PATHOLOGICAL CHANGES IN PATIENTS WITH CHRONICH HEART FAILURE AND IRON DEFICIENCY ANEMIA

Umurkulov Khusniddin
Teacher of pathology and forensic medicine department,
Central Asian Medical University

Abstract; *Chronic heart failure (CHF) and iron deficiency anemia (IDA) often coexist, worsening patient outcomes due to impaired oxygen delivery and increased myocardial workload. CHF leads to impaired myocardial contractility, reduced cardiac output, and systemic hypoxia. In parallel, IDA results in decreased oxygen –carrying capacity, further contributing to tissue hypoxia and metablic dysfunction. The interplay between these two conditions involves complex pathophysiological mechanisms, including altered iron metabolism, chronic inflammation, and neurohormonal activation. Elevated levels of inflammatory cytokines(such as IL-6, and TNF-a) induce hepcidin overexpression, reducing iron absorption and mobilization, thereby promoting functional iron deficiency. This article will explore the pathophysiological mechanisms in heart failure and iron deficiency anemia.*

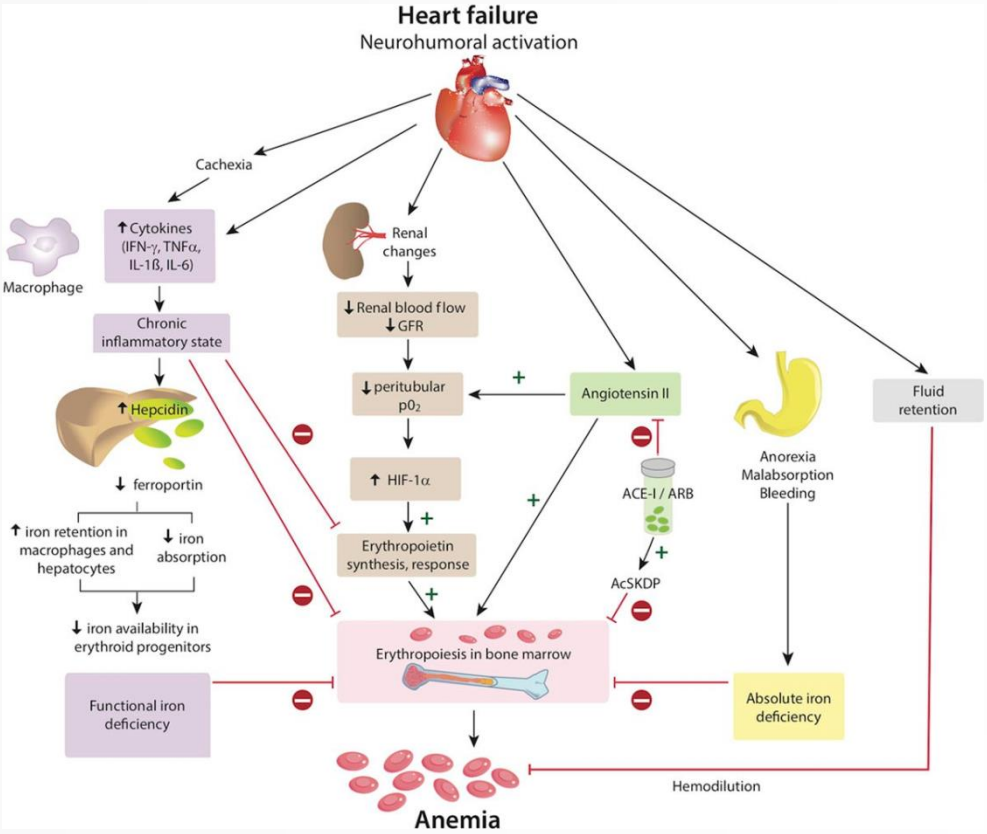
Key words: *Chronic heart failure, Iron deficiency anemia, cytokines, hepcidin.*

