

REVIEW ARTICLE

Role of Hepcidin in Heart Failure with Iron Deficiency – Deception or Disposition

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Abstract

It is well established through clinical studies that Heart Failure [HF] has a strong co-relation with inflammation and inflammatory markers [TNF-Alpha, IL-Beta, IL-6]. Among other co-morbidities, Iron deficiency [ID] is very common in HF patients especially in India with a 76% prevalence.¹ It can lead to reduced exercise capacity, increased Hospitalizations, impairment in the Quality of life and also increased Mortality irrespective of anaemia.²

In HF, there is a constant high demand for energy and energy producing molecules. This leads to increased demand in iron as well. The body iron stores [Ferritin] can supply to a limit but in chronic heart failure due to underlying chronic inflammatory process, the demand exceeds the availability of iron in the body. Thus patients may land up with Iron deficiency much before they present clinically with anaemia. On other hand IL-6 in HF triggers release of Hepcidin [Master regulator of Iron] from liver which tries to protect the remaining body iron stores by blocking the Ferroportin channel, locking the iron in the store. This could further complicate the iron deficiency state in the body.³

Evidence suggest that oral iron is ineffective due to factors like intestinal oedema, reduced GI absorption of iron coupled with GI discomfort of oral iron.² Secondly the doses of oral iron may not be sufficient to overcome the Hepcidin Block. Newer theories postulate and enumerate that IV Iron in high doses increase the intracellular iron levels, can induce new ferroportin channel and may overcome the Hepcidin Block.^{4,5} The Hepcidin – Ferroportin axis and the Hepcidin block are new concepts of ID in HF and more research is needed in this direction to understand their importance. With the current evidence available it is further to be explored whether this concept is a Deception or of strong Disposition in HF with ID.

Pathogenesis of Heart Failure

Heart failure (HF) is primarily a clinical diagnosis that develops secondary to either left ventricular (LV) dysfunctions [systolic and diastolic]. Despite significant advancements in medical therapies designed to prevent HF development and treat HF, the prognosis of patients remains poor. In outpatients with chronic HF, a hospitalization is one of the strongest prognostic predictors for increased mortality. Given the overwhelming burden of chronic HF, in terms of mortality, morbidity, repeated and prolonged hospitalizations, a greater in-depth consideration of the pathophysiological mechanisms merit

accelerated investigation, diagnosis and treatment.²

The traditional concept of HF as haemodynamic disorder failed to completely address the progression of HF. This led to the postulation of neurohormonal hypothesis in which the activation of the sympathetic nervous system and renin angiotensin aldosterone system (RAAS) exert a direct deleterious effect on the heart, independent of the hemodynamic actions. In the 1990s, it became apparent that in addition to neurohormones, cytokines play an important role in

the pathogenesis of HF (cytokine hypothesis). Propagative ideation like the neurohormonal and the cytokine hypothesis have radically changed the understanding of the pathophysiology of HF. Inflammation has been recognized to play an important part in pathogenesis and treatment of both types of HF (acute and chronic). Common to both types of HF is the correlation between elevated serum concentrations of pro-inflammatory markers.³

Inflammation triggers HF in its different aspects. It impacts on the pathogenesis of HF including underlying comorbidities like diabetes and obesity. It can influence progression and outcome of HF. Inflammatory cytokine (TNF- α , IL-1 β , IL-6) levels are increased in HF patients which are independent predictors of mortality in patients with advanced HF.⁴

Cytokines increase cardiomyocyte stiffness, cardiac remodelling and cardiomyocyte apoptosis. They also augment the angiotensin (Ang) II-mediated cardiac fibroblast responses that favour fibrosis and promote eccentric myocardial remodelling

On the other hand, the failing heart induces wall stress, exposing all cells to biomechanical strain leading to the release of cytokines. TNF- α , IL-6, IL-18, ANP Cardiac fibroblasts are in-turn activated triggering the typical inflammatory pathways.⁴

Co-Morbidities in Heart failure affected by underlying inflammation

Heart failure and the underlying inflammation also affect the functioning of Bone marrow, endothelial function, skeletal muscle function, gut permeability and may also induce multisystem inflammation leading

