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Narrative Review

Iron deficiency in chronic and acute heart failure: A contemporary review on intertwined conditions

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ABSTRACT

Iron Deficiency (ID) is increasingly recognized as a prevalent comorbid condition in Heart Failure (HF). Despite this, the pathophysiological mechanisms for progressive ID in either chronic or acute HF are still poorly understood. Beyond the traditional factors for iron deficit in the general population, we ought to review the specificities of such paucity in the HF patient, particularly focusing on the interplay between heightened inflammation, overactivity of the sympathetic nervous system and the so-called cardio-renal-anaemia-ID syndrome. Currently, ID constitutes not only an independent prognostic marker but also a novel safe therapeutic target. Particularly, in selected stable HF patients with reduced left ventricular ejection fraction, intravenous (IV) iron improves symptomatic burden and reduces hospitalizations due to worsening HF. On this topic, the main trials of IV iron with either iron sucrose (Toblli et al., FERRIC-HF and IRON-HF) or ferric carboxymaltose (FAIR-HF, CONFIRM-HF and EFFECT-HF) will be summarized and discussed. Finally, we debate the gaps in knowledge of ID in special populations, namely the unreliability of routine plasmatic surrogate markers to assess iron status in acute and advanced HF, the challenging patient with both HF and Chronic Kidney Disease, as well as efficacy and safety concerns in these settings and the potential role of iron correction in cardiac resynchronization therapy candidates.

1. Introduction

Iron deficiency (ID) is broadly defined in the general population as serum ferritin < 15 μg/L (WHO). However, in heart failure (HF), as a chronic inflammatory systemic syndrome, higher cutoffs are indicated. Accordingly, ID is present in these patients when one of the following is met: ferritin < 100 μg/L or ferritin 100–300 μg/L and transferrin saturation (TSAT) < 20% [1,2]. The burdening prevalence of this comorbid condition is illustrated by the findings of such deficit in 30 to 50% in chronic stable disease [3,4] and 70 to 80% in acute HF [5,6]. Furthermore, ID independently predicts more severe symptomatic burden, higher morbidity, as noted by markedly increased hospitalizations and readmission rates, and mortality [7,8], which underscores its importance in HF.

In this review we ought to discuss the specificities of the aetiology, pathophysiology and management of ID in the HF patient, debating the often found intertwined conditions of anaemia and Chronic Kidney Disease (CKD). Accordingly, we systematically reviewed the literatute for relevant studies. For the remainder of this paper, both ID and HF will be defined as stated by the European and American Societies of Cardiology guidelines, anaemia as stated by World Health Organization, and CKD as per Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, unless otherwise stated.

2. Aetiology, pathophysiology and clinical manifestations

2.1. Regulation of iron metabolism

The daily iron intake averages 15 mg, with a portion of this iron reaching circulation through the duodenal enterocyte's ferroportin, while the remaining is stored as ferritin. In the blood, iron is bound to and transported by transferrin and thereafter delivered to tissues [9]. Afterwards, transferrin is removed from the extracellular fluid due to its binding to Transferrin Receptor-1 (TfR1) and subsequent internalization [10]. TfR1 is expressed in all cells (except mature red cells), especially in erythroblasts, hepatocytes and muscle cells [11]. In the former, iron is used in the synthesis of haemoglobin, which, if impaired, leads to decreased oxygen transport and fatigue. Liver cells, on the other hand, produce hepcidin, a major homeostatic regulator of iron metabolism, in response to increased iron concentration. Its effect leads

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to blocking of ferroportin, which in turn inhibits iron absorption and availability of circulating iron [12]. It is worth mentioning that the liver is also the major site for iron storage, mainly in the form of ferritin, a surrogate serum marker of iron stores [13]. Finally, in the myocyte, iron is involved in the synthesis of myoglobin, a fundamental protein for oxygen storage [10], and is a cofactor for both respiratory and redox reactions in the mitochondria [14]. Given the crucial role of each factor towards balanced iron metabolism, dysregulation in any of the aforementioned steps may culminate in ID.

2.2. Mechanisms of iron depletion in heart failure

Similarly to the general population, ID in HF may be due to either (i) reduced iron intake, (ii) impaired iron absorption and/or (iii) increased iron body losses. Failure to achieve the recommended iron intake of 10–15 mg per day [15] may lead to ID. A small study noted that iron intake was markedly decreased in HF patients, aggravating with increased disease severity [16]. Also, impaired iron absorption, consequential to increased hepcidin levels, intestinal wall oedema and adverse effects from commonly prescribed drugs, further compromises iron depletion. Hepcidin upregulation is a well-known feature of chronic inflammatory conditions [10] and early HF is no exception [17]. It's role is to block intestinal ferroportin, thus inhibiting iron absorption [10]. Right-sided HF may be associated with mucosal oedema and consequent reduced absorption [18]. Several drugs, namely proton pump inhibitors and histamine-2 receptor antagonists [19], are known to decrease iron absorption. Data concerning the association between ID and antiplatelet and/or anticoagulant agents are conflicting, although occult bleeding does not seem to be the primary cause of ID in the great majority of HF patients [7] (Fig. 1).

