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Current Research Progress of Iron Deficiency in Heart Failure

Jiahao Song, Zhimin Fang, Jiaqi Sun

The Second Affiliated Hospital of Xinjiang Medical University, Urumqi 830000, Xinjiang, China

Abstract: ***Iron is an essential element for human life activities, and it plays an important role in various life activities, such as oxygen transport and storage, electron transport in the oxidative respiratory chain, catalyzing the synthesis and decomposition of proteins, lipids or nucleic acids, iron-dependent cell death, etc. Iron deficiency is extremely common in patients with heart failure Iron deficiency (ID) is a common comorbidity in patients with heart failure, impairs exercise capacity, reduces the quality of life, increases hospitalisation rate and mortality risk regardless of anaemia. Intravenous iron therapy in patients with heart failure and iron deficiency has achieved considerable results, but how to effectively identify patients who are most likely to benefit from intravenous iron therapy remains controversial. This article reviews the mechanism of iron homeostasis in the body, and current diagnosis and treatment of iron deficiency in heart failure.***

Keywords: Heart Failure, Iron Deficiency, Ferritin, Iron Homeostasis**.**

1. Introduction

Heart failure (HF) is a group of clinical syndromes caused by abnormal changes in cardiac structure and/or function due to various reasons, resulting in ventricular systolic and/or diastolic dysfunction. Due to its high morbidity, high mortality, poor quality of life, and high treatment costs, it has brought a huge public health burden to China [1]. There is an urgent need to take effective prevention and treatment measures. Iron deficiency (ID) is a common complication of HF patients. Regardless of whether anemia is present, iron deficiency is associated with quality of life, decreased cardiac function, and poor prognosis [2]. Intravenous iron therapy has achieved considerable results in patients with HF and ID [3]. However, how to effectively identify patients who may benefit from intravenous iron therapy remains controversial. The complex regulatory network composed of multiple factors may affect the diagnosis and treatment of HF combined with iron deficiency. Therefore, this article reviews the systemic iron homeostasis and the diagnosis and treatment of HF combined with iron deficiency.

2. Iron Homeostasis

Under physiological conditions, all the body's iron comes from the diet. Heme-bound iron is transported into the intestinal epithelial cells by heme carrier protein 1 (HCP1); free ferrous iron is transported into the intestinal epithelial cells by divalent metal transporter 1 (DMT1) in the duodenum and upper jejunum; ferric iron is reduced to ferrous iron by ferroreductase in an acidic environment and then absorbed by DMT1. In intestinal epithelial cells, part of the iron is stored or consumed by the cells, and the rest is exported to the circulating blood through ferroportin (FPN1) [4].

In the circulation, in addition to intestinal epithelial cells taking up iron from the diet, macrophages phagocytize old and damaged red blood cells and release iron into the serum. Other iron-storing cells also release iron into the circulating blood through FPN1. The iron in serum exists mainly in the form of transferrin-bound iron (TBI). Under physiological conditions, transferrin saturation is relatively low. However, under pathological conditions associated with severe iron overload, such as hemochromatosis, excessive iron enters the blood circulation, exceeding the carrying capacity of transferrin, resulting in the formation of non-transferrin -bound iron [5] (NTBI), which is a redox-active and potentially toxic form of iron.

The body loses about 1 to 2 mg of iron per day during epithelial cell shedding and bleeding. Since the loss of iron in the body is unregulated, the key to systemic iron regulation is iron absorption by intestinal epithelial cells, which can increase by as much as 10 times when demand increases (such as bleeding and hemolysis). Hepcidin maintains iron homeostasis by binding to Fpn1 on the cell surface and triggering its internalization and lysosomal degradation [6].

