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Review Article

Revisiting Anemia in Heart Failure

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Abstract

Anemia in heart failure is associated with decreased effort tolerance and increased mortality. The etiology is multifactorial including decreased erythropoietin production owing to renal dysfunction, marrow defects, drugs, and nutritional deficiencies mainly iron. Modalities of treatment in anemia have been studied intensively. Treatment with ESAs has been found to increase hemoglobin levels but without much improvement in clinical outcomes and with more adverse events like thromboembolic and ischemic strokes. Hence the routine use of ESA is not recommended. Whether anemia is the marker of the severity of heart failure or it is a therapeutic target is yet unclear. Intravenous Iron administration in patients with heart failure with iron deficiency improves symptoms and exercise capacity but long-term safety data is still awaited.

Keywords: *Anemia; Heart Failure*

Introduction

Definition and prevalence

According to WHO definition, Anemia is defined as hemoglobin levels < 13g/dl in men and < 12g/dl in women [1]. The prevalence of anemia in heart failure has got a wide range (from 17 - 70%) due to variability in definition, comorbidities, demographic details, and severity of heart failure [2-4]. Compared to the prevalence of < 10% in the general population, it is 30% in stable and 50% in hospitalized patients irrespective of whether the patients have HFpEF or HfrEF [5-7]. Patients are generally of older age with female preponderance and likely to have comorbidities like CKD, poor exercise capacity, low blood pressure, increased diuretics requirement, greater edema and higher pro-inflammatory cytokines activation [7,8]. Studies show that prevalence increases with the severity of heart failure but the mechanism between the relationship is not well explained [9].

Etiology of anemia in heart failure

Etiology is multifactorial. CKD accounts for 58%, Iron deficiency21% [10], other nutritional deficiency (8%). There are several other causes like chronic bleeding due to long-term use of antiplatelet and anticoagulants [7]. People with CKD, diabetes, and older age are at more risk of developing anemia. Nutritional deficiencies mainly iron deficiency is present in more than one-half of the patients. Any underlying chronic inflammation gives rise to erythropoietin resistance leading to Iron deficiency anemia. Heart failure patients with coexisting CKD are at higher risk of developing anemia due to inadequate levels of erythropoietin. Further, Intrinsic bone marrow defects lead to marrow unresponsiveness despite preserved erythropoietin production in patients with heart failure increasing the susceptibility to anemia. In these patients, high EPO levels are associated with unfavorable outcomes. Another mechanism leading to the so-called pseudo anemia is due to renin-angiotensin system activation leading to sodium and water retention and anemia of hemodilution [11]. Apart from this, there are several medications used to treat heart failures like ACE inhibitors and carvedilol which can be responsible for

causing anemia. The proposed mechanism is that ACE inhibitors lead to inhibition of hematopoietic activity via N-acetyl-seryl-aspartyl-lysyl-proline which was documented in SOLVD (study of left ventricular dysfunction) done with enalapril. [12,13] while Carvedilol causes low hemoglobin by blocking beta-2 adrenergic receptors [14].

Pathogenesis of anemia in heart failure

It is multifactorial as depicted in figure 1. Low PO2 is the primary stimulus for erythropoietin production. Erythropoietin is produced in the renal cortex and outer medulla and further stimulates RBC production. Though renal dysfunction is common in heart failure there occurs no structural damage to the kidneys which can inhibit the production of erythropoietin. However, in heart failure, there is reduced renal blood flow and filtration rate leading to sodium reabsorption in renal tubules which cause an imbalance between oxygen supply and demand. This imbalance results in the low renal Po2 further activating hypoxia-induced factor 1alpha and inducing erythropoietin gene transcription [15]. Erythropoietin is increased in proportion to the heart failure severity but is low in proportion to the degree of anemia.

