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# Introductory Chapter: Anaemia and Iron Deficiency in Heart Failure

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## 1. Introduction

The condition of an erythrocyte could be able to affect the internal and external conditions of all the vital and non-vital organs of a human body. These little biconcave disk-shaped red structures of approximately 8  $\mu\text{m}$  in diameter and of about 2.5  $\mu\text{m}$  in thickness can reflect the extent and type of parasitic, bacterial, and viral infections such as malaria, diarrhoea, and covid 19. Lack of enough healthy red blood cells to carry oxygen results in anaemia. Anaemia is a condition that occurs due to reduced haemoglobin (Hb) in the blood. Thus, the oxygen-carrying capacity of the blood is reduced. When the oxygen-carrying capacity is reduced, the heart must work harder and faster to deliver the required oxygen to the body. If unrecognised, this process could result in serious damage to various organs of the body including the cardiovascular system.

Commonly encountered symptoms of anaemia are generalised weakness, fatigue, pale appearance, shortness of breath, irritable mood, lack of concentration etc. However, if gone untreated, anaemia could result in, precipitate, or aggravate heart failure (HF). It could also result in arrhythmias & precipitate heart attacks (type 2 myocardial infarction). Anaemia is usually caused by inefficient production of red blood cells or the haemoglobin within these cells; by the loss of blood due to haemolysis within the circulation or bleeding issues; or due to other chronic medical conditions like kidney disease or cancer. However, the most common reason for anaemia remains iron deficiency (ID) which is critical to produce Hb. ID could exist with and without anaemia.

## 2. Anaemia and iron deficiency in heart failure

Anaemia & ID are common in patients with heart failure. They are associated with poor clinical status and worse prognosis [1]. Compared to a 10% prevalence of anaemia in the general population it is found in 30% of patients with stable heart failure and 50% in those hospitalised, inclusive of heart failure with reduce ejection fraction (HFrEF) or heart failure with preserved ejection fraction (HFpEF) [2–4]. Although the pathogenesis of anaemia in heart failure is multifactorial including deficiency of vitamin B12 & folate, low erythropoietin production due to renal involvement in heart failure, inflammatory components suppressing the production of red blood cells and Hb, ID remains one of the major contributors [4–7].

In heart failure it is the ID rather than anaemia that serves as the predictor for clinical outcome [8]. impaired quality of life (QoL), reduced exercise capacity,

greater morbidity, and mortality all could be predicted by the ID [8–10]. In fact ID has been shown to be a strong predictor for patient outcome than anaemia. ID without anaemia carries higher risk and poorer outcome compared to an anaemic patient without ID [8].

### **3. Management strategies**

Earlier studies have suggested that anaemia is common in HF and carries worse prognosis yet measures to increase haemoglobin through red blood cell transfusion or erythropoiesis stimulating agents have not shown any beneficial effect in long term [4, 11, 12].

Unfortunately, this approach may not only did not improve the outcome in patients with HF but were associated with higher risk of adverse effects. This was demonstrated in a large study of public discharge database of 596456 patients admitted with heart failure [13]. Anaemia was present in 27% patient. The adjusted risk mortality was 70% higher in that receiving blood transfusion compared to 10% in those who did not. Thus, packed cell transfusion could be beneficial in acute anaemic states in heart failure but not in the chronic management.

As regards treatment with erythropoiesis stimulating agents (ESA), a meta-analysis of 11 earlier studies comprising 794 patients showed benefit in peak oxygen consumption, NYHA class, BNP levels and QoL but no significant effect on all-cause mortality [14]. Subsequently, a large study randomising 2278 patients with heart failure and anaemia but no iron deficiency when followed for 28 months did not confirm any benefit with the ESA darbopoetin, neither on the primary composite outcome of death from any cause, hospitalisation or worsening of heart failure. The lack of effect was equally present in subgroups as well as on the secondary outcomes of fatal MI, stroke, hypertension, and heart failure [15].

As against failure of blood replacement or ESA to demonstrate beneficial effect in heart failure, the scenario is different when it comes to treating ID with iron replacement. As mentioned earlier, ID is quite common in HF, affecting nearly 50% of patients with or without anaemia [8, 16–18]. Iron deficiency in patients with HF could be absolute or functional. Total iron is reduced in absolute ID but in the functional ID the total body iron is normal or increased but inadequate to fulfil the need of body tissues due to sequestration of the storage pools. Studies have shown that reversing ID in patient with or without anaemia and HF could improve patient outcomes [19], improve QoL and exercise capacity as well as improve depression which is also prevalent in patients with HF.

For the treatment of ID, it is important to consider the route of supplementation, whether oral or intravenous (IV). The dietary iron is absorbed in the duodenum by the enterocytes and subsequently taken up into circulation, bound to transferrin [7]. However, in HF there is gastrointestinal oedema leading to impairment of absorption of iron and duodenal iron transport [10]. Also, in HF the hepcidin level increases which further reduced the iron levels [20]. Several studies and meta-analysis data have studied the role of intravenous iron therapy in patients with HF and ID [21], showing its beneficial effect on NYHA class, QoL and 6 min walk test. FAIR-HF (Ferinject Assessment in Patients with Iron Deficiency and Chronic Heart Failure) randomised 459 patients with ID to IV iron or saline. IV iron therapy improved the QoL, 6 min walk test, NYHA level significantly but all-cause mortality or first hospitalisation remained unchanged [21]. However, a subsequent study [22] with similar recruitment criteria conducted on 304 patients but monitored for longer duration (52 weeks) showed significant improvement in primary end point of 6 min walk test, the benefit sustaining for 1 year. There was improvement

in secondary end points NYHA class, QoL, fatigue score and there was reduction in the risk of hospitalisation for worsening of HF. However, the all-cause mortality did not change. Subsequent studies also showed lower rates of hospitalisation and cardiovascular mortality [21].

While advocating IV iron replacement in patients with HF one need be cautious with the potential adverse effects of iron overload. As iron is not excreted from the body in any form, the mechanism to control iron levels in the body is through regulation of its absorption through duodenum [23] which is bypassed when IV iron is given. Excess iron can cause cardiomyopathy, widespread tissue damage and endothelial dysfunction, all related with adverse cardiovascular outcomes [24]. It is therefore critical to prevent iron overload when correcting ID in patients with HF.

#### 4. Conclusion

In this book, we are describing the novel and traditional approaches taken by different scientists around the world to relate the status of an erythrocyte (Red blood cell) with chronic and acute conditions such as heart failure, which can be happening slowly over a period or can happen suddenly.

Heart failure is associated with anaemia about 50% of the patients. Iron deficiency is one of the important caused of anaemia in HF. This is predominantly due to lack of absorption of iron from the duodenum that is often inflamed/congested in heart failure. Thus, iron replacement is pivotal in the management of HF with ID. Intravenous iron Administration of intravenous iron has been proved to be beneficial in improving symptoms as well as prognosis in patients with HF and ID.

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