2.1 BMP-SMAD Pathway Regulates Hepcidin Expression

Bone morphogenetic proteins (BMPs) are a group of proteins in the TGF-β superfamily that activate downstream signaling pathways by binding to cell surface BMP receptors [7]. Sinusoidal endothelial cells produce BMP-2 and BMP-6, which form hexamers with BMP1 and type II receptors on the surface of hepatocytes in a paracrine manner. Type II receptors then phosphorylate and activate type I receptors. BMP1 phosphorylates regulatory Smad proteins. After Smad1/5/8 are phosphorylated, they form a complex with Smad4 and transfer to the nucleus to bind to the BMP response element in the promoter region of the target gene to regulate gene transcription [8]. Endothelial cells of the liver sinusoids can sense changes in iron concentration in the body and upregulate Bmp2 and Bmp6. The mechanism is currently unclear. Nuclear factor NF-E2-related factor (Nuclear factor-erythroid 2-related factor 2, NRF2) and amino -terminal kinase (c-Jun N-terminal kinase, JNK) [9,10] It may play a key role in regulating the expression of Bmp proteins. Bmp2 is the main ligand for maintaining basal hepcidin. Under normal circumstances, its expression is about 12 times higher than that of Bmp6. Under conditions of iron overload, Bmp6 is upregulated in an iron-dependent manner and promotes hepcidin secretion.

Hereditary Hemochromatosis Protein (HFE) and transferrin receptor (TFR) are involved in regulating SMAD1/5/8

phosphorylation and hepcidin expression [11]. HFE and iron-bound transferrin have a common binding site on TFR1. The increase in the concentration of iron-bound transferrin competes for the binding site of HFE and TFR1, making HFE free. HFE is believed to interact with the Bmp receptor ALK3 and increase its stability, thereby enhancing Bmp signaling.

Increased erythropoietic activity in vivo also inhibits hepcidin expression through the BMP-SMAD pathway [12]. Under the action of erythropoietin, erythroid precursor cells produce erythroferrone (ERFE). In the perisinusoidal space of the liver, ERFE interacts with BMP-2 and BMP-6 and interferes with their contact with BMP receptors, thereby downregulating the BMP-SMAD pathway. Other mechanisms may also lead to the inhibition of hepcidin when erythropoietic activity increases. For example, when erythropoietic activity increases, erythropoietin-dependent TFR1 expression on the surface of nucleated red blood cells increases [13], resulting in rapid consumption of iron-bound transferrin from plasma, HFE binding to TFR1, and reduced secretion of hepcidin.

2.2 Hepcidin is an Acute Phase Protein, and Its Level is Also Controlled by Inflammatory Signals

Infection, injury, and metabolic disorders can cause an increase in inflammatory cytokines (such as interleukin 6, interleukin 1, and tumor necrosis factor α). IL-6 may play a key role in regulating hepcidin synthesis in hepatocytes. Binding of IL-6 to the hepatocyte surface receptor GP130 can activate the JAK2-STAT3 signaling pathway. Phosphorylated STAT3 translocates to the nucleus, binds to the STAT3 response element on the hepcidin promoter, and activates the expression of its target genes [14]. The inflammatory hepcidin response may be to prevent the production of NTBI during infection to prevent the rapid growth of NTBI-dependent extracellular microorganisms. However, inflammation - induced increases in hepcidin can also limit the use of iron for erythropoiesis and lead to inflammatory anemia.

3. Intracellular Iron Homeostasis

Most cells obtain iron from transferrin through receptor-mediated endocytosis. Transferrin binds to TfR1 and takes iron into the cell through endocytosis. The iron that enters the cell exists in the form of highly active Fe2+ in the unstable iron pool and participates in the synthesis of iron-sulfur clusters and hemoglobin.

Highly active Fe2+ may cause cell membrane peroxidation and cell damage. Fe2+ catalyzes reactive oxygen to obtain electrons from cell membrane lipids, leading to oxidative damage and iron-dependent programmed cell death. Cells use ferritin to isolate active Fe2+ in cells, keeping the intracellular Fe2+ at a lower level, thereby reducing Fe2+-mediated lipid peroxidation and cell death. Ferritin is a cage-like multimeric protein composed of two different subunits (light chain I and heavy chain H), which can contain up to about 4500-5000 iron atoms. As an iron storage protein, it exists in almost all forms of cells. Most ferritin in the human body exists in cells and binds to iron to prevent the generation of free radicals. A small amount exists in plasma, mainly derived from macrophage secretion [15]. Serum ferritin can reflect the body's iron reserves to a certain extent, but inflammation, tumors, liver damage, etc. also affect serum ferritin levels.