INTRODUCTION

Chronic heart failure (CHF) remains one of the leading causes of morbidity and mortality worldwide, affecting millions of individuals. CHF results in impaired cardiac output, leading to systemic hypoxia and metabolic distrubances. Iron plays a crucial role in oxygen transport, mitoxondrial function, and energy metabolism. In patients with CHF, chronic inflammation, neurohormonal dysregulation, and gastrointestinal malabsorbtion contribute to iron deficiency, even in the absence of anemia. Moreover, elevated levels of inflammatory cytokines, such as interleukin-6(IL-6) and tumor necrosis factor –alpha (TNF-a), stimulate hepcidin production, leading to decreased intestinal iron absorbtion and impaired iron mobilization from storage sites. This functional iron deficiency limits hemoglobin synthesis and reduces oxygen delivery to peripheral tissues, compounding the effects of CHF- related hypoxia. Several studies have demonstrated that iron deficiency, even without anemia, is associated with reduced exercise capacity, increased hospitalizations, and higher mortality rates in CHF patients. Consequently, understanding the intricate relationship between CHF and IDA is essential for optimizing treatment strategies and improving patient outcomes. This article aims to explore the pathophysiological mechanisms linking CHF and IDA, focusing on altered iron metabolism, chronic inflammation, and neurohormonal activation. The pathogenesis of anemia in CHF is multifactorial. IDA is

common in CHF and is discussed separately. However, deficiencies of hematinic vitamins (B12 or folate) are infrequent.

Erythropoietin, which stimulates the production of red blood cells (RBCs), is produced primarily within the renal cortex and outer medulla by specialized peritubular fibroblasts and is often abnormal in HF. Low Po2 is the primary stimulus for erythropoietin production. Renal dysfunction is common in CHF, but structural renal disease, which could reduce erythropoietin production, is infrequent. Erythropoietin levels are increased in proportion to CHF severity but are lower than expected for the degree of anemia, suggesting blunted erythropoietin production. We can understand the relationship mechanism of CHF and IDA the following figure.



Picture-1. Picture was taken from ahajournals.org website.

Multiple, interrelated mechanisms contribute in various degrees to the development of anemia in HF. Of these, functional or absolute iron deficiency, erythropoietin synthesis and response, and the effects of various medications may represent the most important factors. ACE-I indicates angiotensin-converting enzyme inhibitor; AcSDKP, N-acetyl-seryl-aspartyl-lysyl-proline; ARB, angiotensin receptor blocker; GFR, glomerular filtration rate; HIF-1α, hypoxia-inducible factor-1α; IFN-γ, interferon-γ; IL, interleukin; and TNF-α, tumor necrosis factor-α.

The renin-angiotensin system plays an important role in erythropoietin pathophysiology through multiple pathways. First, angiotensin II decreases Po2 by reducing renal blood flow and increasing oxygen demand and thereby stimulates erythropoietin production. Angiotensin II also directly stimulates bone marrow

erythroid progenitor cell production. Therefore, angiotensin-converting inhibitors and angiotensin receptor blockers cause a modest reduction in hemoglobin by decreasing production of erythropoietin and erythroid progenitors and by preventing breakdown of the hematopoiesis inhibitor N-acetyl-seryl-aspartyl-lysyl-proline. Finally, anemia might be related to hemodilution, although clinically euvolemic patients have normal plasma volume, and measurement of hemoglobin reflects “true anemia” as assessed by RBC volume in the vast majority of anemic patients with CHF.

METHODS:

A total of 46 patients diagnosed with CHF (NYHA class III-IV) and IDA were enrolled in the study. Laboratory tests included hemoglobin (Hb), erythrocyte count, serum iron, ferritin, and total iron-binding capacity (TIBC). Echocardiographic measurements included left ventricular ejection fraction (LVEF) and left ventricular end-diastolic diameter (LVEDD). CHF severity was classified based on NYHA functional status. Data analysis was performed using SPSS 26.0, with statistical significance set at $p < 0.05$.

RESULTS:

Patients with CHF and IDA exhibited significantly lower hemoglobin levels (95 ± 15 g/L), reduced erythrocyte counts (3.2 ± 0.5 × 10^{12}/L), and diminished serum iron (7 ± 3 μmol/L) and ferritin (15 ± 5 ng/mL) concentrations. These findings indicate a pronounced impairment in iron homeostasis, suggesting that CHF-related iron dysregulation is not merely a consequence of reduced intake but rather a complex interplay of multiple pathophysiological mechanisms.

