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Iron deficiency in heart failure: diagnosis and clinical implications

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Iron deficiency is a widely prevalent finding in patients with heart failure, observed on average in 50% of outpatients and up to 80% of acute patients, regardless of the ejection fraction and the presence of anaemia, being an independent predictor of worst functional capacity and reduced survival. The definition of iron deficiency in heart failure considers the state of chronic inflammation that characterizes the pathology, recognizing a discriminating role for transferrin saturation. The studies conducted so far, which focused on the patient with heart failure with at least moderately reduced ejection fraction, have shown clinical benefit with intravenous supplementation of ferric carboxymaltose in terms of functional capacity, quality of life, laboratory markers of disease and inflammation, and possible reduction of re-hospitalizations, but not in terms of mortality. Based on this evidence, guidelines recommend intravenous ferric carboxymaltose in decompensated and iron-deficient patients, while research is at work to investigate the clinical impact of supplementation in contexts not yet examined, such as that of decompensation in patients with heart failure and preserved ejection fraction.

Defined as a condition in which the availability of iron is insufficient to meet the body's needs,[1] iron deficiency is a common laboratory finding in heart failure, affecting a variable percentage between 37 and 61% of patients with stable disease and up to 80% of those with disease reacutization,[2] and is associated with poorer functional capacity and quality of life, as well as reduced life expectancy, regardless of the presence of anaemia or left ventricular ejection fraction.[3] Risk factors for the development of iron deficiency in heart failure include female sex, a more advanced stage of the disease, as also evidenced by the association with higher levels of aminoterminal fragment of the natriuretic propeptide type B (NT-proBNP), and higher serum levels of C-reactive protein (CRP).[4]

The underlying causes of the association between iron deficiency and heart failure can be multiple, ranging from reduced intake and insufficient absorption due to undernutrition, inappetence, and congestion of the gastrointestinal tract mucosa, to altered distribution and use secondary to chronic low-grade inflammation, up to losses, especially from the gastrointestinal tract, at least in part attributable to the use of antiplatelet and anticoagulant drugs (*Figure 1*).[3] In particular, proinflammatory cytokines such as tumour necrosis factor-α and interleukin-6 (IL-6), which are increased in heart failure, inhibit the production of erythropoietin by modulating the activity of its transcription factors, thereby inhibiting the proliferation of erythroid progenitor cells of the bone marrow.[3] The action of these proflogistic mediators helps us to explain the common observation that erythropoietin levels are only slightly increased in relation to the extent of the iron deficiency in heart failure.[3] Chronic inflammation, specifically through IL-6, acts on the molecular pathway JAK/STAT3, inducing an increase in the hepatic

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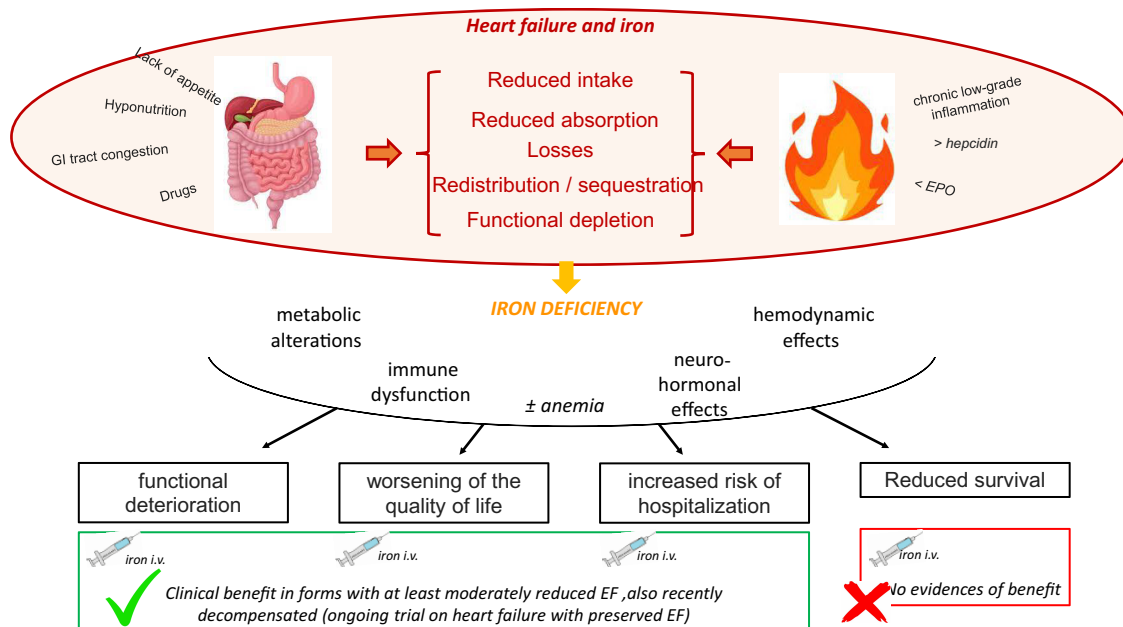
Figure 1 Main determinants and clinical consequences of iron deficiency in heart failure and the effect of iron supplementation. EPO, erythropoietin; HF, heart failure; EF, ejection fraction.

