Why is Iron Deficiency Recognised as an Important Comorbidity in Heart Failure?

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Abstract
There is an increasing awareness of the prevalence of iron deficiency in patients with heart failure (HF), and its contributory role in the morbidity and mortality of HF. Iron is a trace element necessary for cells due to its capacity to transport oxygen and electrons. The prevalence of iron deficiency increases with the severity of HF. For a long time the influence of iron deficiency was underestimated, especially in terms of worsening of cardiovascular diseases and developing anaemia. In recent years, studies with intravenous iron agents in patients with iron deficiency and HF showed new insights into the improvement of iron therapy. Additionally, experimental studies supporting the understanding of iron metabolism and the resulting pathophysiological pathways of iron have been carried out.

The aim of this mini review is to highlight why iron deficiency is recognised as an important comorbidity in HF.

Keywords
Iron deficiency, heart failure, comorbidity

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Iron is an essential trace element that is present in a number of molecular systems, and it is increasingly recognised as an important cofactor for a variety of cell systems. It has been acknowledged that iron plays an important role in oxygen transport, as well as in cell growth and proliferation. In recent years, more insight has been gained into iron physiology and the regulation of cellular iron homeostasis.

Iron deficiency occurs, for example, when the dietary intake is inadequate, during times of digestive blood loss or menstrual periods or during states that excessively increase iron requirements, particularly during childhood growth or pregnancy. However, in patients with chronic illnesses, iron may become unable to be immobilised as a consequence of chronic inflammation, thus leading to functional iron deficiency. Many studies have shown that iron deficiency is very common in patients with heart failure (HF), and its prevalence increases with increasing New York Heart Association class.

Prevalence and Prognostic Factors of Iron Deficiency
A large meta-analysis of major HF trials showed that the prevalence of iron deficiency is nearly 50% in all patients with HF, and that iron deficiency has important prognostic and quality of life implications, irrespective of the presence of anaemia. However, iron deficiency, whether absolute or functional, is a frequent finding in HF patients also presenting with anaemia, affecting up to 80% of these individuals. In humans, intracellular iron is stored as ferritin and reflects body iron stores. However, ferritin is also an acute-phase reactant whose levels may increase during inflammatory processes. Transferrin saturation reflects the relative amount of transferrin that is loaded with iron. In contrast to ferritin, transferrin is a negative acute-phase reactant. Importantly, neither serum iron nor serum transferrin alone should be used as indicators of iron status. In addition, it is important to understand that different cut-off values indicate iron deficiency in healthy individuals and in patients with chronic illness.

Approximately half of all patients with HF have either absolute iron deficiency or functional iron deficiency defined as transferrin saturation <20% and serum ferritin 100–300 μg/L, and this finding is only partly associated with the presence of anaemia. Indeed, many HF patients present with iron deficiency, many with anaemia and some of these with both.

Mechanism of Iron Deficiency
It is important to understand the mechanisms of iron absorption and distribution. There are two different pathways of iron absorption, one for haem iron across a haem transporter, and another for iron in its ferrous form, across the divalent metal transporter. Iron absorption across the gut wall is only possible in the ferrous form, and ferric iron that is found in vegetables needs to be reduced before absorption. The cytosolic protein that accumulates iron is ferritin. Ferritin protects cells from iron toxicity and prevents iron from reacting with other cellular constituents. Under normal conditions, nearly the total amount of circulating iron is transported by transferrin. The amount of iron transported in ferritin is low compared with transferrin-iron.
Co-morbidities

Cohen et al. suggested that serum ferritin is not a major pathway of systemic iron transport, but locally secreted ferritin may play such a role in selected tissues.\(^\text{16}\) Despite there being some insight, the detailed pathways that enable iron trafficking from the endosome to the mitochondria and to other cellular sites are not well understood.\(^\text{17}\)

Generally, a large number of proteins need iron as a cofactor, and the two major elements that require iron are haem and iron–sulphur (Fe-S) clusters.\(^\text{18}\) Under iron replete conditions, iron regulatory protein 1 binds Fe-S clusters and acts as an aconitase when Fe-S cluster synthesis is normal. The presence of Fe-S clusters determines the function of the aconitase.

Aconitase is an essential enzyme in the citrate cycle that catalyses the reaction from citrate into aconitate, and requires Fe-S clusters as cofactors. When cellular iron levels are low, iron regulatory protein loses aconitase activity, and there is a corresponding reduction in Fe-S cluster synthesis.\(^\text{19}\) Mitochondrial function requires iron, since iron is a cofactor for haem proteins that are involved in electron transfer, and in adenosine triphosphate and energy production in the cells. The reason why iron may have an effect on HF irrespective of anaemia and haemoglobin values is that iron is an essential constituent of myoglobin, which is found in the cytoplasm, and avidly binds and releases oxygen.\(^\text{20}\)

