



Iron Therapy

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Abstract

Iron deficiency (ID) is one of the most common co-morbidities in patients with heart failure (HF). It has its highest prevalence in elderly subjects, women, decompensated subjects, and patients with numerous co-morbidities. ID is associated with worse symptoms, poorer quality of life, reduced exercise capacity, and a high morbidity and mortality. Both ID and the anaemia it can lead to can be harmful in HF. Repletion of iron stores has been shown to be effective in HF and detection and treatment of ID are now recommended in major HF guidelines. This paper summarises iron therapy for ID in HF patients.

Keywords: heart failure; iron; iron deficiency; anaemia; iron supplementation therapy

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Introduction

Iron deficiency (ID) belongs to the most common co-morbidities in patients with heart failure (HF), with the highest prevalence in elderly subjects, women, decompensated subjects, patients with numerous co-morbidities, including those with diabetes and chronic kidney disease (CKD).[1-3] ID has several unfavourable consequences for patients with HF, including augmented HF symptoms, poor quality of life, reduced exercise capacity, high morbidity and mortality.[1-3] ID itself needs to be differentiated from ID-related anaemia (IDA). Although untreated and long-lasting ID can lead to anaemia, ID itself has several clinical negative consequences in HF. Luckily, there are safe and effective therapeutic options, which thorough the repletion of ID (regardless of concomitant anaemia), bring clinical benefits for patients with HF.[4-6]

Pathophysiology of iron deficiency in heart failure

Iron plays a crucial role for optimal functioning of both haematopoietic and non-haematopoietic cells, being directly involved mainly in aerobic cellular energy metabolism in mitochondria.[1,7] Therefore, iron is particularly crucial for optimal functioning of tissues with high energy demand, such as myocardium and skeletal muscles.[1] This is in opposition to traditional approach, which has related ID with the development of anaemia, immunodeficiency and coagulopathy.[1,8]

The underlying mechanisms of the origin of ID in patients with HF is unknown. Based on our historical understanding of iron metabolism, the development of ID is associated with reduced iron intake, excessive iron loss and/or abnormal iron distribution to body compartments, where it remains unavailable for cells

requiring iron for their metabolic needs. Some evidence suggests that ID can be secondary to inadequate dietary iron intake [9,10] or/and reduced gastrointestinal iron bioavailability (due to intestine wall oedema, use of drugs increasing gastric pH, food reducing iron absorption) in patients with HF.[11,12] ID can result from gastrointestinal iron loss, due to local inflammation or concomitant therapy with antiplatelets or/and anticoagulants. It should be noted that none of these potential pathomechanisms have been proven to promote ID in the course of HF.

Although anticipated, the pathogenesis of ID in the course of HF is different from the pathomechanisms leading to ID in the course of CKD. Patients with CKD develop predominantly functional ID, as a consequence of augmented inflammation and high circulating hepcidin, which traps iron in the mononuclear phagocyte system and makes it unavailable for metabolic needs.[7,13-15] It should be emphasised that – although hypothesised – there is no evidence linking inflammation and ID in patients with HF. Importantly, patients with HF both in chronic [2] and acute settings [3] demonstrate extremely low (but not high) circulating hepcidin, indicating severely depleted iron stores in the body. ID in the course HF is absolute in the vast majority of cases.

Diagnosis of iron deficiency in heart failure

Based on haematological practices, bone-marrow aspiration with the assessment of iron content directly in bone marrow is the 'gold standard' method to identify ID.[8,16-19] Due to its invasiveness and limited accessibility in a daily clinical practice (particularly among patients with cardiovascular diseases), the

approach based on the assessment of circulating iron biomarkers is more convenient for the diagnosis of ID in patients with HF. Circulating ferritin is a reliable surrogate of iron stored in the body (mainly in hepatocytes and reticuloendothelial cells). In general, the lower the serum ferritin, the more depleted are the iron stores in the body. But ferritin is also an acute phase protein, hence its production is increased in case of accompanying inflammation. [8,19,20] Therefore, in a general population, absolute ID is diagnosed when serum ferritin is $<30 \mu\text{g/L}$ or even $<12\text{--}15 \mu\text{g/L}$ [8,19,21] However, due to concomitant low-grade inflammation present in the course of HF, higher cut-off values of serum ferritin are valid for the diagnosis of ID in patients with HF.