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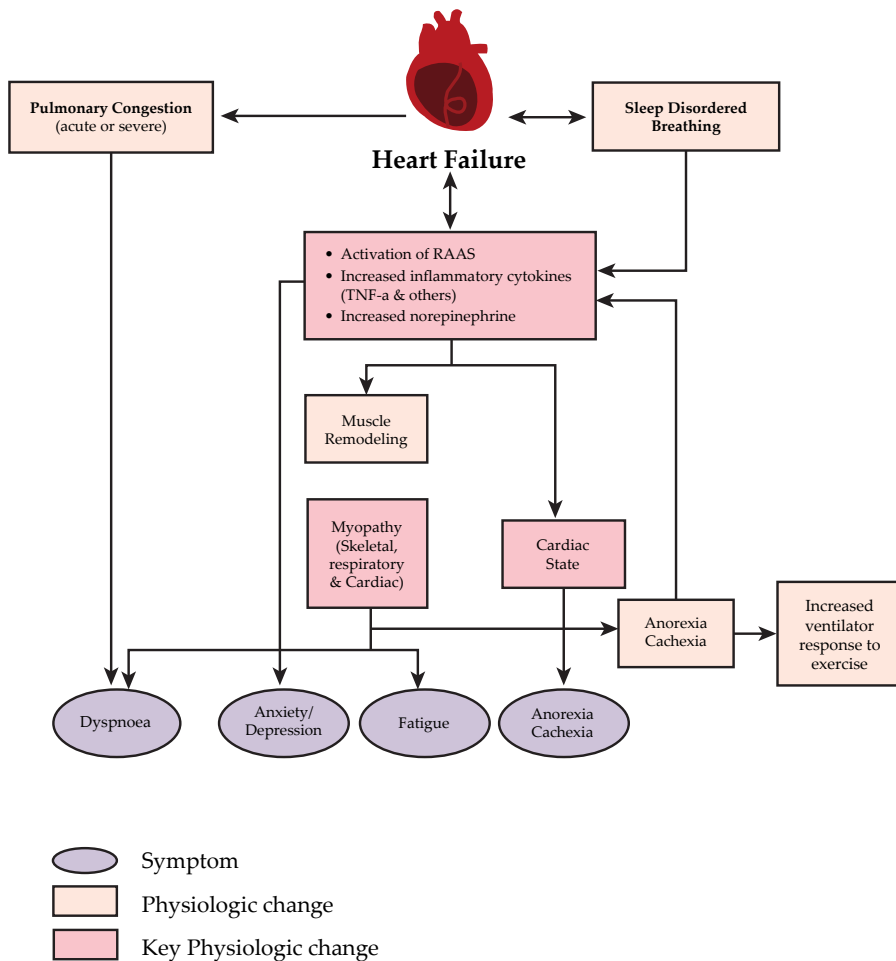


Fig. 1: Heart Failure and Inflammation

to reduced skeletal muscle function resulting in fatigue, reduced absorption from the intestines, overall poor quality of life, anaemia and also iron deficiency [ID].

Iron is an essential trace element present in a number of molecular systems, and it is increasingly recognized as an important co-factor for a variety of cell systems. It has been documented that iron plays an important role not only in the oxygen transport but also in cell growth and proliferation, as a cofactor for functioning of various mitochondrial enzymes and proper functioning of cardiomyocytes and skeletal muscle cells.¹³

Iron Deficiency in Heart failure [ID in HF]

A cohort study with population worldwide noted that prevalence of ID in HF was as high as 50%. An Indian study reported the prevalence to be around 76% in Chronic HF. It is also well established now that ID is an independent predictor of mortality in

HF patients and increases the risk of Mortality by 40 - 50%. Pathophysiology of ID in HF is multifactorial. The impending mechanisms include.⁶

- Reduced intake of Iron
- Increased loss of iron
- Altered gastrointestinal absorption due to intestinal oedema
- Drugs that increase gastric pH (like Proton Pump Inhibitors, H2 antagonists, etc)
- Ingestion of food that reduces calcium absorption (calcium, tannins, oxalates, phytate, phosphates, antacids)
- Gastrointestinal disorders (peptic ulceration, esophagitis, gastritis, duodenitis)
- Menstrual blood loss
- Re-distribution of this microelement to tissue compartments (entrapment in the reticuloendothelial system) where it is not available for metabolic processes.

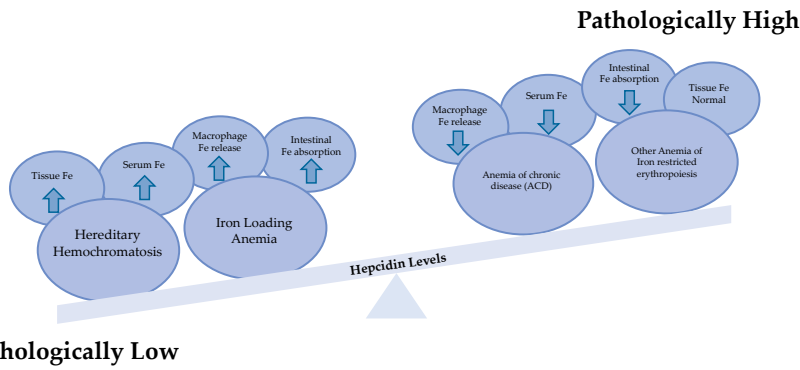
- Hecpudin Block [Hecpudin Ferroportin Axis derangement]