Beyond the traditional proposed mechanisms for ID in HF (Table 1), one should also consider the role of systemic inflammation and sympathetic nervous overactivity, as well as the negative iron metabolism balance consequent to common comorbidities. In particular, the syndromic interplay between HF, renal dysfunction, anaemia and ID has long been recognized, and each independently leads to worse prognosis [20]. Both HF and CKD are independently associated with heightened inflammation and overactivity of the sympathetic nervous system [21,22], which in turn may lead to impaired iron balance and anaemia. In addition, progressive CKD leads to a relative deficiency of erythropoietin (EPO), the main driver of erythropoiesis [23]. In short, anaemia is often the result of compromised iron stores and/or impaired transportation. Alternatively or in addition to ID, multiple other factors can contribute to anaemia, including inflammation, renal dysfunction and haemodilution [1,2]. To conclude, despite the multitude of pathophysiological mechanisms and numerous related pathways associating HF to CKD, anaemia and ID (Fig. 2), these are still poorly understood, hampering the search for novel and effective therapeutic strategies.

Table 1
Aetiology of iron deficiency in the general population and heart failure patients.

Traditional aetiological factors
Poor nutritional status and reduced iron intake (< 10–15 mg/day)
Rapid growth and increased demands (e.g., during EPO therapy)
Malabsorption due to inflammatory intestinal disease (especially proximal disease)
Malabsorption due to GI surgery (especially gastroduodenal and pancreatic surgery)
Acute or chronic systemic inflammation
Increased iron losses due to acute bleeding (e.g., menses)
Increased iron losses due to chronic bleeding (e.g., repeated therapeutic phlebotomy)
Iron losses due to occult GI bleeding
Reduced iron absorption or increased loss due to commonly prescribed drugs
Miscellaneous causes (e.g., haemosiderinuria, haemoglobinuria, pulmonary haemosiderosis, TMPRSS6 gene variants)
Heart failure specific factors
Overactivity of the sympathetic nervous system
Systemic inflammation and hepcidin upregulation
Cardiorenal-ID-anaemia syndrome
Intestinal wall mucosal oedema due to right ventricular dysfunction
Congestive symptoms and hemodilutional anaemia (pseudo-anaemia)
Adverse events from commonly prescribed drugs in HF:
- PPI and H2R-antagonists (prolonged achlorhydria)
- Antiplatelet and anticoagulants (increased losses)

EPO = erythropoietin; GI = gastrointestinal; HF = heart failure; TMPRSS6 = transmembrane protease Serine 6 (also known as matriptase-2); ID = iron deficiency; PPI = proton pump inhibitors; H2R = histamine-2 receptor.

2.3. Defining iron deficiency in heart failure

Despite the widely accepted and reported definitions [1,2], plasma surrogate markers may have limitations as compared to the current theoretical gold-standard to define ID, i.e. bone marrow biopsy with iron staining [24]. In a study enrolling 37 patients with decompensated advanced HF and severe anaemia (defined as haemoglobin ≤ 12 g/dL in men and ≤11.5 g/dL in women), ID anaemia was confirmed by bone marrow aspiration in 73% of the population. The mean ferritin value of these patients was 75.3 ± 59.1 µg/L [25], which is in accordance with the currently used higher cut-off. However, investigators have not consistently found ferritin to be an optimal plasma surrogate marker for ID in HF.

A study with 42 patients with HF and reduced left ventricular ejection fraction (LVEF) (≤45%) undergoing median sternotomy for

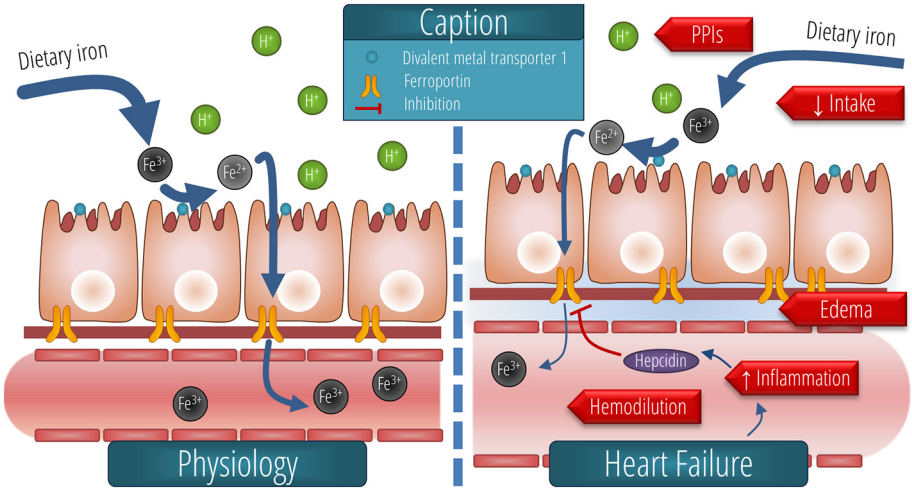

Fig. 1. Specific mechanisms for Iron Deficiency in the Heart Failure population. In these patients, iron intake is often reduced and absorption may be compromised due to several mechanisms, as noted by decreased gastric acidification, gut wall oedema and impaired ferroportin activity. Exacerbated inflammation with upregulation of hepcidin has a fundamental role in hindering the activity of ferroportin. Also, volume expansion, as occurs during acute decompensations of Heart Failure, might be responsible for further plasma ferritin decrease and pseudo-anaemia. PPI = Proton Pump Inhibitor.