Iron Supplementation in Heart Failure

Subjects: Cardiac & Cardiovascular Systems

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Iron deficiency is a significant comorbidity of heart failure (HF), defined as the inability of the myocardium to provide sufficient blood flow. However, iron deficiency remains insufficiently detected. Iron-deficiency anemia, defined as a decrease in hemoglobin caused by iron deficiency, is a late consequence of iron deficiency, and the symptoms of iron deficiency, which are not specific, are often confused with those of HF or comorbidities. HF patients with iron deficiency are often rehospitalized and present reduced survival. The correction of iron deficiency in HF patients is associated with improved functional capacity, quality of life, and rehospitalization rates. Because of the inflammation associated with chronic HF, which complicates the picture of nutritional deficiency, only the parenteral route can bypass the tissue sequestration of iron and the inhibition of intestinal iron absorption. Given the negative impact of iron deficiency on HF progression, the frequency and financial implications of rehospitalizations due to decompensation episodes, and the efficacy of this supplementation, screening for this frequent comorbidity should be part of routine testing in all HF patients.

iron deficiency heart failure transferrin saturation coefficient serum ferritin ferric carboxymaltose

1. Introduction

Heart failure (HF) is the inability of the myocardium to provide sufficient blood flow to meet the body's metabolic needs. The main clinical signs of HF are shortness of breath, severe fatigue, and lower-extremity edema. According to the 2016 European Society of Cardiology recommendations, three categories of HF are defined according to the left ventricular ejection fraction (LVEF) value: reduced ejection fraction (LVEF < 40%), preserved (LVEF > 50%), and intermediate (LVEF of 40–50%) HF. The severity of HF is often semi-quantified with the New York Heart Association (NYHA) functional stages, from stage I (no limitation) to stage IV (extreme restriction).

HF can be the consequence of ischemic (infarcts, angina), toxic (alcohol, chemotherapy), or infectious myocardial pathologies; it can also result in abnormal loading conditions (hypertension, valvulopathy) or infiltrative pathology (amyloidosis, sarcoidosis, hemochromatosis) [1].

HF is the most common cardiovascular disease, with an estimated prevalence of 1–2% of the adult population in developed countries (10% in the age group >70 years) [1]. The incidence of chronic HF increases with the aging of the population and the improved management of other cardiovascular diseases. However, diagnosis can be

difficult. Comorbidities are frequent, and symptoms can be non-specific in early HF. The improvement of diagnostic methods leads to an earlier detection of the disease and could then prevent its progression. Thus, natriuretic-peptide measurements are essential for diagnosing and monitoring HF. Natriuretic peptides (BNPs) or the inactive fragment of pro-BNPs (NT pro-BNPs) are solely produced by the cardiac tissue, and their concentrations increase with the cardiac-wall stress in proportion to the severity of HF [1]. Although they are correlated, their optimal cut-off concentrations differ and may vary with age (see [2] for complete recommendations).

2. Iron Deficiency, the Most Common Comorbidity of Heart Failure

HF is frequently associated with comorbidities, the most common being chronic kidney disease (40%) [3], diabetes (30–40%) [4], and chronic obstructive pulmonary disease (20.5%) [5]. These comorbidities have a significant impact on hospitalizations and mortality.

Iron deficiency is often associated with chronic HF [6][7], with or without anemia, as the most common nutritional deficiency. Indeed, iron deficiency is most often discovered in anemia [8]. Iron-deficiency frequencies from 37% to 61% were reported in different studies [9][10][11]. In the study by Klip et al. on European cohorts of 1500 HF patients, iron deficiency was diagnosed in 61.2% of patients with anemia and 45.6% without anemia [12]. The CARENFER study recently conducted in France on 1661 HF hospitalized patients reported that 49.6% had iron deficiency [13].

Even in the absence of anemia, iron deficiency is a poor prognostic factor in HF [14]. Iron deficiency increases the relative risk of death by 40–60%. For example, a prospective study on nearly 550 patients with NYHA class II–III chronic HF (mean LVEF of 26%) reported that the adjusted relative risk of the composite endpoint of all-cause death or heart transplantation was increased by 58% hen iron deficiency was present. In contrast, anemia was not an independent risk factor [15]. Another study in the United Kingdom included 150 patients with HF [16]. Compared with patients without anemia and iron deficiency, the relative risk of death was not significantly increased in anemic patients without iron deficiency.