production of hepcidin. This protein binds the membrane transporter ferroportin and induces its internalization and degradation, thus reducing the duodenal absorption of iron and its release from the storage sites, i.e. the reticulo-endothelial cells and hepatocytes (accumulation pool), thereby conditioning a state of relative iron depletion in erythroid cells and non-erythroid tissues (functional pool).[3]

Taking into account the non-specific significance of the increase in ferritin as an acute phase protein in conditions characterized by latent inflammation, such as heart failure, iron deficiency in this setting is generally diagnosed for ferritin levels <100 ng/mL or between 100 and 299 ng/mL if the transferrin saturation (TSAT) is <20%.[5,6] Also used in clinical trials of iron supplementation, this double definition includes both individuals with absolute and relative iron deficiency but has been criticized for the difficulty in attributing to ferritin a threshold value, or a range, that was adequate to reflect the actual depletion of iron deposits.[7] The depletion of iron in the bone marrow is a very specific finding for iron deficiency and, since it is not affected by inflammation, it represents the gold standard for the definitive diagnosis of this condition.[3] However, the clinical applicability of the bone marrow examination for the diagnosis of iron deficiency is limited by invasiveness, high costs, and operator-dependence in the execution and reporting phases. Transferrin saturation and sideremia seem to be the single most sensitive and specific parameters for identifying the real iron deficiency in the patient with heart failure, showing a prognostic value that was not observed for ferritin. In fact, low values of TSAT (<20%) and sideremia (≤ 72.6 µg/dL), but not of ferritin (<100 ng/mL), were not only more reliable in reflecting

iron depletion in the bone marrow but were also associated with increased all-cause mortality compared with normal values in individuals with heart failure, regardless of ejection fraction.[7,8] In addition, TSAT was the only marker that was able to predict the greatest benefit in terms of reduction in hospitalizations and overall mortality among individuals with heart failure and an ejection fraction equal to or <45% undergoing intravenous martial supplementation.[8] High circulating levels of the soluble transferrin receptor represent another reliable and cost-effective option to help discriminate between true iron deficiency and functional deficit during inflammation.

As a highly efficient trace element in electron transfer, iron acts as a cofactor in a wide variety of biochemical reactions, including oxidative phosphorylation, the citric acid cycle, and the production of nitric oxide and oxygen radicals, so that all active metabolic cells, including cardiomyocytes, depend on iron for their functions and their structural integrity.[9] In vertebrates, the second main role of iron concerns the bond with oxygen in the complex known as haem, a constituent element of haemoglobin and myoglobin.[9] As far as the immune system is concerned, iron stimulates the proliferation of lymphocytes and the activation of macrophages in a proinflammatory sense, and its availability during infection is strongly regulated by innate defence mechanisms, aimed at stealing from the pathogens one of the fundamental elements for their proliferation.[9] Therefore, the clinical consequences related to iron deficiency in heart failure are manifold (*Figure 1*). First of all, martial deficiency affects erythropoiesis, favouring the development of anaemia. The prevalence of anaemia, defined as haemoglobin values below 13 g/dL in men and 12 g/dL in

women, is around 30% (stable patients) and 50% (hospitalized patients) during heart failure, regardless of the ejection fraction. These percentages are significantly higher than those observed in the general population, in which a proportion of between 10 and 20%, depending on age (< or >85 years), is affected by anaemia.[9] Anaemia is independently associated with increased mortality and hospitalizations in patients with heart failure. The reduced supply of oxygen to the tissues in anaemic subjects triggers haemodynamic and neuro-hormonal alterations that aggravate the myocardial workload, contributing, over time, to left ventricular remodelling. In this context, the numerous comorbidities typical of these patients, including chronic renal failure and cardiac cachexia, contribute to precipitating the clinical picture.

In addition to its impact on erythropoiesis and oxygen transport, iron deficiency in heart failure negatively affects oxidative metabolism and oxygen availability for the myocardiocyte, resulting in impaired mitochondrial metabolism and left ventricular dysfunction.

Based on this epidemiological and pathophysiological basis, correction of iron deficiency has become an important goal in the management of heart failure. Several clinical trials have been conducted to examine the impact of oral or intravenous iron supplementation in heart failure with reduced or moderately reduced ejection fraction, while a study is underway to verify the efficacy of intravenous iron carboxymaltose supplementation in terms of functional capacity, quality of life, functional class, mortality, and risk of hospitalization in patients with preserved ejection fraction (*Effect of IV Iron in Patients With Heart Failure With Preserved Ejection Fraction*, FAIR-HFpEF). In fact, even in this category of patients, martial deficiency is highly prevalent and has been associated with worse functional capacity and quality of life.[10] In the FAIR-HF study (*Ferric Carboxymaltose Assessment in Patients With Iron Deficiency and Chronic Heart Failure*), conducted on 459 outpatients with chronic heart failure (New York Heart Association, NYHA, II or III) treated, in a 2:1 ratio, with intravenous ferric carboxymaltose on a weekly basis until normal blood iron was restored and then with a maintenance dose or placebo for a total of 24 weeks, a significant improvement in NYHA class, walking test and quality of life in treated individuals was documented, regardless of the presence of anaemia at enrolment, without differences in terms of adverse events, but neither in terms of mortality or hospitalizations for cardiovascular causes, between the groups.[11]

