PATHOPHYSIOLOGY AND MANAGEMENT OF IRON DEFICIENCY IN HEART FAILURE : A LITERATURE REVIEW

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ABSTRACT

When the availability of iron is insufficient to meet the needs of the body with or without anemia, it is classified as iron deficiency characterized by a serum ferritin concentration of less than 100 ng/ml or a 100-299 ng/mL with a transferrin saturation (TSAT) less than 20% in patients with heart failure. Reduced intake, low iron absorption due to increased hepcidin secretion, iron secretion in the reticuloendothelial system as a result of inflammation, and blood loss from the gastrointestinal system are mechanisms believed to cause iron deficiency (ID). With 25–42% of Heart Failure (HF) patients having ID when anaemia is absent, ID is frequent regardless of the presence of anaemia in HF. ID management in HF requires a shift in the therapeutic focus from dealing with anemia to iron supplementation, both oral and intravenous (IV). Current guidelines also support the use of IV iron. New drugs also focus on iron metabolism, which these drugs are still in development.

Keywords: *Iron deficiency, heart failure, inflammation, hepcidin*

ABSTRAK

Ketika ketersediaan besi tidak mencukupi untuk memenuhi kebutuhan tubuh dengan atau tanpa anemia, itu diklasifikasikan sebagai kekurangan besi yang ditandai dengan konsentrasi ferritin serum kurang dari 100 ng/ml atau 100-299 ng/mL dengan saturasi transferrin (TSAT) kurang dari 20% pada pasien dengan gagal jantung. Mengurangi asupan, penyerapan zat besi yang rendah karena peningkatan sekresi hepsidin, sekresi besi dalam sistem retikuloendothelial sebagai akibat peradangan, dan kehilangan darah dari sistem gastrointestinal adalah mekanisme yang diyakini menyebabkan kekurangan besi. (ID). Dengan 25-42% pasien gagal jantung (HF) memiliki ID ketika anemia tidak ada, ID sering terjadi terlepas dari adanya anemia pada HF. Manajemen ID dalam HF membutuhkan pergeseran fokus terapeutik dari menangani anemia ke suplemen zat besi, baik oral maupun intravena. (IV). Panduan saat ini juga mendukung penggunaan besi IV. Obat-obatan baru juga berfokus pada metabolisme zat besi, yang obat-obatan ini masih dalam pengembangan.

Kata kunci: Kekurangan zat besi, gagal jantung, peradangan, hepcidin

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INTRODUCTION

The most significant essential trace element in the body is iron (1), a micronutrient that is metabolically active, a vital cofactor for enzymes, and a crucial component of structural proteins.(2) Both nonhematopoietic functions (such as substrate utilization and mitochondrial energy production) and haematological processes (such as erythropoiesis, oxygen transport, and storage) depend on iron. Because of this, iron deficiency can result in decreased oxygen delivery and poor oxygen utilization (3,4), both of which can increase dyspnoea and lower exercise tolerance.(5)

Heart failure (HF) is a complex syndrome in which the heart does not pump enough blood and nutrients through the body to meet its needs (6) and either 1) a left ventricular ejection fraction (LVEF) □40% (HF with reduced EF/HFrEF) or 2) a plasma NT-proBNP level □125 ng/L. Those with an LVEF >40% and an NT-proBNP level □125 ng/L were further divided into two groups: those with preserved EF (HFpEF) (LVEF □50%) and those with HF with LVEF in the mid-range (LVEF 41%-49%).(5) HF still puts a significant strain on global public health, with a shockingly high mortality rate of up to 75% at just 5 years.(7)

Regardless of sex, race, anaemia, or LVEF, iron deficiency (ID) is a fairly prevalent comorbidity in HF. Overall, low levels of accessible iron are present in close to 50% of individuals with HF, whether or not they have anaemia.(8) Women are more likely than men to have ID, and it rises as the New York Heart Association (NYHA) functional class becomes worse.(9) The frequency is much higher in individuals with acutely decompensated HF, ranging from 72 to 83%.(10)