In contrast, it was twice as high in nonanemic patients with iron deficiency [17]. In the European-cohort analysis by Klip et al., iron deficiency was an independent mortality risk factor (relative risk increased by 42% in multivariate analyses), along with the classic risk factors (sex, age, NYHA class, diabetes, hypertension, etc.) [12]. Anemia was not an independent risk factor.

3. Iron Is an Essential Element for the Correct Functioning of the Heart Muscle

Iron plays a significant role in erythropoiesis and oxygen transport. However, it also participates in DNA replication and repair, cell growth and differentiation, brain function, dioxygen storage in myoglobin, and energy metabolism of striated muscles and heart (ATP synthesis) [18][19] (**Figure 1**). Cardiomyocytes are characterized by a high myoglobin concentration in the cytosol and contain numerous mitochondria, which produce the energy necessary

for cardiac-muscle contractions. Iron plays a significant role in mitochondrial functions as a cofactor in iron–sulfur-cluster-containing proteins, heme-containing proteins, and iron-ion-containing proteins (**Figure 2**). Approximately 90% of the ATP required for the proper functioning of the heart muscle (i.e., for contraction) is produced by the mitochondrial enzymatic complexes of the respiratory chain [20]. Cellular iron deficiency was shown to result in reduced activity of Fe-S-cluster-based complexes in the mitochondria of human cardiomyocytes and to be associated with impaired mitochondrial respiration and morphology, ATP production, and contractility (**Figure 1**) [21][22]. Interestingly, restoring intracellular iron concentrations can reverse these effects on muscle [22][23].