3.1 IRP-IRP Interactions Regulate Gene Expression

Iron regulatory protein (IRP) is an RNA-binding protein [16] that regulates cellular iron metabolism post-transcriptionally by interacting with the iron responsive element (IRE) on mRNA. IRE is a highly conserved stem-loop structure located in the 5′ and 3′ untranslated regions of mRNA that can bind to IRP. IRP1 has dual activity. When intracellular iron is abundant, it can bind to the cytoplasmic FeS cluster and exert aconitase activity; when iron is deficient in the cytoplasm, it dissociates from the FeS cluster and binds to IRE [17]. IRP2 is constitutively active and is degraded by ubiquitin when iron is abundant in the body. When IRP binds to the IRE at the 5' end of mRNA, it blocks the binding of mRNA to the small ribosome subunit and reduces gene expression. When IRP binds to the IRE at the 3' end of mRNA, it prevents mRNA from being hydrolyzed by ribonucleases and increases gene expression. When intracellular iron is deficient, IRP binds to the IRE at the 5' end of mRNA of genes such as FTL, FTH1, and SLC40A1, and reduces the expression of ferritin and iron transporter through a steric mechanism, reduces cellular iron output, and increases intracellular active iron. It binds to the IRE at the 3' end of TFRC to increase tFR expression and increase cellular iron uptake. At the same time, the IRP-IRE system also regulates the expression of many other proteins [18] (such as ALAS2, heme, and HIF-2α).

3.2 Hypoxia-inducible Factor

HIF is constantly expressed in vivo. However, under oxygen-rich conditions, HIF is hydroxylated by the coenzyme PDH and then ubiquitinated for degradation. In addition to oxygen, this process also requires the interaction of Fe2+ and 2-OG. Iron deficiency/hypoxia can stabilize HIFα in the cytoplasm [18], increasing its level in the cytoplasm and then binding to nuclear cofactors to regulate the expression of genes such as TF, TFRC, HMOX1, SLC11A2, and SLC40A1. At the same time, the interaction between IRP-IRE also regulates the gene expression of EPAS1 (encoding hif2).

3.3 Oxidative Stress Pathway

The transcription factor NRF2 is constitutively active in tissue cells. Under physiological conditions, the redox sensor KEAP1 binds to NRF2 and induces its ubiquitination and degradation. When the intracellular ROS level increases, KEAP1 is oxidized or alkylated, and the stability of NRF2 in the cytoplasm increases. It binds to sMAF in the nucleus and induces the expression of more than 250 ARE-containing genes [19]. The expression products of these genes play an important role in anti-oxidation, reducing iron-induced cell damage and maintaining iron homeostasis.

Iron homeostasis in cardiomyocytes is also regulated through the above pathways, but unlike systemic iron regulation, cardiac hepcidin has an important autocrine effect [20]. When iron is deficient, cardiac hepcidin levels are upregulated to protect cardiomyocyte iron. In addition to the pathways mediated by TfR1 and DMT1, NTBI influx into cardiomyocytes through calcium channels and zinc transporters is not regulated by these cellular regulatory

mechanisms [21].

4. Mechanisms of Iron Deficiency in Patients with Heart Failure

Iron deficiency is a common complication in heart failure. Approximately 50%-63% [22,23] of heart failure patients suffer from iron deficiency. Iron deficiency is divided into absolute iron deficiency due to insufficient iron intake, impaired absorption or chronic blood loss, which leads to depletion of iron reserves and reduced systemic iron supply, and relative iron deficiency due to impaired iron utilization caused by excessive hepcidin secretion, depending on the mechanism of its occurrence.

In the early stages of heart failure, relative iron deficiency occurs because inflammatory responses such as ischemic cardiomyopathy, scar formation, and ventricular remodeling increase IL-6 [24] and upregulate hepcidin expression through the JAK-SATA pathway. However, iron deficiency in most patients with heart failure cannot be attributed solely to hepcidin-mediated iron sequestration within the reticuloendothelial system. Multiple factors (such as 1) long-term functional iron deficiency leading to dietary iron absorption disorders; 2) occult gastrointestinal and urogenital blood loss due to the use of antiplatelet and anticoagulant drugs; 3) intestinal edema during heart failure leading to reduced absorption; 4) dietary nutritional deficiencies; 5) use of proton pump inhibitors leading to reduced iron absorption) can all lead to absolute iron deficiency, which may be superimposed on the state of functional iron deficiency. It may be difficult to strictly distinguish between relative iron deficiency and absolute iron deficiency.