Reduced intake, decreased dietary iron absorption due to increased hepcidin secretion, iron sequestration within the reticuloendothelial system as a result of inflammation, and subclinical gastrointestinal blood loss—all of which may be common in people taking antithrombotic medications—are just a few of the suggested mechanisms for the development of ID in patients with HF.(11) ID lowers quality of life, decreases exercise ability, boosts mortality risk, and raises hospitalization rates. ID has recently been revealed to play a crucial role in the pathophysiology of HF and the disease's course, raising the possibility that

it may be more than just a comorbidity in HF.(12–14)

METHODS

The literature review approach is the research design that was used. The process of conducting a literature review involves gathering numerous books and journal articles that are pertinent to the issue at hand and the study's goals, summarizing the key points, and compiling them into a single paper. To gain a brief but thorough overview of the pathogenesis and treatment of iron deficiency in heart failure, we searched journal papers about the relationship between iron deficiency and heart failure, as well as about their pathophysiology and therapy.

RESULT AND DISCUSSION

Definition of Iron Deficiency in HF

A "health-related condition in which iron availability is insufficient to meet the body's needs and which can be present with or without anaemia" is classified as ID.(8) A serum ferritin concentration of less than 100 ng/mL or a ferritin concentration of 100-299 ng/mL along with a transferrin saturation (TSAT) of less than 20% make up the definition of ID that is typically employed in the cardiovascular (CV) profession. These cut-offs, which have a sensitivity of 82% and a specificity of 72% for the detection of ID in patients with HFrEF who underwent bone marrow aspiration with iron staining, have been taken from the field of nephrology where they were suggested to have good performance in terms of sensitivity and specificity.(15,16) The American Heart Association /American College of Cardiology/Heart Failure Society of America (AHA/ACC/HFSA) Guidelines for the Management of Heart Failure from 2022 and the European Society of Cardiology (ESC) Guidelines from 2021 both use the same definition.(17)

If a patient has HF or atherosclerotic heart disease, serum ferritin may not be a reliable indicator of diagnosis.(18) The release of ferritin may result from any type of cell damage, including the activation of inflammatory pathways; an increase in serum ferritin may happen even in the presence of ID. Even when ferritin levels are high, a bone marrow biopsy, the gold standard for diagnosing ID, may show the disease.(5) The definition of ID according to biomarkers (19) has been verified by Grote Beverborg et al. TSAT ≤19.8% and serum iron ≤13 mol/L were significantly superior cut-offs than ESC definition with enhanced sensitivity (94%) and specificity

(88%) for ID diagnosis.(2,20) For predicting bone marrow iron depletion in HF patients, serum concentrations of transferrin receptor (sTfR), which mediates the endocytosis of transferrin-iron complexes into cells, perform better than serum ferritin concentrations or TSAT (21) because circulating sTfR levels quantitatively reflect the body's demand for iron in addition to the rate at which erythroid proliferate. Similar to bone marrow investigation, Sierpinski et al. discovered that in clinically stable HF patients, ID defined as serum sTfR of □1.25 mg/L is more reliable than bone marrow staining for detecting ID.(21)

Criteria of Iron Deficiency in HF

Iron deficiency can be classified as absolute or functional based on pathophysiological processes. Both types of iron shortage can occur in HF patients.(22)

1. Absolute iron deficiency: Although iron homeostasis is unaffected, the body's total stocks of iron are decreased. The standard definition is serum ferritin less than 100 g/L. The pathophysiological alterations in HF that result in impaired iron intake and iron loss cause absolute iron shortage.
2. Functional iron deficiency: Despite normal total body iron storage (ferritin 100–300 g/L), the supply of iron is insufficient to support erythropoiesis and other cellular processes. It is typically described as having a TSAT of 20% or less. Heart failure-related systemic inflammation is the cause of functional iron insufficiency.
3. In conclusion, it seems difficult to define ID in HF using traditional biochemical iron criteria. TSAT or serum iron alone are better indicators of systemic ID, while sTfR may outperform them all.(20)

Clinical Symptoms

In HF, an iron deficit is linked to a worse prognosis.(22) The effects of ID (with and without anaemia) on aerobic capacity, endurance capacity, physical performance, and work efficiency have been demonstrated in humans in a number of studies.(23) In patients with ID who did not have anaemia, Ebner et al. discovered a reduced maximal aerobic capacity; in individuals who had both anaemia and ID, the capacity was substantially lower. Independent of NYHA functional class and haemoglobin level, a correlation between aerobic capacity and TSAT and ferritin was found.(19) Additionally, an iron deficit had an effect on how well a person performed cognitively, emotionally, physically, and behaviourally. Iron treatment enhanced cognitive function and exercise performance in iron-deficient patients.(23)

