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EDITORIAL COMMENT

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The New Iron Age?*

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"Neither did the Iron Age period end due to the lack of iron, nor will the age of hydrocarbons end due to the lack of hydrocarbons. The reason lies in the development of human civilization because new knowledge leads mankind to a higher level."

—Eraldo Banovac[1]

Iron is essential to the maintenance of the oxygen-carrying capacity of the blood and for oxygen transport, delivery, and utilization. In addition to being a key component of hemoglobin, myoglobin, and other enzymes involved in cellular respiration, oxidative phosphorylation, citric acid cycle, nitric oxide generation, and oxygen radical production, iron is necessary to maintain the structure and function of metabolically active cells, including myocytes and skeletal muscle cells.[2] As such, deficiency of iron is associated with significant impact on the structure and function of numerous organs, including the heart.

Notably, iron deficiency (ID) is present in almost 50% of patients with heart failure (HF), regardless of sex, race, anemia, and left ventricular ejection fraction (LVEF).[2] ID can be due to a decrease in total body iron (absolute ID), or to iron sequestration in the storage pool (functional ID) or both. Regardless of type, ID is associated with impaired exercise capacity and quality of life and an unfavorable prognosis independently of anemia and LVEF. In this regard, several studies have been conducted since 2006 to evaluate the effects of intravenous iron in patients with HF and reduced LVEF (heart failure with reduced ejection fraction [HFrEF]).[3] Importantly, recent studies have shown that administration of intravenous iron may be associated with clinically significant improvements in functional capacity and quality of life, with improvement in walk distance, symptoms, and health status. Recent studies have also reported a significant decrease in the risk of hospitalizations for worsening HF but no difference in all-cause mortality.[4,5]

A noteworthy aspect about recent trials of iron administration is the heterogeneity of how ID was defined: most studies defined ID according to international guidelines (ferritin <100 μg/L or a ferritin level ranging between 100 and 300 μg/L plus transferrin saturation [TSAT] <20%),[3] but ambiguity remained regarding which is the best definition of ID. This has meaningful clinical consequences, as the results of some studies suggest that iron repletion may have substantial benefits for patients with HF, improving symptoms and possibly reducing events such as hospitalization.

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In this issue of the *Journal,* Masini et al[6] investigated the effect of different ID definitions on the prognosis of 4,442 patients referred to the Hull Life-Lab clinic between 2001 and 2019. Thirty-two percent of the patients had HFrEF, 19% had HF with mid-range LVEF, 41% had HF with preserved LVEF, and 8% had HF with an N-terminal pro-B-type natriuretic peptide level ≥125 ng/L if information on LV function was unavailable. Anemia was defined as a hemoglobin level <12 g/dL in women and <13 g/dL in men. Four definitions of ID were evaluated: 1) guidelines' criteria; 2) ferritin <100 μg/L; 3) TSAT <20%; and 4)

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serum iron levels ≤13 μmol/L. In agreement with multiple previous reports, ID was present in ~50% of this large cohort of ambulatory patients with HF. A key finding of the study is that the Guideline definition of ID did not predict outcomes, and, in fact, lower serum ferritin concentrations were associated with better survival. Indeed, the highest ferritin levels were found in patients with New York Heart Association functional class III-IV symptoms, in those with the highest quintile of N-terminal pro-B-type natriuretic peptide and high-sensitivity C-reactive protein levels, anemia, and LVEF >40%. Among the other definitions of ID, those based on a TSAT <20% and serum iron level ≤13 μmol/L were independently associated with death regardless of HF phenotype. Importantly, ~30% of the patients fulfilling the Guidelines' ID criteria had a TSAT >20% and serum iron levels >13 μmol/L.