The absence of iron in the blood of patients with HF may also be reflected as reduced iron load in the bone marrow and in the myocardium.\(^\text{21,22}\) Interestingly, a subset of patients in whom myocardial transferrin receptor expression was measured showed upregulation of the receptor. Such upregulation hints at iron deficiency inside the myocardium. In addition, left ventricular stiffness was correlated with peak oxygen uptake, but not with the ferritin level or transferrin saturation.\(^\text{23}\) The symptoms and signs of iron deficiency are partially explained by the presence of anaemia, but experimental evidence suggests that iron itself improves muscle function and exercise capacity in animals without changes in haemoglobin levels.\(^\text{24-26}\)

Iron Deficiency and Exercise Capacity

Iron deficiency independently relates to exercise intolerance expressed as reduced peak oxygen uptake and augmented ventilatory response to exercise in patients with chronic HF.\(^\text{27,28}\) This finding emphasises the role of iron as a cofactor in skeletal and cardiac muscle function. A recent study showed that iron is important for muscle function.\(^\text{29}\) In recent years, different therapeutic possibilities embrace iron replacement by oral or IV routes.\(^\text{30,31,32}\) The IV route is more effective than the oral route, mostly as a consequence of the limited absorption capacity in the duodenum and due to the side-effects of oral iron therapy that are encountered in up to 20% of all patients treated with oral iron.\(^\text{33}\)

The Iron Repletion Effects on Oxygen Uptake in Heart Failure (IRONOUT-HF) trial previously demonstrated that oral iron supplementation minimally increased iron stores and did not improve exercise capacity in patients with HF with a reduced ejection fraction and iron deficiency.\(^\text{34}\)

Current guidelines of the European Society of Cardiology for the diagnosis and treatment of HF state that all patients should be screened for iron deficiency and anaemia, a class I recommendation based on meta-analysis (level of evidence: A, because two large trials, Ferinject Assessment in Patients with Iron Deficiency and Chronic Heart Failure [FAIR-HF] and Ferric Carboxymaltose evaluation on perFormance in patients with Iron deficiency in coMbination with chronic Heart Failure [CONFIRM-HF], published positive results). Patients who remain symptomatic in New York Heart Association classes II–IV benefit from iron supplementation, preferably via the IV route.\(^\text{35}\) However, it has to be taken into account that the definition of iron deficiency used by the European Society of Cardiology in the current version of the HF guideline has been validated in clinical trials only in patients with HF with reduced ejection fraction. As no validations exist for HF with preserved ejection fraction, it should be regarded with caution in this population.

Ongoing Studies

Several studies with intravenous iron are ongoing; for example, the iron or Placebo for Anaemia in Intensive Care (IRONMAN study) (NCT03037931, NCT03833336, NCT02997454, NCT03218384, NCT0242562). That study will address whether the additional use of IV iron (iron isomaltoside) on top of standard care will improve the outlook for patients with HF and iron deficiency.

Other studies are the FAIR trials. The purpose of the FAIR HF study is to determine whether intravenous iron supplementation (ferric carboxymaltose) reduces hospitalisation and mortality in patients with iron deficiency and HF (NCT03036462). The FAIR HFpEF study addresses whether treatment with IV iron (ferric carboxymaltose) for patients with HF with preserved ejection fraction and iron deficiency can improve exercise capacity and symptoms while being safe (NCT03074591).

Future Developments

In addition to the ongoing studies with the known IV iron treatments, some new IV iron drugs are being tested. For example, ferric bepectate, a new iron drug, was studied in 33 iron-depleted anaemic patients who had undergone cardiac surgery.\(^\text{36}\) They were treated with either 200, 500 or 1500 mg ferric bepectate compared with 500 mg ferric carboxymaltose. They showed that with ferric bepectate, the iron excretion in urine was reduced compared with ferric carboxymaltose.

Recent results of the FERRIC Iron in Heart Failure (FERRIC HF II) trial showed that iron isomaltoside was safe and well tolerated in patients with chronic HF and iron deficiency.\(^\text{37}\) Moreover, they showed that iron isomaltoside was associated with faster skeletal muscle energy measured in the form of adenosine triphosphate and phosphocreatine after 2 weeks, implying better mitochondrial function. Additionally, these results showed that iron per se is an obligate component of mitochondrial enzymes that generate cellular energy in the form of adenosine triphosphate and phosphocreatine. Augmented skeletal muscle energetics might be an important mechanism by which iron repletion confers benefits in chronic HF. The exact mechanisms by which chronic heart failure patients develop iron deficiency are still not completely understood.

Moliner et al. recently showed an interplay between raised sympathetic nervous system activity and systemic iron deficiency in patients with chronic HF and, particularly, with those biomarkers that suggest impaired iron transport (transferrin saturation <20%) and increased iron demand (raised soluble transferrin receptor levels).\(^\text{38}\) This impressively supports the hypothesis that iron deficiency might not just be a comorbidity, but may also be a key element in the pathophysiological sequence leading to, and promoting the progression of, chronic HF. However, many questions remain and require further research. We look forward to future research to answer important questions about the use of iron agents in HF.
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