Role of Hecpudin in Heart Failure

Hecpudin is the iron regulatory hormone produced by the liver in response to the fluctuating level of iron in the hepatocyte or in response to elevated cytokine (IL6) levels induced by inflammation or infection. Inappropriate elevation of hecpudin is an important mechanism of anaemia of chronic disease. In inflammatory conditions, higher levels of hecpudin coincide with elevated inflammatory markers (IL6) and more severe disease. In HF, the opposite relationship has been demonstrated, with serum hecpudin levels found to be inversely related to the severity of disease. The postulated role of hecpudin in inflammation and infection is to deprive pathogens or cells with high demand of essential iron; forming part of our innate immunity.⁷ In healthy individuals since there is more iron in stores and transferrin, there is noticeably more hecpudin release which stops the export. But hypoxia and intensified erythropoiesis after blood loss leads to less Hecpudin release and more Iron export and utilization.

When iron or cytokine levels are high, hecpudin synthesis is stimulated resulting in the removal of ferroportin from the duodenal enterocyte, macrophage, and hepatocyte cell membranes diminishing iron efflux into the bloodstream. Conversely, in ID and hypoxia, hecpudin synthesis is down-regulated allowing ferroportin to remain in the cell membrane and iron to be absorbed or released into the plasma.⁸

In a case-control study of 321 patients with chronic HF, high hecpudin levels were found in patients with mild symptoms of HF (NYHA I/II). Hecpudin levels were not associated with Hb levels, IL6 levels were low, and ferritin levels were high, suggesting that the elevation of hecpudin was secondary to high iron levels and that iron homeostasis was deranged. With increasing severity of disease prevalence of ID anaemia increased and hecpudin levels were lower, both regardless of increased levels of IL6, again suggesting that hecpudin levels are more responsive to iron than inflammatory markers in HF. While similar results were found in another



Pathologically Low

Fig. 2: Hepcidin Expression in different Pathological conditions

smaller cohort of patients with HF, further studies are required in this area.⁸

Hepcidin downregulates ferroportin expression on the cell surface. The binding of hepcidin to FPN leads to its phosphorylation, internalization, and degradation. Low levels of FPN expression reduce iron absorption in the gut, lower iron release from the liver, and prevent iron recycling by tissue macrophages.¹⁰

In a study, injection of hepcidin into mice resulted in a dramatic drop in serum iron within just 1 h. Even though hepcidin is rapidly cleared from the plasma, the effect of a single dose was apparent for up to 72 h, likely because of the time required to resynthesize sufficient amounts of the hepcidin receptor, ferroportin. Ferroportin is both the hepcidin receptor and the only known cellular iron exporter in vertebrates. The binding likely involves disulphide exchange between one of disulfide bonds of hepcidin and the exofacial ferroportin thiol residue. Ferroportin expression can also be regulated independently of hepcidin, by cellular iron content. Cellular iron has been shown to have an effect both at the transcriptional and translational level, the latter through a mechanism involving cytoplasmic iron-regulatory proteins and their corresponding binding sites on one of the ferroportin mRNA isoforms.¹⁴

Furthermore, neurohormones may mediate reduction in transferrin receptor expression on the cardiomyocyte resulting in intracellular ID which in turn may induce changes in the cardiomyocyte, decreases its ability to work and increases the risk of cellular apoptosis an unwanted stress on a failing myocardium.⁷

Role of IV Iron in Overcoming Hepcidin Block

Oral iron supplementation is usually “the first choice therapy” for ID, but frequently the response to the treatment is suboptimal. It is a judicious option for healthy subjects without absorption disorders, in whom ID is usually mild and prompt replenishment is not obligatory. In a retrospective study, regarding ID patients with HF rEF, oral iron supplementation over 180 days did not reveal any clinical benefits beyond improvement in serum iron indices and haemoglobin; particularly, there was no difference regarding re-hospitalization rates. In another study in HF patients with anaemia, substitution with oral iron for 1 year was not associated with any clinical benefits in the perspective of improvement in NYHA status, exercise capacity, and the need for hospitalization. In the recently presented prospective, randomized clinical trial (IRON-OUT), oral iron 150 mg twice daily for 16 weeks had little effect in replacing iron stores and did not improve peak VO₂, 6-min walking distance and HRQoL score in anaemic HF rEF patients.