The primary signs of ID in HF patients are fatigue and decreased exercise capacity, which are caused by decreased oxygen storage in myoglobin, decreased energy efficiency, and mitochondrial dysfunction. Because myocardial iron stores may be low in HF, this may further encourage the use of glucose rather than fatty acids, which, when combined with poor reactive oxygen species (ROS) defences, can lead to myocardial dysfunction and unfavourable remodelling.(1) ID is linked to worse clinical outcomes, decreased quality of life, a higher likelihood of hospitalization, and a higher chance of death due to its role in peripheral and heart muscle dysfunction.(19)

Pathophysiology

Iron homeostasis is regulated in a complex and dynamic manner in both healthy physiology and chronic disease states. The pathophysiology of ID in HF is predominantly brought on by iron metabolism imbalance, however other contributing variables such decreased caloric intake, systemic congestion, poor intestinal absorption, and overt and/or occult blood loss may also play a role.(1,2) Hepcidin, a hepatocyte-produced protein that controls the activity of ferroportin, a transmembrane protein responsible for iron export out of both gut enterocytes (i.e., absorption) and hepatocytes and macrophages of the liver's reticuloendothelial system (i.e., mobilization), regulates both iron absorption and mobilization. Iron cannot be absorbed from the stomach or mobilized from the liver once hepcidin has been linked to ferroportin and is degraded by lysosomal enzymes. In proinflammatory situations like HF, hepcidin levels are continuously high, which hinders iron homeostasis and gradually leads to functional and eventually absolute ID.(2,5)

The root reasons of ID are not well understood. Numerous mechanisms are probably in use. Advanced age, kidney disease, being a woman, malnutrition, chronic inflammation, reduced iron absorption, increased iron loss, and the severity of HF have all been demonstrated to be independently linked with ID in HF. It should be noted that many of the risk variables listed above are hypothesized based on observational research and have not yet been proven to cause HF in individuals, therefore they are still speculative. Since iron status is the sum of input and outflow, there are three main factors that might contribute to iron shortage in HF: decreased iron intake, decreased iron absorption, and increased iron loss.(20)

1. Reduced Iron Intake and Low Iron Bioavailability

   According to studies, between 35% and 78% of HF patients are malnourished, making low nutritional status a potential factor in ID in HF. Malnutrition is a complicated aetiology that is assumed to be multifaceted. Fatigue, dyspnoea, swallowing issues, nausea, anxiety, meal monotony, reduced appetite, and early satiety may all be contributing factors. The nutritional status of specific HF patients may be harmed by the (controversial) recommendation to restrict dietary salt consumption. Iron bioavailability, which is referred to as how much iron is absorbed from the consumed diet, is strongly related to iron absorption. The type of iron consumed—haeme or non-haeme iron—which has various absorption mechanisms—determines how much of it is bioavailable.(24) Because poor food and eating habits appear to be a risk factor for ID in HF, advising optimal nutritional intake may be the most important non-pharmacological advise for treating ID in HF.(20)

2. Reduced Iron Absorption

   The kind of iron consumed, iron absorption enhancers and/or inhibitors, and iron status all affect how much iron is absorbed by healthy people. Because it helps explain why some oral iron preparations do not work to restore iron stores in iron-deficient HF but IV iron does, reduced iron absorption is regarded to be a significant role in the development of ID in HF. It is believed that a number of factors decrease iron absorption, resulting in ID in HF.(20)

a. Impaired Intestinal Function

Patients with HF have altered intestinal morphology, permeability, and absorption. Venous congestion in HF patients reduces blood flow to the intestine, leading to intestinal hypoperfusion and, as a result, nonocclusive bowel ischemia, increased mucosal permeability, bowel oedema, cachexia, and changed mucosal bacterial composition. All of this could lead to a malabsorption of micronutrients like iron in the end. According to a study, morphological and functional compensatory mechanisms are significant adaptation mechanisms that increase intestinal iron absorption in rats with absolute ID (IDA). Increased cell proliferation, mucosal thickness, epithelial surface area, and villus length and width are a few of these mechanisms. These adaptive mechanisms may not be functional to physiologically correct ID in HF due to altered intestinal morphology and function. In contrast to IDA rats without HF, it was discovered that, despite reduced hepcidin expression, intestinal expression of key genes for intestinal iron absorption, such as duodenal cytochrome b (Dcyt-b), divalent metal transporter 1 (DMT-1), and