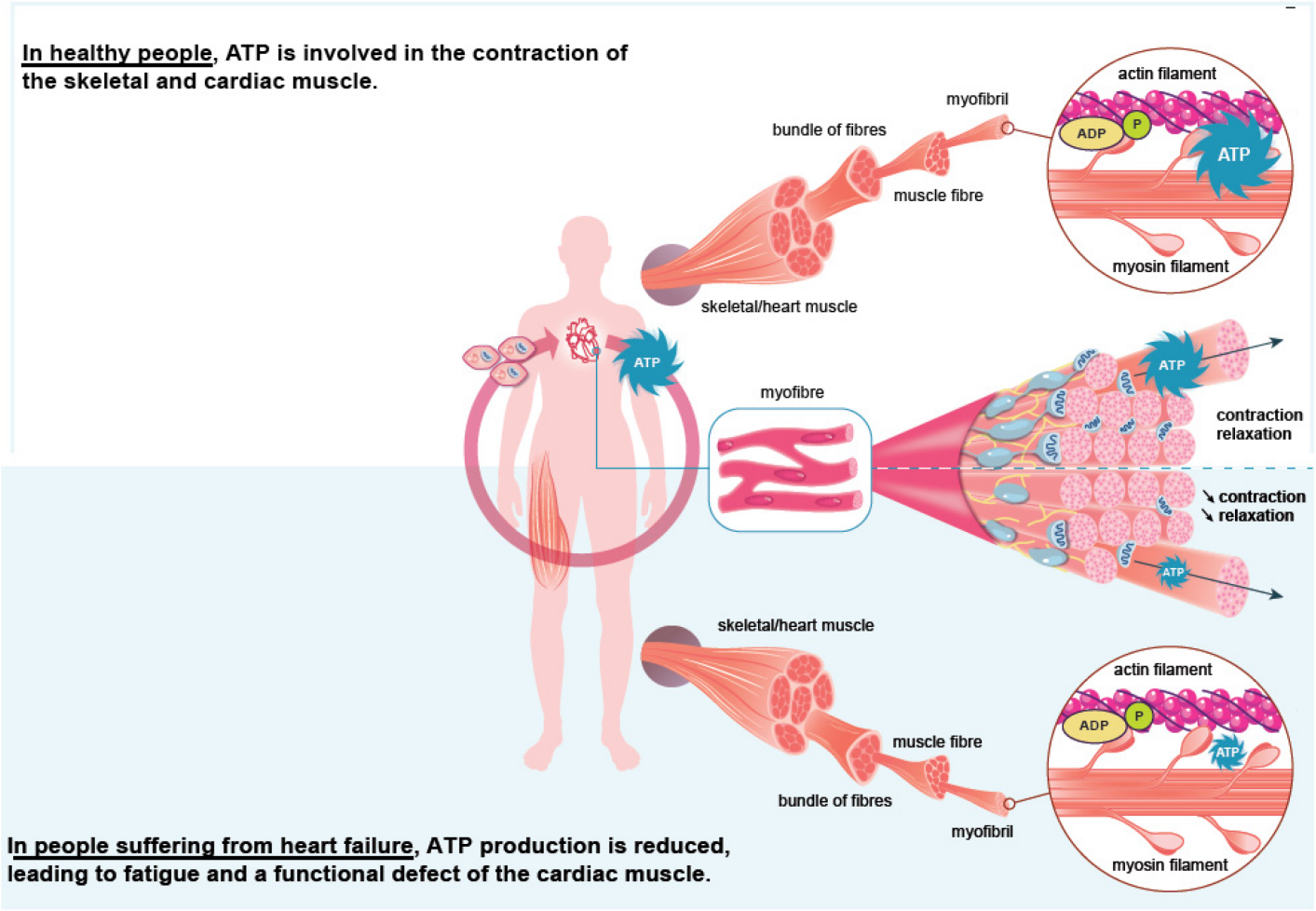

Figure 1. Role of iron in the heart muscle's functioning. Iron is notably mandatory for the energy production involved in heart contractions and for the oxygenation of the muscle, which ensures its correct function over time.

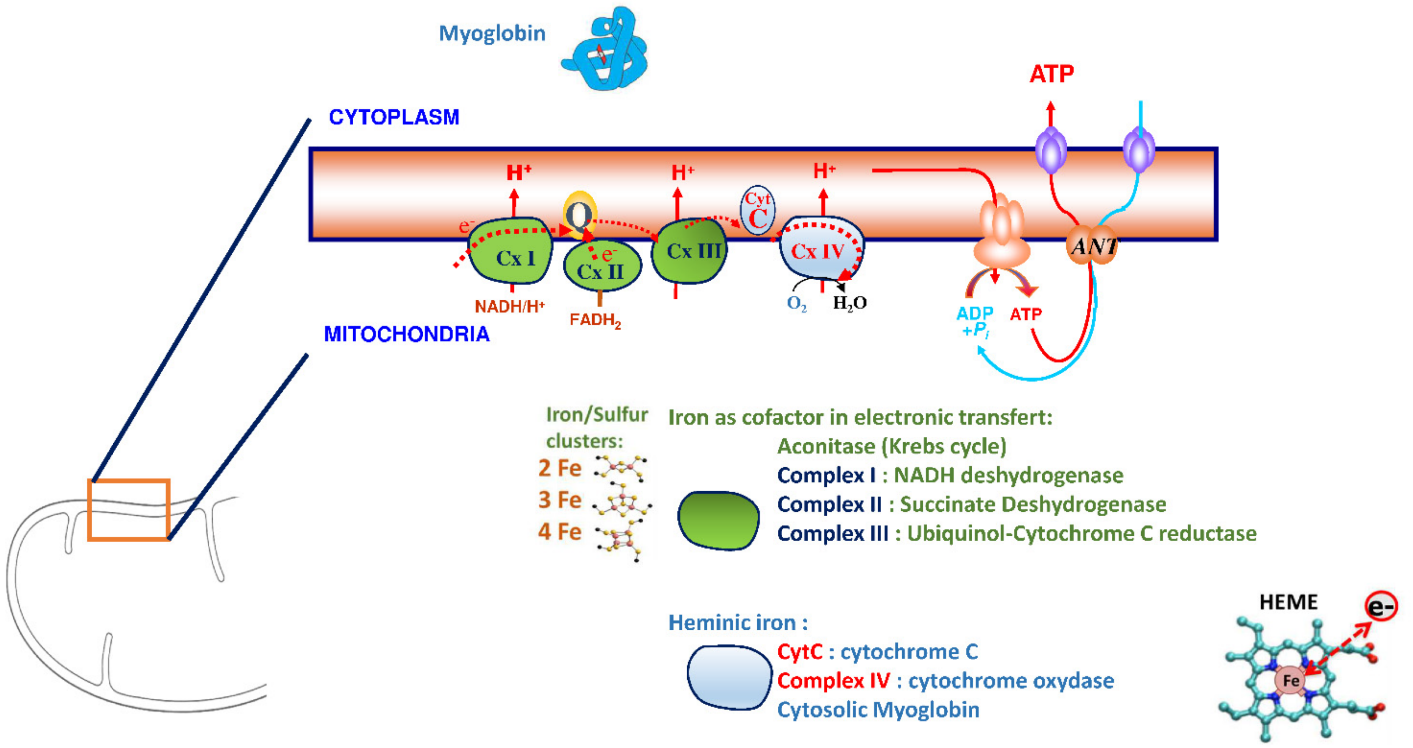

Figure 2. Role of the iron outside of hematopoiesis. Iron is an essential cofactor in most proteins involved in oxidative phosphorylations and anti-oxidative enzymes. As shown in the present figure, iron is a constitutive element of numerous proteins, either as a component of the heme ring in hemoproteins (such as Myoglobin, involved in muscle oxygenation, or cytochromes, involved in oxido-reductive reactions) or in iron–sulfur clusters involved in electronic transfers.