These results were confirmed and partially extended in two subsequent studies. In the CONFIRM-HF study (*Ferric CarboxymaltOse evaluatioN on perFormance in patients with IRon deficiency in combination with chronic Heart Failure*), treatment with intravenous ferric carboxymaltose over a period of 1 year compared with placebo was associated with an improvement in functional capacity, symptoms, and quality of life in patients with heart failure and ejection fraction of 45% or less and martial deficiency, with evidence of a parallel reduction in the risk of hospitalization for the underlying disease but with no effect on mortality.[12] In contrast to intravenous administration, oral administration has not proved

useful in patients with heart failure. In the IRON-HF study (*Iron Supplementation in Heart Failure Patients With Anemia*), conducted on patients with NYHA Class II-IV, ejection fraction <40%, preserved renal function, and martial deficiency defined as TSAT <20% and ferritin <500 ng/mL, only intravenous administration of iron (as iron saccharate) compared with the oral one (as ferrous sulphate) was associated with an improvement in functional capacity 3 months after enrolment, although the anaemia was corrected by both methods of supplementation.[13] Correcting anaemia by administering erythropoietin stimulating agents, on the other hand, is another strategy not only without clinical benefit, but also associated with an increased risk of thrombotic events in the patient with heart failure.[14]

In agreement with the finding that oral iron supplementation was ineffective in the course of heart failure, oral supplementation in the form of iron polysaccharides for 16 weeks in patients with reduced ejection fraction (<40%) and martial deficiency defined as TSAT < 20% and ferritin 100-299 ng/mL was not associated with any clinical benefit (maximal oxygen uptake, gait test, NT-proBNP levels, and quality of life) in the IRONOUT HF (*Iron Repletion Effects on Oxygen Uptake in Heart Failure*) study.[15]

Although taken individually, the studies on intravenous iron supplementation in decompensated patients conducted up to before 2020 have only sporadically documented the effectiveness of this measure in reducing major clinical events, meta-analytical evidence has indeed shown a benefit in this regard, with a reduction in the risk of hospitalization in relation to treatment.[16]

Specifically, a meta-analysis of 10 randomized trials comparing iron supplementation with placebo (including 8 studies based on intravenous formulations), involving a total of 1404 individuals with heart failure and iron deficiency with or without anaemia, showed a benefit of intravenous iron therapy on various clinical aspects, such as the reduction of hospitalizations for decompensated heart failure, improvement in NYHA class, performance on the six-minute walk test, left ventricular ejection fraction, and serum markers of heart failure (NT-proBNP) and inflammation (CRP).[17] However, there was no difference in survival between treated vs. untreated patients (*Figure 1*).[16-18] In agreement with this, more recently, the multicenter study AFFIRM-AHF (*A Randomized, Double-Blind Placebo Controlled Trial Comparing the Effect of Intravenous Ferric Carboxymaltose on Hospitalizations and Mortality in Iron-Deficient Patients Admitted for Acute Heart Failure*), conducted on 1132 patients hospitalized for heart failure exacerbation with ejection fraction <50% and iron deficiency (ferritin <100 ng/mL or TSAT < 20%), showed a significant decrease in the risk of hospitalizations for heart failure in the following year among those randomized to receive intravenous ferric carboxymaltose (relative risk: 0.74, 95% CI 0.58-0.94) compared with individuals randomized to placebo, but no difference in terms of cardiovascular mortality.[19]

Based on this evidence, the European and US guidelines for the management of heart failure recommend

that all patients with heart failure undergo anaemia and serum iron level study by evaluating serum ferritin and TSAT.[5,6] Both guidelines also recommend treatment with intravenous ferric carboxymaltose.[5,6] The types of patients in whom this treatment is recommended, according to European guidelines, are those with iron deficiency and symptomatic heart failure with an ejection fraction <45%, in order to improve symptoms and quality of life, as well as recently hospitalized individuals with left ventricular ejection fraction <50%, in order to reduce the risk of re-hospitalization.[6] According to American guidelines, iron supplementation is indicated for patients with heart failure with reduced ejection fraction and documented iron deficiency.[5] Ferric carboxymaltose, whose single weekly dose cannot exceed 1000 mg, leads to a rapid and pronounced increase in serum ferritin levels, even beyond 500 mg/L. The re-evaluation of the iron panel will be useful after about 3-6 months. This therapeutic protocol does not differ from that applied in the absence of heart failure and it is not known whether alternative doses can offer greater advantages.

In conclusion, while evidence from recent clinical trials that were focused on the patient with at least moderately reduced ejection fraction has shed light on some important features of iron deficiency in chronic or decompensated heart failure, shadows still persist in the pathophysiology of these clinical events that are waiting to be at least in part dispelled by ongoing research for their potential therapeutic implications.

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