There are at least ten parenteral (IV or intramuscular) iron formulations approved for therapeutic use: ferric sorbitol, iron dextrans (high- and low-molecular weight dextran), iron poly maltose, iron sucrose (ISC), ferric gluconate, ferric carboxymaltose (FCM), iron isomaltoside 1000, and ferumoxytol. There are many clinical trials using different IV Iron in ID with HF. Maximum trials exist with the use of FCM in HF with ID. Evidences also suggest that high doses of IV Iron increase the intracellular iron and overcome the Hepcidin block by inducing overexpression of Ferroportin channels. One of the studies showed

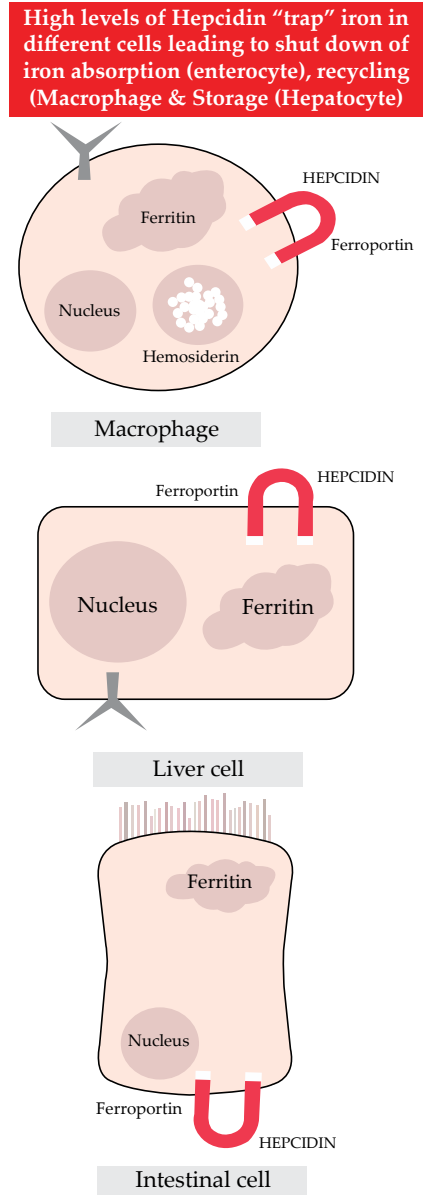


Fig. 3: Hepcidin Binding to the ferroportin channels of Enterocytes, hepatocytes and Macrophages

that direct exposure of murine or human hepatocytes to ferric iron, did not induce hepcidin mRNA, and higher concentrations of iron suppressed it.¹⁵

FCM and Isomaltoside are two of the IV iron preparations that are available for use. They both have a better safety profile [no test dose required] as compared to other I/V iron preparations and can be given in high doses. But Isomaltoside is a dextran derivative and needs a longer duration of administration [60 min] for a dosage of >1000 mg. Very few published evidences for use of Isomaltoside exist. On the other hand FCM can be given in

high doses in a short amount of time. CONFIRM-HF and EFFECT-HF trials used 1000 mg FCM as starting dose in most of the patient after calculating the deficit in the ID patients. FCM is useful for rapid and high-dose replenishment of depleted iron stores. It has been observed that serum iron concentration increases rapidly after administration of a single dose of IV FCM equivalent to 100–1000 mg of iron. FCM is rapidly distributed from plasma not only to bone marrow, but also liver and spleen. Rapid iron uptake by the bone marrow occurs in the first 10 min following FCM administration, with subsequent uptake occurring at a slower but steady rate. In patients receiving a single dose of FCM equivalent to 100–1000 mg of iron, the half-life of elimination of FCM from the plasma is 7–12 h. Renal elimination of iron is negligible. Weekly administration of FCM (up to two infusions of 1000 mg of iron and four infusions of 500 mg of iron) does not result in accumulation of iron in the serum. Being dextran-free, FCM does not react with anti-dextran antibodies and a test dose is not required.⁶

Summary and Conclusion

Inflammation and heart failure are strongly interconnected and mutually reinforce each other. This indicates the difficulty to counteract inflammation and heart failure once this chronic vicious circle has started and points out the need to control the inflammatory process at an early stage avoiding chronic inflammation and heart failure. Inflammation also plays a crucial role in complicating ID via Hepcidin block. Only IV iron [FCM in majority] has proven to be beneficial in HF patients with ID. High dose IV iron can overcome the hepcidin block. FCM can be given in High doses in short duration of time and by postulation may overcome the Hepcidin block correcting the iron deficiency along.

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