One key contributor is inflammation-driven iron sequestration, which leads to functional iron deficiency despite low circulating iron levels. Elevated levels of inflammatory cytokines, such as IL-6 and TNF-α, upregulate hepcidin synthesis, which inhibits intestinal iron absorption and reduces iron mobilization from storage sites. As a result, iron remains trapped in macrophages and hepatocytes, limiting its bioavailability for erythropoiesis.

Additionally, CHF-associated renal dysfunction may contribute to anemia by impairing erythropoietin production. Despite a compensatory increase in erythropoietin levels relative to CHF severity, they remain inappropriately low for the degree of anemia observed, indicating a blunted erythropoietic response. This, combined with chronic inflammation and oxidative stress, exacerbates anemia and further compromises oxygen delivery to peripheral tissues.

Furthermore, the reduced serum ferritin levels observed in these patients suggest that iron depletion occurs alongside functional iron deficiency, worsening the anemic state. The combination of absolute and functional iron deficiency in CHF highlights the need for targeted iron supplementation strategies, as traditional anemia treatments may be insufficient in addressing the underlying pathophysiological mechanisms.

CONCLUSION:

The coexistence of CHF and IDA leads to a synergistic decline in cardiac function and systemic oxygenation, driven by hepcidin-mediated iron sequestration, chronic inflammation, and impaired erythropoiesis. Reduced hemoglobin levels increase myocardial workload, exacerbating heart failure symptoms and further decreasing cardiac efficiency. Early diagnosis and targeted iron supplementation strategies may alleviate disease burden, improve oxygen transport, and enhance overall clinical outcomes in this high-risk population. Future studies should explore the impact of intravenous iron therapy and erythropoiesis-stimulating agents in this patient cohort.

REFERENCES:

1. Anker, S. D., & von Haehling, S. (2019). Iron deficiency in chronic heart failure: A practical guide. European Heart Journal, 40(15), 1286–1297. https://doi.org/10.1093/eurheartj/ehy811

2. Cohen-Solal, A., Damy, T., Ter Maaten, J. M., & Voors, A. A. (2021). Iron deficiency in heart failure: A common comorbidity that needs correct diagnosis and treatment. Cardiac Failure Review, 7(1), 45–51. https://doi.org/10.15420/cfr.2021.07

3. Jankowska, E. A., Tkaczyszyn, M., Suchocki, T., Drozd, M., von Haehling, S., Doehner, W., & Anker, S. D. (2018). Effects of iron deficiency and its treatment in chronic heart failure. European Journal of Heart Failure, 20(2), 166–175. https://doi.org/10.1002/ejhf.1025

4. McDonagh, T., Damy, T., Doehner, W., Lam, C. S. P., Sindone, A., van der Meer, P., Cohen-Solal, A., & Ponikowski, P. (2021). Screening, diagnosis and treatment of iron deficiency in chronic heart failure: Practical guidance. ESC Heart Failure, 8(4), 2361–2377. https://doi.org/10.1002/ehf2.13424

5. Ponikowski, P., van Veldhuisen, D. J., Comin-Colet, J., Ertl, G., Komajda, M., Mareev, V., Ruschitzka, F., & Anker, S. D. (2015). Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic chronic heart failure and iron deficiency. European Heart Journal, 36(11), 657–668. https://doi.org/10.1093/eurheartj/ehu385

6. Silverberg, D. S., Wexler, D., Sheps, D., Blum, M., Keren, G., & Baruch, R. (2018). The importance of correcting iron deficiency in patients with heart failure. American Journal of Nephrology, 47(2), 101–113. https://doi.org/10.1159/000488235

7. von Haehling, S., Ebner, N., Evertz, R., Ponikowski, P., & Anker, S. D. (2019). Iron deficiency in heart failure: An overview. Journal of the American College of Cardiology, 73(11), 1467–1480. https://doi.org/10.1016/j.jacc.2018.11.033