ferroprotein, was not upregulated in Dahl salt-sensitive HF rats. Surprisingly, IDA-HF rats did not exhibit an increase in intestinal hypoxia-inducible transcription 2 (HIF-2) expression, although IDA rats without HF did. By boosting iron absorption, intestinal HIF-2 upregulation is a crucial adaptive strategy to combat ID. All of these supports a dysfunctional iron regulatory system in HF, which hinders physiologically appropriate adaptive responses to correct ID.(20)

b. Inflammation: Role of Interleukin-6 and Hepcidin

Inflammatory indicators such interleukin-1 (IL-1), interleukin-6 (IL-6) and tumour necrosis factor alpha (TNF-□) are produced in greater amounts when HF is present. The primary inflammatory catalyst for elevated hepcidin expression is IL-6. Other cytokines, such TNF-□, interferon alpha, and activin B, or those that operate directly and independently of IL-6, like oncostatin M and interleukin-22, can also increase the expression of hepatic hepcidin. The only known iron exporter, ferroportin, is internalized and degraded by hepcidin, which also causes "iron trapping" in macrophages, hepatocytes, and enterocytes.(19) By reducing iron absorption and mobilization from the reticuloendothelial system, elevated hepcidin levels cause mostly functional ID in HF. Recent research on both chronic and acute heart failure, however, revealed that hepcidin levels are actually lowered in HF.(20) As a result, the original theory that ID in HF is caused by reduced circulatory iron availability caused by metabolic processes prompted by chronic inflammation is replaced with the theory that ID in HF is actually caused by depleted iron reserves.(25)

In vitro models showed that treating immortalized human gastrointestinal epithelial cells with TNF-α led to reduced iron uptake significantly. TNF-α intraperitoneal administration in mice resulted in ID through lowering DMT1 expression, which in turn decreased intestinal iron absorption, with no alterations in hepatic hepcidin synthesis. TNF-α was not significantly greater in HF patients with ID, as demonstrated by Weber et al. in a very small cohort of HF patients (n = 60), which may imply that TNF-α may not be the primary factor causing ID in HF.(19,20)

c. Hypochlorhydria and Excess Alkalinization

In order to absorb non-haeme iron, gastric acids are crucial. Prior to being absorbed by DMT1, non-bioavailable ferric (Fe3+) iron must be converted to ferrous (Fe2+) iron by ascorbic acid or Dcytb, which requires a low pH. Oral iron absorption is significantly decreased by impaired stomach acid production brought on by long-term use of gastric acid-inhibiting drugs

including proton-pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2Ras). PPIs and H2Ras raise pH, which inhibits the absorption of iron. These drugs are frequently used in clinical settings to treat gastroesophageal reflux disease, peptic ulcers, dyspepsia, and/or to prevent gastrointestinal bleeding in patients taking antiplatelet medications like clopidogrel and/or warfarin.(20)

3. Increased Iron Loss

   Utilizing medicines can exacerbate occult blood loss. In comparison to the general population, HF patients are more susceptible to GI lesions because they have higher risk factors for GI bleeding, including as advanced age, multimorbidity, and polypharmacy, or taking numerous drugs that can induce intestinal abnormalities. Antiplatelet and/or anticoagulant medications, such as aspirin, warfarin and clopidogrel, are known to promote GI bleeding by inducing GI lesions, especially when used in combination. This may imply that HF patients have a weak gastric mucosa and are more vulnerable to GI lesions while taking such drugs to treat another HF ailment. The use of antiplatelet and/or anticoagulants has not been consistently linked to ID in HF, nevertheless.(20)