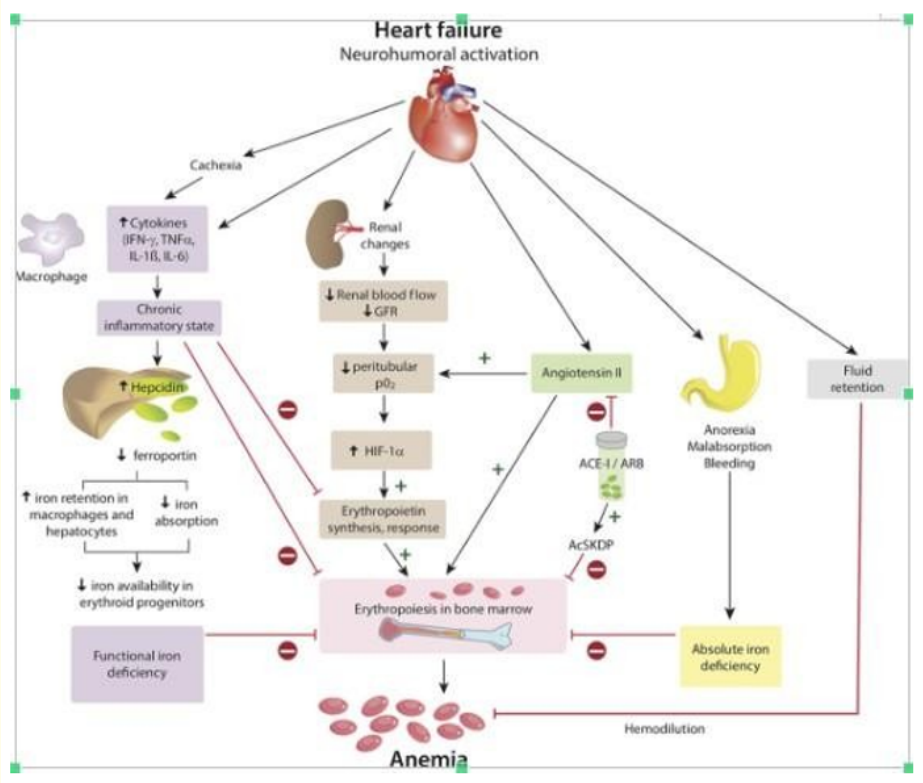

Figure 1

Another important mechanism is reduced erythropoietin production due to the production of inflammatory markers like Interleukin-6, TNF - alpha, and other proinflammatory cytokines. These cytokines also lead to inhibition of bone marrow erythroid progenitor cell proliferation giving rise to anemia. The mechanism responsible for anemia due to drugs like ACE inhibitors is explained via RAAS activation. Angiotensin II decreased renal Po2 by reducing renal blood flow and increasing oxygen demand thereby stimulating erythropoietin production.

Angiotensin II also plays an important role in directly stimulating bone marrow erythroid progenitor cell production. Thereby, ACE inhibitors and ARB's cause a drop in hemoglobin by reducing erythropoietin production, inhibiting bone marrow progenitor production, and preventing the breakdown of hematopoiesis inhibitor N-acetyl-Seryl-aspartyl-lysyl-proline [16]. The reduction in hematocrit due to these drugs is minimal in cases of normal renal functions but is more pronounced in patients with renal dysfunction. The decrease in hematocrit due to ACE inhibitors is least in the first 3 months of therapy and then eventually becomes stable. Discontinuation of these drugs leads to the normalization of hematocrit values. NSAIDs may cause anemia due to chronic blood loss as well as due to the fact that prostaglandins stimulate the process of erythropoiesis.

Table 1 defines all possible mechanisms due to ACE inhibitors induced anemia [17].

Renal
Decrease in the synthesis of endogenous EPO bone marrow
Decrease in the response to EPO
Inhibition of the growth of erythroid precursors
Change in the response to treatment with rHu EPO
Decrease in IGF-1 levels
Inhibition of the catabolism of N-acetyl-seryl-aspartyl-proline, a peptide that reduces the proliferation of precursors of the red cell series
*EPO indicates erythropoietin; IGF-1, insulin-like growth factor 1; rHuEPO, recombinant human erythropoietin.