The second iron biomarker required for the diagnosis of ID is transferrin saturation (Tsat), which indicates a reduced pool of utilized iron. Tsat is the percentage of transferrin which binds iron, and is calculated as a ratio of serum iron and TIBC $\times 100\%$ (TIBC, total iron binding capacity—by transferrin).[1] It is worthy of note that neither serum iron nor serum transferrin alone are recommended for the diagnosis of ID in patients with HF.

The 2016 ESC/HFA guidelines on HF management recommend routine screening for ID using serum ferritin and Tsat among all patients with HF, regardless of haemoglobin level, LVEF, renal function, etc.[22] They recommend to use the following definition of ID: serum ferritin $<100 \mu\text{g/L}$, or ferritin between $100\text{--}299 \mu\text{g/L}$ and Tsat $<20\%$. [22] This definition has been used in CKD [20] and also in major clinical trials in HF with intravenous and oral iron supplementation.[4-6,23]

Other novel iron biomarkers are under investigation in HF, but so far without any clinical implications. Our group has recently proposed a new pathophysiological definition of ID using the combination of low serum hepcidin (indicating depleted iron stores more accurately than ferritin, regardless of concomitant inflammation) and high serum soluble transferrin receptor (sTfR) (indicating intracellular iron depletion).[2,3] TfR is the membrane molecular pathway for iron import into the cell; it is upregulated when intracellular metabolic needs for iron are not met, as the augmented membrane expression of TfR facilitates the iron influx to the cells; the overexpressed TfR is later shed to the circulation and is detected as a soluble form.[24]

Prevalence of iron deficiency in heart failure

ID is a common co-morbidity in patients with HF. When applying the definition of ID recommended by the 2016 ESC/HFA guidelines on HF management [22], the prevalence of ID in a general population of HF patients ranges between 37-74%. [2,3,25-32] ID is present across the whole spectrum of HF, regardless of LVEF.[27,31-33]

The following clinical features increase the risk for ID among patients with HF: female gender, advanced NYHA class, high plasma N-terminal pro-B-type natriuretic peptide (NT-pro-BNP), high serum high-sensitivity C-reactive protein (hsCRP), low haemoglobin level and decompensated status.[26,27,29,33]

Clinical consequences of iron deficiency in heart failure

ID translates into impaired aerobic performance expressed as lower peak oxygen consumption VO_2 (peak VO_2), higher

ventilatory response to exercise (VE- VCO_2 slope) in patients with HFrEF and HFpEF [25,30,34], and reduced submaximal exercise capacity reflected by the shorter 6-minute walking test (6MWT) distance in patients with HFrEF and HFpEF.[30] It should be noted that the unfavourable impact of ID on both peak VO_2 and VE- VCO_2 slope in patients with stable HFrEF has been independent and much stronger than the effect of anaemia on these parameters.[34] ID also worsens health related quality of life (HRQoL) expressed, for example using the Minnesota Living with Heart Failure Questionnaire in patients with HF.[35,36]

Among cohorts including patients within the whole spectrum of HF, ID (regardless of accompanying anaemia) has been shown to be an independent predictor of higher all-cause mortality, an increased risk of heart transplantation, and an increased risk of the composite endpoint of mortality and nonfatal cardiovascular events (HF hospitalization, acute coronary syndrome, severe arrhythmia or stroke).[3,25,26,27,29,37,38,39]

Oral iron supplementation in heart failure

Until now, only one study investigating oral iron supplementation in patients with HF has been executed and published, the IRONOUT-HF study.[23] Patients with symptomatic HFrEF (LVEF $\leq 40\%$, NYHA class II-IV) and ID defined as previously (serum ferritin $15\text{--}100 \mu\text{g/L}$, or serum ferritin $101\text{--}299 \mu\text{g/L}$ with Tsat $<20\%$; with a haemoglobin level $9\text{--}15 \text{g/dL}$ for males and $9\text{--}13.5 \text{g/dL}$ for females) were randomized to either oral iron polysaccharide (150mg twice daily) ($n=111$) or placebo ($n=114$) for 16 weeks. The primary endpoint, a change in peak VO_2 , did not differ between the oral iron and placebo groups; in addition there were no differences between treatment groups in changes in 6MWT distance. Oral iron supplementation as compared to placebo treatment resulted in clinically meaningless increases in Tsat ($+3\%$, $p=0.003$) and serum ferritin ($+11 \mu\text{g/L}$, $p=0.06$, borderline).[23] These results do not support the use of oral iron supplementation in patients with HFrEF.

