, to intravenous ferric carboxymaltose, and demonstrated that iron IV in those patients with HF improves their functional status after 4 weeks and increases Hb, and that is independent of anemic status.[11]

In conclusion, iron is an important biometal and its deficiency is seen in many chronic diseases such as CHF. Correction of iron deficiency is important for those patients with or without anemia and CHF because it improves the symptoms and quality of life, and that justify more research.

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Table 1. Studies of Intravenous Iron Supplementation in Patients With Heart Failure

References	Study Design/ No of pts	Period	Criteria/Features	Treatment	Main Results
Bolger et al, 2006	Uncontrolled/ 16 pts	92±6 d	Hb<12 g/dl, mean age 68, NYHA class II-III, mean EF 26%	1 g IV iron sucrose x 12 d	↑Hb/Ferritin/TSat/MLHFQ/6MWD ↓Sx
Tobli et al, 2007	Double-blind, randomized / 40 pts	6 months	Hb<12.5 g/dl, TSat<20%, Ferritin<100 ng/ml, CrCl<ml/min, EF<35%, NYHA class II-IV	IV iron sucrose 200 mg / week x 5 weeks	↑Hb/TSat/Ferritin/CrCl/ MLHFQ /6MWD ↓NYHA class/NT-ProBNP
Okonko DO, 2008	FERRIC-HF: randomized/ 35 pts	16 weeks	Mean age 64, MVO2 14, Hb 12.5, Ferritin<100 ng/ml or ferritin 100-300 & TSat<20%	IV iron sucrose	↑Hb/TSat/Ferritin/MVO2 ↓NYHA class
Usmarov 2008	Uncontrolled / 32 pts	26 weeks	H<11 g/dl, NYHA class II-IVb	IV iron	↑Hb ↓remodeling/NYHA class
Drakos et al, 2009	Randomized / 16 pts	3 months	Iron-deficiency anemia	2 groups: IV iron / IV iron+EPO	↑Hb
Comi-Colet, 2009	Uncontrolled / 65 pts	15 months	Mean age 74, EF 34.5%, Hb 10.9, Cr 1.5, NT-proBNP 4256, NYHA III-IV	IV iron+EPO	↑Hb ↓NT-proBNP/NYHA class / mortality/ hospitalization
Anker et al, 2009	FAIR-HF, randomized / 459 pts	24 weeks	EF<40%, NYHA II, EF<45%, NYHA III, Hb 9.5-13.5g/dl, ferritin <100 µg/L or 100-299 µg/L	IV iron vs placebo	↑Hb/ferritin/%TSat/ MCV/ ↓PGA / NYHA class

CrCl = creatinine clearance; EF = (left ventricular) ejection fraction; EPO = erythropoietin; FAIR-HF = Ferinject Assessment in patients with Iron deficiency and CHF; FERRIC-HF = Ferric iron sucrose in Heart Failure; Hb = hemoglobin; IV = intravenous; MCV = mean corpuscular volume; MLHFG = Minnesota Living with Heart Failure score; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; PGA = patient global assessment; pts = patients; p VO2 = peak oxygen consumption; TSat = transferrin saturation; 6MWD = 6 minute walking distance;

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