The lack of correlation between ferritin and outcomes[6] should not be surprising. Although a serum ferritin level <15 ng/mL may be specific for ID, in inflammatory states, including HF, ferritin is nonspecifically elevated as an acute-phase reactant. Therefore, the higher survival of patients with lower ferritin levels may reflect milder HF because inflammatory pathways are further up-regulated when HF evolves from a disease of the heart to a systemic illness. Also unsurprising are the findings that serum iron levels and TSAT were highly correlated with each other and independently associated with outcomes. Bone marrow iron depletion is highly specific for ID and not affected by inflammation, and its assessment is considered the gold standard for the diagnosis of true ID. Several studies have shown that, as individual variables, TSAT <20% and serum iron levels ≤13 μmol/L had the strongest correlation with decreased bone marrow iron stores. Furthermore, patients with ferritin levels <100 ng/mL but TSAT >20% did not have bone marrow ID, whereas the lowest TSAT and serum iron levels occurred in the same groups of patients with the highest ferritin values.

The data presented by Masini et al[6] confirm that true ID predicts unfavorable outcomes. These results provide important guidance to clinicians evaluating their patients with HF, in whom a TSAT <20% or serum iron level ≤13 μmol/L should be considered the most reliable approach for the detection of ID. These results also identify a path forward for further research efforts to best identify those with ID and study its treatment. Indeed, a prespecified subgroup analysis of an individual patient data meta-analysis of 4 trials compared ferric carboxymaltose versus placebo in subjects with HFrEF and ID.[7] It found a significant interaction between baseline TSAT tertiles and treatment effect on all 3 composite outcomes (cardiovascular hospitalizations and cardiovascular mortality, recurrent HF hospitalizations and cardiovascular mortality, and recurrent cardiovascular hospitalizations and all-cause mortality): the benefit of ferric carboxymaltose was significant only in the lowest TSAT tertile (<12.7%). These findings raise the key question of whether intravenous iron benefits only patients with HFrEF who have severe ID. Future trials should press forward to better understand this question.

In addition, the question of whether ID is only a marker of more severe HF or a causal factor for the progression of HF remains unanswered. As HF progresses, levels of inflammatory cytokines increase. Among these, interleukin-6 up-regulates hepatic hepcidin production via Janus kinase/signal transducer and activator of transcription 3, which result in degradation of ferroportin. This causes impairment of iron absorption into the blood from enterocytes and retention of iron in the liver and reticuloendothelial cells. Together, these effects result in relative iron depletion in erythroid and nonerythroid cells. Inflammatory cytokines also attenuate renal erythropoietin production and responsiveness of erythroblasts to this hormone. Hepcidin itself inhibits erythroblast proliferation, further decreasing hemoglobin synthesis.[2] In fact, in the study by Masini et al,[6] the highest rates of TSAT <20% and serum iron levels ≤13 μmol/L occurred in patients with anemia and in the highest quintile of high-sensitivity C-reactive protein. These facts support the notion that ID is a marker of HF severity. However, in one study, the myocardial iron content of 91 patients with HF was lower than that detected in the myocardium of 38 organ donors with normal cardiac function and correlated with decreased activity of citric acid cycle enzymes, and of enzymes protective against the detrimental effects of reactive oxygen species, as well as with reduced mitochondrial oxygen consumption.[8] These metabolic abnormalities favor glucose over fatty acid utilization and, in combination with increased reactive oxygen species, may themselves increase myocardial dysfunction and adverse remodeling. In fact, in a murine model, ID that was induced by inactivation of transferrin receptor-1 caused a fatal cardiomyopathy.[9] These observations support a causative role of ID in the progression of HF.

In the future, better definitions of ID and treatments superior to intravenous iron should be investigated. Diagnostically, soluble transferrin receptor levels may have the strongest correlation with the

gold standard of bone marrow iron deficit,[10] whereas new treatments such as blockade of hepcidin, a key modulator of iron absorption and distribution, may emerge as an effective treatment for both absolute and functional ID.[11]

Ultimately, the study by Masini et al[6] places us squarely in a new iron age and underscores the great need for more investigation of the pathophysiology, clinical consequences, and treatment of iron deficiency in all patients with HF.

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