5. Diagnostic Criteria for Iron Deficiency in Patients with Heart Failure

Bone marrow aspiration iron staining is considered the “gold standard” for diagnosing ID, but its invasiveness limits its clinical application. The ESC heart failure guidelines [25] define ID as serum ferritin <100 ng/mL or transferrin saturation (TSAT) <20% when ferritin is 100-299 ng/mL, with these criteria being based primarily on the opinion of nephrologists. However, recent studies [26] have shown that this definition does not adequately identify patients at highest risk for adverse events or those with heart failure who are most likely to benefit from intravenous iron therapy.

In a prospective study of 4,422 patients with heart failure, TSAT <20% and serum iron ≤13 μmol/L were associated with a higher 5-year mortality rate. In another prospective study of 42 patients with heart failure who underwent coronary artery bypass grafting [27], these patients underwent bone marrow puncture and iron staining, and the guideline criteria were found to have a sensitivity of 82% and a specificity of 72%, while the definition based only on TSAT ≤19.8% or serum iron ≤13 μmol/L had a sensitivity of 94%, a specificity of 84%, and a specificity of 88%, respectively. These results suggest that ferritin, as an acute phase response protein, is affected by factors such as inflammation and cell damage in its serum level, and excessive reliance on it in the diagnosis of ID may lead to misjudgment of the patient's iron level.

6. Iron Supplementation for Patients with Heart Failure

6.1 Oral Iron Supplements

Iron supplements can be naturally absorbed in the duodenum and proximal jejunum, and oral iron supplementation is more in line with the physiological state. During ID, hepcidin levels are downregulated, which increases the expression of FPN1 on the surface of enterocytes, causing iron to leave the enterocytes and enter the circulation. When serum iron levels return to normal, hepcidin production in the liver increases and prevents further iron release from enterocytes. Due to this feedback mechanism, oral iron supplementation is generally safe and rarely causes systemic iron overload. However, as mentioned above, in chronic inflammatory diseases, increased hepcidin synthesis may hinder the absorption of oral iron by enterocytes, making oral iron supplementation ineffective. In IRON-HF [28] and IRONOUT [29], oral iron supplementation failed to increase peak oxygen consumption and the distance of the 6-minute walk test compared with placebo, suggesting that oral iron supplementation is ineffective for HF patients with ID or mild anemia.

6.2 Intravenous Iron Supplementation

Unlike oral iron, a single IV iron dose delivers up to 1,500 mg of iron directly into the circulation, and multiple trials have shown that IV iron supplementation reduces the risk of HF or cardiovascular hospitalization or death and/or improves cardiac function (as measured by a 6-minute walk test or peak VO2) [30-32]. IV iron supplementation can rapidly and significantly correct iron indices, particularly in settings where absorption is impaired (e.g., in patients taking proton pump inhibitors). However, this route of administration bypasses systemic iron regulation mechanisms and may result in local iron overload of endothelial and myocyte cells through non-transferrin receptor-mediated iron uptake. Furthermore, iron supplementation in patients with heart failure and infection may increase their risk of infection [33].

7. Summary and Outlook

ID has long been associated with anemia, and hemoglobin levels are often considered an indicator of iron status. However, impaired hemoglobin synthesis is a late consequence of ID, and only one-third of iron-deficient patients will experience anemia, and non-anemic ID has been neglected. Hemoglobin and sTFR concentrations are effective in diagnosing red blood cell iron deficiency, but assessing the iron status of non-red blood cell tissues remains challenging. In heart failure, multi-system involvement and the use of multiple drugs make the assessment of the body's iron status more complicated. Analyzing the mechanisms of iron homeostasis at the cellular and molecular levels will help us manage the iron status of heart failure patients in a more individualized manner.

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