Intravenous iron supplementation in heart failure

It should be emphasised that earlier parenteral iron preparations were administered as an iron oxyhydroxide complex [40,41], which induced a lot of free and toxic iron, translating into oxidative stress and related adverse events, such as: hypotension, nausea, vomiting, abdominal and lower back pain, peripheral oedema and a metallic taste.[42,43] The contemporary parenteral formulas (mainly ferric carboxymaltose, FCM) contain iron in a core surrounded by a carbohydrate shell, which has allowed to eliminate the aforementioned adverse reactions and side effects.[44]

The majority of clinical evidence regarding intravenous iron supplementation in patients with HF comes from 3 clinical trials. [4-6] In the FAIR-HF study [4], the Ganzoni formula [45] was used to calculate the required cumulative FCM dose, based on current body weight, actual and the target haemoglobin level of a supplemented patient. The dosing frequency was 200mg of FCM weekly until iron repletion was achieved (the correction phase) and then every 4 weeks during the maintenance phase. In the CONFIRM-HF study [5] as well as in the EFFECT-HF study [6], FCM was administered according to a fixed scheme based on the subject's weight and haemoglobin concentration at screening and administered at weeks 0 and 6. Further FCM



doses could be administered at weeks 12, 24, and 36 if ID was still present, but more than 75% of patients required only 2 doses in total. This new dosage pattern was in alignment with the total iron dosing applied in the FAIR-HF study.[46]

In the FAIR-HF study, 304 ambulatory patients with symptomatic HF with LVEF $\leq 40\%$ (NYHA II) or $\leq 45\%$ (NYHA III), with ID (serum ferritin $< 100 \mu\text{g/L}$, or serum ferritin $100\text{--}300 \mu\text{g/L}$ and T_{sat} $< 20\%$) with haemoglobin $9.5\text{--}13.5 \text{ g/dL}$ were randomized in a 2:1 ratio to either intravenous FCM (dosing already explained above) or intravenous saline. Primary endpoints were self-reported patient global assessment (PGA) at week 24 and NYHA class at week 24, adjusted for baseline NYHA class, both of which improved in the FCM arm as compared to a saline control.[4] The improvement in aforementioned characteristics were seen separately in both anaemic and non-anaemic patients, even though the clinical improvement in non-anaemic patients was not accompanied by an increase in haemoglobin level.[46] The treatment with FCM (as compared with placebo administration) resulted also in an increase of the 6MWT distance and quality of life assessments. The rates of death, adverse events, and serious adverse events were similar in the two study groups.[4]

In the CONFIRM-HF study, ambulatory patients with HF in NYHA class II-III with LVEF $\leq 45\%$, BNP $> 100 \text{ pg/mL}$ or NT-proBNP $> 400 \text{ pg/mL}$, with ID (defined as in the FAIR-HF study) and haemoglobin level $< 15 \text{ g/dL}$ were randomized 1:1 to either FCM or placebo for 52 weeks (doses as described above). Treatment with FCM as compared to placebo increased the 6MWT distance at week 24 (primary endpoint).[5] The treatment effect of FCM was consistent in all clinical subgroups and was seen up to week 52. Throughout the study, an improvement in NYHA class, PGA, QoL, and Fatigue Score in patients treated with FCM was demonstrated with a statistical significance confirmed from week 24 onwards. Treatment with FCM as compared to placebo was associated with a reduction in the risk of HF hospitalizations at week 52 (one of the secondary endpoints). The number of deaths and adverse events were similar in both study groups.[5]