4. Myocardial Iron Deficiency: Role of Neurohormonal Activation

   Myocardial ID (MID) was found to be poorly correlated with systemic iron homoeostasis indicators in HF, indicating that MID may be brought on by factors other than a decline in systemic iron availability. Myocardial ID is believed to be primarily caused by neurohormonal activation, a characteristic of HF. Transferrin receptor 1 (TFR1) is the principal channel through which iron enters cardiomyocytes, and Maeder et al. demonstrated decreased iron concentration in the myocardium of patients with HF corresponding with a lower mRNA expression of TFR1. In an experimental setting, they discovered that a decrease in TFR1 expression is associated with an increase in the neuroendocrine system's activation, especially when it comes to aldosterone and norepinephrine. This shows that TFR1 downregulation may activate neurohormones, which in turn may promote myocardial ID. The importance of iron-regulatory proteins (IRP-1 and IRP-2) to the heart in maintaining myocardial iron was further underlined by Haddad et al. More recently, Tajes et al. showed that neurohormonal stimulation causes MID accompanied by mitochondrial dysfunction in mice with isoproterenol (B-adrenoceptor agonist)-induced HF by decreasing extracellular iron uptake and increasing intracellular iron release. This suggests that ID may be more than just a comorbidity and that neurohormonal stimulation worsens HF by lowering myocardial iron. According to

these results, patients with end-stage heart failure (New York Heart Association class II or III) have cardiac iron content that is two times lower than patients with non-advanced HF (class II or III) with reduced ejection fraction, which may indicate that MID develops or worsens over the course of HF.(20)

Management

Changing the Target: From Anemia to ID

In the past, it has been thought to be beneficial to increase red blood cell production in HF patients by administering erythropoietin (EPO) in order to alleviate anemia, a significant comorbidity in HF. (19) After promising findings from a few early, modest studies (19), larger trials that followed failed to show any clinical improvement after EPO treatment. Contrarily, darbepoetin-treated patients had a higher risk of ischemic stroke and embolic events.(26) Following these unimpressive findings, ID was recognized as a new potential therapeutic target in HF.

Oral iron therapy

The most popular types of iron salts are ferrous fumarate, ferric gluconate, and ferrous sulphate. Additional oral iron formulations include polysaccharide iron complex, ferric maltol, iron bisglycinate, and iron protein succinylate.(2) Despite being widely accessible and reasonably priced, oral iron is unlikely to offer the best iron replacement when treating iron insufficiency in HF patients since it:

- Poorly tolerated due to GI side effects, which frequently prompt patients to stop taking their medications, including nausea, flatulence, abdominal pain, diarrhoea, constipation, and black stools.(19)
- Poorly absorbed due to high hepcidin, which restricts iron absorption by lowering transmembrane ferroportin on enterocytes and reducing iron transfer from enterocytes to blood.(1) This elevated hepcidin might be caused by inflammatory cytokines or oral supplementation itself.(27,28) GI oedema and decreased GI blood flow linked to CHF are also present, and it takes a long time (more than 6 months) to replenish iron stores.
- Interactions with dietary ingredients and some medicines cause poor absorption. Moreover, evidence from clinical studies, including a small randomized trial (IRON-HF24) that compared the effects of oral and IV iron replacement on exercise capacity in iron-deficient HF patients, suggests that oral iron therapy is unlikely to be effective in patients with HF.(29,30) Other trial, the Oral Iron Repletion Effects On Oxygen Uptake in Heart Failure (IRONOUT

HF) trial, 16 weeks of treatment with 300 mg of elemental iron daily (polysaccharide iron complex) only modestly increased Tsat by 2% and ferritin by 18 ng/ml and the primary endpoint, a change in peak oxygen uptake from baseline to 16 weeks, did not differ between groups at the end of the follow-up. The secondary endpoints of the 6-min walking test (6MWT) and NT-proBNP levels showed no significant increases either. For absolute iron shortage, oral iron should be provided for at least 3 months, with an assessment of iron replenishment after 1 month. If oral therapy is ineffective or intolerable, oral therapy should be halted and intravenous iron should be given. Since oral iron is ineffective in this clinical situation, intravenous iron must be administered initially in cases with functional iron insufficiency.(23)