This essential role of iron as a cofactor in the structure of proteins involved in oxidative phosphorylation and anti-oxidative enzymes (**Figure 2**) impacts the pathophysiology of progressive cardiac remodeling in HF patients [15][17][24]. Martens et al. included patients with HF and iron deficiency receiving cardiac-resynchronization therapy [25] and evidenced that iron supplementation improved cardiac function and the cardiac-force–frequency relationship [15]. Intravenous (IV) iron supplementation improved cardiac remodeling, particularly via a significant increase in LVEF. The heart muscle is consequently susceptible to iron deficiency, but those deleterious effects can be corrected—at least in part—by iron supplementation [26].

4. Iron Supplementation in Heart Failure

In case of iron deficiency, iron can be provided either via the oral or parenteral route. Although cheap and readily available, the oral route is frequently (up to 70%) associated with poor gastrointestinal tolerance and various levels of efficacy and compliance [27][28]. The IV route of new-generation iron preparations [29] might be associated with limited gastrointestinal side effects, injection-site reactions, and infrequent anaphylactic reactions; the safety is considered quite satisfactory [30].

Published in 2017, the double-blind IRONOUT-HF study on 225 patients with chronic stable HF (NYHA classes II–IV) and iron deficiency showed that oral iron administration (150 mg × 2/day) for 16 weeks was comparable to placebo in terms of functional capacity as assessed via peak oxygen consumption and walking [31]. In contrast, the FAIR-HF, CONFIRM-HF, FERRIC-HF, and EFFECT-HF studies demonstrated the efficacy of IV iron on HF symptoms [32][33][34][35]. This difference in the effectiveness of the oral and IV routes is explained by a high concentration of hepcidin in chronic HF [31].

In the AFFIRM-HF study, the effect of IV iron supplementation on mortality was evaluated in chronic HF patients (LVEF < 50%) with iron deficiency (according to the 2016 ESC criteria) hospitalized for an acute episode of HF [33]. At discharge, stabilized patients were randomized to IV iron carboxymaltose or placebo. After a 52-week follow-up (1108 evaluable patients), the relative risk of hospitalization for a new decompensation was reduced by 26%, without significant effects on cardiovascular mortality.

Jankowska et al.'s [16] meta-analysis included five randomized studies totaling 851 patients with systolic HF and iron deficiency. Patients were treated with IV iron or a comparator (oral or IV placebo, oral iron). In all patients (with or without anemia), the relative risk of composite endpoint "all-cause death or hospitalization for cardiovascular reasons" was reduced by 56%, and the relative risk of composite endpoint "cardiovascular death or hospitalization for progression of chronic heart disease" was reduced by 61%.

Another meta-analysis by Anker et al. [36] included four randomized [33][36][37][38], double-blind studies (FER-CARS-01, FAIR-HF, EFFICACY-HF, and CONFIRM-HF) with a total of 839 patients with chronic systolic HF and iron deficiency to compare IV iron carboxymaltose and placebo. The relative risk of cardiovascular hospitalization or death was reduced by 41% in the iron-supplemented group.

IV iron supplementation, therefore, has a demonstrated clinical benefit in iron-deficient chronic HF patients, anemic or not. Iron deficiency should be considered an independent therapeutic goal in this population [9].

According to 2017 US recommendations, IV iron supplementation for iron deficiency has to be considered in NYHA II–III patients [39]. The iron status should be reassessed during routine visits (once or twice a year) and after each hospitalization for HF. The recently updated European Society of Cardiology guidelines (2021) indicate that IV iron carboxymaltose therapy should be considered in patients with symptomatic chronic HF with LVEF ≤ 45% and iron deficiency defined as serum ferritin < 100 µg/L or serum ferritin at 100–299 µg/L with TSAT < 20% to alleviate symptoms, and improve function and quality of life [40]. Iron supplementation with IV iron carboxymaltose should also be considered in patients recently hospitalized for HF with LVEF < 50% and iron deficiency according to the exact definition to reduce the risk of HF-related rehospitalization.

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