Table 1: *Possible Anemia-Inducing Mechanisms of Angiotensin-Converting Enzyme Antagonists and Angiotensin I Antagonists**

Consequences and outcomes of anemia in heart failure

In a meta-analysis of 153,180 patients with HF, the mortality risk of anemia was an odds ratio of 1.96 (95% confidence interval:1.74 - 2.21) and the adjusted hazard ratio was 1.46 (95% confidence interval: 1.26 to 1.69) with similar results in patients with reduced or preserved left ventricular ejection fraction [2]. Anemia, CKD, Iron deficiency, and heart failure often exist concomitantly and their coexistence is a sign of poor outcomes. It is yet unclear whether anemia in advanced heart failure leads to a poor outcome or is just a sign of advanced disease. In patients with hemoglobin levels of 4 - 6g/dl with normal LV functions, many compensatory mechanisms come into play due to reduced oxygen-carrying capacity. Decreased oxygen-carrying capacity is compensated by an increase in the heart rate and stroke volume and since this compensatory phenomenon is already impaired in heart failure, there occurs aggravation of symptoms like dyspnea, reduced effort tolerance, and impaired quality of life. As a compensatory mechanism owing to the reduced oxygen-carrying capacity, there also occurs an increase in 2,3DPG that displaces the Hb-oxygen dissociation curve to the right leading to increased tissue oxygenation. Low hemoglobin causes NO-mediated vasodilation and a reduced number of circulating RBCs causing the reduction in systemic vascular resistance. The result is reduced arterial blood pressure which causes baroreceptor mediated neurohormonal activation as seen in low output heart failure. Increased sympathetic and RAAS activation leads to reduced renal blood flow causing sodium and water retention with an expansion of extracellular and plasma volumes. All these alterations along with the proinflammatory cytokines lead to increased

myocardial workload leading to LV remodeling and LV hypertrophy. So, severe anemia can itself give rise to a condition simulating high output failure in patients with normal LV functions and anemia correction in such patients helps in regression of symptoms [18]. However, it is unclear whether similar mechanisms also play role in cases of HFrEF. In a study conducted, where patients with CKD and moderate anemia were given erythropoietin leading to an increase in hemoglobin from 8.5 to 10 to 14g/dl, cardiac output reduced progressively in proportion to increasing in hemoglobin which concludes that increasing hemoglobin in patients with HFrEF increases systemic vascular resistance, raise the LV afterload causing the EF to decrease thus explaining the inverse relationship of hemoglobin with LVEF. This also explains why the correction of anemia in HFrEF patients has not improved outcomes [7]. Anemia in both HFpEF and HFrEF is associated with increased hospitalizations and mortality. In a meta-analysis of 33 studies with > 150,000 patients with HF, the risk of death was doubled due to anemia and in patients with concomitant CKD, the risk further increased to 1.5 folds [2].

Whether we should treat anaemia in heart failure? Role of blood transfusions?

It has been observed that anemia is quite common in heart failure and is associated with poor outcomes. Hence it is paramount to consider if treating anemia is beneficial. Packed RBCs transfusion can be used as a short-term measure but the transfusion has been found to be associated with risks and provides only temporary benefit. A large study of 596456 patients by Kao demonstrated that 27% of all patients had anemia. Untreated anemia had 10 percent mortality while there was 70% adjusted mortality for patients who received transfusions [19]. Another study of 4102 patients also concluded that patients who received transfusion had worse outcomes [20]. The TRICS III trial (Transfusion Requirements in Cardiac Surgery) in moderate- to high-risk patients undergoing cardiac surgery found that the primary outcome of death due to any cause myocardial infarction (MI), stroke, and new-onset renal failure with dialysis was observed in 11.4% of those who were assigned restrictive transfusion strategy i.e. intraoperative or postoperative transfusions for hemoglobin < 7.5 g/dL compared with 12.5% in the liberal strategy of transfusions for hemoglobin < 9.5 g/dL which implies that a restrictive transfusion strategy is non-inferior to a liberal strategy. This concludes that blood transfusion may not necessarily be helpful always but may result in deleterious consequences [21]. So, in asymptomatic patients with non-acute anemia, blood transfusion is not recommended [22]. Careful consideration of factors like age, comorbidities, and need for surgical intervention is to be taken while deciding for blood transfusion based on different threshold guidelines. Since there are risks of acute hemolytic reactions, infection, acute lung injury, allergic reaction along with a lack of evidence of suggesting liberal transfusion strategy, the American college of physicians recommend restrictive transfusion therapy (threshold of 7 - 8g/dl) in patients with heart disease [23].