IV iron therapy

There are now five distinct formulations that are appropriate for intravenous iron supplementation that are offered in the USA and Europe.(24) The formulations and single-setting doses of iron sucrose (200 mg), ferric carboxymaltose/FCM (up to 1,000 mg in 50 mg/ml solution), and ferric derisomaltose are most frequently utilized in investigations of individuals with HF.(17) With IV administration, iron can skip the GI tract, avoiding the problems with absorption and GI-related side effects that come with oral iron, but at a higher cost and with more complicated administration requirements.(2,29) Every existing intravenous iron product has the potential to produce mild side effects like flushing and trunk arthralgias /myalgias.(2) Intravenous iron is made up of an iron hydroxide core encased in a carbohydrate shell that detoxifies the body while also regulating the release of iron.(31) IV iron replacement is beneficial in HF patients who are iron deficient, according to Increasing of clinical study evidence. Most early clinical investigations looking into IV iron replacement in HF patients used iron sucrose as their iron source.

These small-scale studies—including the FERRIC-HF single-blind randomized trial in anaemic and non-anaemic iron-deficient HF patients—repeatedly demonstrated the correction of iron deficiency and improved cardiac function (NYHA functional class and LVEF), symptoms, exercise tolerance, and quality of life. Ferric carboxymaltose has been the key component of more recent research that have confirmed the therapeutic advantages of IV iron replacement observed in the earlier smaller trials. These larger-scale investigations include the 6-month FAIR-

HF study, the longer duration CONFIRM-HF trial, which had an extended observation period of 12 months, and the 6-month EFFECT-HF trial, which featured exercise capacity as the primary endpoint. The Australia and New Zealand 2018 guidelines for the prevention, detection, and management of heart failure, as well as other international guidelines, advise that IV iron replacement be taken into consideration in iron-deficient HF patients to provide symptomatic relief and enhance exercise capacity and QoL. This recommendation is based on the data from FAIR-HF and CONFIRM-HF. The long-term benefits of IV iron supplementation in HF have still to be demonstrated, however, and the findings of ongoing large outcome trials with this objective are awaited. Two meta-analyses of randomized clinical trials have evaluated the impact of IV iron therapy on the hard endpoints of hospitalization and mortality: a standard meta-analysis (5 trials; n=851) and an individual patient data meta-analysis (4 trials; n=839). They found statistically significant improvements in NYHA class, exercise capacity, QoL, and symptoms along with statistically significant decreases in all-cause mortality, cardiovascular hospitalization, and HF hospitalization linked to IV iron replacement in iron-deficient HF patients.(29,30)

The use of intravenous iron for the treatment of iron deficiency is supported by the 2022 ACC/AHA/HFSA Guideline for the Management of Heart Failure and the 2021 European Society of Cardiology (ESC) Guidelines for the diagnosis and treatment of acute and chronic HF, respectively, with a class of recommendation and level of evidence of 2a/B-R and IIa/A by each guideline. While the ACC/AHA/HFSA remain neutral regarding other treatment options, the ESC guidelines recommend intravenous FCM as the preferred approach. It should be noted that the fact that these recommendations were released before the IRONMAN study adds to the clinical trial evidence supporting the use of ferric derisomaltose in HF.(2,29)

CONCLUSION

Iron is one of the most important essential elements in the body where a deficiency of this substance can lead to a decrease in oxygen supply and poor oxygen usage leading to fatigue and reduced exercise capacity, reduced energy efficiency, and mitochondrial dysfunction. Iron deficiency is a common comorbidity in heart failure patients. This iron deficiency can be classified as absolute, characterized by serum ferritin values less

than 100 g/L or functional, characterized by a normal ferritine level of 100-299 ng/mL with a transferrin saturation (TSAT) less than 20%. There are three main factors that can contribute to iron deficit in cardiac failure: reduced intake, reduced absorption, and increased loss of iron. Management of iron deficiency in heart failure includes changing the therapeutic target focus from anemia to iron supplementation with both oral and intravenous supplements. (IV). However, research so far has not supported the use of oral iron supplements due to their inadequate effectiveness IV and can also cause many side effects especially on the gastrointestinal system. The use of IV iron has been supported by the ACC/AHA/HFSA guidelines in 2022 and the European Society of Cardiology (ESC) guidelines in 2021. There are currently several new drugs in the process of research which target iron metabolism either by affecting the hepcidin-ferroportin axis, IL-6 activity, or by modulating the PHD/HIF pathway.

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