In the EFFECT-HF study, ambulatory patients with HF in NYHA class II-III with LVEF $\leq 45\%$, a reproducible peak VO₂ of 10 to 20 mL/kg/min, BNP $> 100 \text{ pg/mL}$ or NT-proBNP $> 400 \text{ pg/mL}$, with ID (defined as in the FAIR-HF study) and haemoglobin level $< 15 \text{ g/dL}$ were randomized 1:1 to either FCM or standard care for 24 weeks (doses as in the CONFIRM-HF study).[6] At 24 weeks, peak VO₂ (primary endpoint) decreased in the control group, but was maintained on FCM ($p < 0.05$). PGA and NYHA class also improved on FCM as compared to standard of care.[6]

In other smaller studies in patients with HFrEF, the following beneficial effects of intravenous iron therapy were demonstrated: within echocardiography parameters (an increase in LVEF, a reduction in LVSD, LVDD, LVPW, IVS thickness, left ventricular mass index, left ventricular end systolic volume, an improvement in S', E', a decline in E/E', a reduction in peak systolic strain rate) [47-51] and within some biomarkers (a reduction in plasma NT-proBNP and CRP).[48]

Recently 2 meta-analyses (one based on a classical methodological approach [52], the other one using individual patient data [53]) have provided additional evidence regarding

the safety and efficacy of intravenous iron supplementation in patients with HF.

The meta-analysis of Jankowska EA et al. included 5 trials in iron deficient patients with HF and LVEF $\leq 45\%$ (509 patients received intravenous iron therapy - the majority were treated with FCM - compared with 342 controls), with at least a single-blind randomization without a concomitant therapy with erythropoiesis-stimulating agents.[52] This meta-analysis revealed that intravenous iron therapy in iron deficient patients with HF and LVEF $\leq 45\%$ reduced the risk of the combined endpoint of all-cause death or cardiovascular hospitalization, the risk of the combined endpoint of cardiovascular death or HF hospitalization, and the risk of HF hospitalization, but without an effect on either all-cause or cardiovascular mortality (which may be due to a low number of reported events and a relatively short follow-up).[52]

The meta-analysis of Anker SD et al. utilized the individual patient data extracted from four clinical trials comparing FCM ($n=504$) with placebo ($n=335$) in iron deficient patients with systolic HF.[53] As compared with a placebo group, patients receiving FCM had lower rates of recurrent CV hospitalizations and CV mortality, lower rates of recurrent HF hospitalizations and CV mortality, lower rates of recurrent CV hospitalizations and all-cause mortality.[53] Time-to-first-event analyses showed similar findings, with a somewhat attenuated treatment effects.[53]

Clinical implications

All aforementioned evidence led to the formulation of the following recommendations regarding the diagnosis and treatment of ID in patients with HF in 2016 ESC/HFA guidelines on HF management [22]:

“The following diagnostic tests (including ferritin and transferrin saturation) are recommended for initial assessment of a patient with newly diagnosed HF in order to evaluate the patient's suitability for particular therapies, to detect reversible/treatable causes of HF and comorbidities interfering with HF (Class of recommendations I, Level of evidence C).”

“Intravenous FCM should be considered in symptomatic patients with HFrEF and iron deficiency (serum ferritin $< 100 \mu\text{g/L}$, or ferritin between $100\text{--}299 \mu\text{g/L}$ and transferrin saturation $< 20\%$) in order to alleviate HF symptoms and improve exercise capacity and quality of life (Class of recommendations IIa, Level of evidence A)”.

Future directions

ID is highly prevalent and has numerous unfavourable consequences for patients with HF across the whole spectrum of LVEF, but surprisingly its origin still remains unknown. Although intravenous iron supplementation has been shown to improve exercise capacity, improve quality of life and alleviate HF symptoms in iron deficient patients with HFrEF, there is no definitive data that this therapy would also improve clinical outcomes in this patient population. Also, it has not been demonstrated if intravenous iron supplementation is safe and effective in iron deficient patients with acute HF and patients with HFmrEF/HFpEF. Therefore, a series of trials is ongoing in order to validate the aforementioned concepts (HEART-FID, AFFIRM-AHF, FAIR-HF2, FAIR-HFPEF, PREFER-HF, IRONMAN).



Declarations of interest

The authors declare no conflict of interest.

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