Erythropoietin stimulating agents

Various smaller studies were conducted between 2000 - 2010 and most of them found symptomatic improvement with the use of ESA in heart failure. The largest pivotal trial was conducted as RED-HF trial in 2013 with 2278 patients with HFrEF, NYHA class II to IV HF, LVEF ≤ 40%, and mild to moderate anemia (hemoglobin, 9.0 - 12.0 g/dL) Patients with Iron deficiency with transferrin saturation (TSAT) of < 15%, patients with a history of bleeding, creatinine >3 mg/dL, blood pressure > 160/100 mm Hg were excluded. Patients were randomized to receive Darbepoetin Alfa (with a target of 13 to14.5 g/dl) or a placebo. IV iron therapy was allowed in both groups [24]. The results declared an increase in the hemoglobin without any change in the primary endpoints of hospitalization and mortality due to worsening heart failure while the rate of thromboembolic events was increased significantly in the intervention group. This raised the alarm as a similar increase in the rate of adverse events was observed in the patients of CKD and cancer-related anemias. By and large, data does not support the use of ESA in treating mild-moderate anemia and increasing hemoglobin levels in HFrEF patients due to failure in improving outcomes and the high rates of thromboembolic events [25].

Iron therapy

It has been documented that the prevalence of iron deficiency is quite high, approximately 70% in anemic patients and 50% in all HF patients. This recent awareness and the repercussions of iron deficiency have led to the invention of trials of iron therapy without ESAs

compared to the previous ones where oral iron therapy was studied along with ESAs. Oral iron has got some practical advantages but the use is limited in HF patients due to poor compliance owing to its gastrointestinal side effects and impaired uptake. The only randomized controlled phase II trial IRON-OUT (oral iron repletion effects on oxygen uptake in heart failure) included 225 patients with reduced EF and iron deficiency [26]. Patients received 160 mg of polysaccharide iron complex or placebo twice daily for 16 weeks which showed a marginal increase of 11 microgram/l of ferritin and 3% TSAT with oral iron and no significant improvement in exercise capacity or NT Pro-BNP. It was also concluded that patients who responded to oral iron were the ones who had low hepcidin levels.

Hepcidin is upregulated in chronic inflammation and blocks the iron exporter ferroprotein inhibiting uptake from gut and iron release from macrophages hence explaining the neutral results of this study. There were 5 RCTs where the effects of intravenous iron were studied and patients were recruited based on their ferritin and TSAT levels. Though the strategies differ in all, the results were almost similar showing improvements in NYHA functional class, exercise capacity, and quality of life. Trials FAIR-HF (Ferinject assessment in patients with iron deficiency and chronic heart failure) and CONFIRM-HF (Ferric carboxymaltose evaluation on performance in patients with Iron deficiency in combination with chronic heart failure [27] there was a significant rise in the hemoglobin levels post-therapy. Another study EFFECT-HF (effect of ferric carboxymaltose on Exercise capacity in patients with iron deficiency and chronic heart failure) showed an increase in VO2 max in patients treated with carboxymaltose compared with the control group [28] By and large, the effects of intravenous iron therapy on clinical endpoints are yet to be established but it is recommended to screen all patients with HF for iron deficiency independent of their Hb level. In most trials, iron deficiency was taken as TSAT < 20% and ferritin of < 100 or 110 - 300 micrograms/l however the ferritin levels are unreliable as it is also an acute phase reactant. A recent study validated the cut-off of TSAT < 20% by using bone marrow staining with ferritin showing no diagnostic value [29].

Current recommendations

ACC and ESC recommend focus on understanding underlying etiology and treatment in HF. Iron deficiency should be determined and intravenous ferric carboxymaltose to be used as a treatment modality. The routine use of ESA darbepoetin-alfa is not recommended given its adverse effects [30].

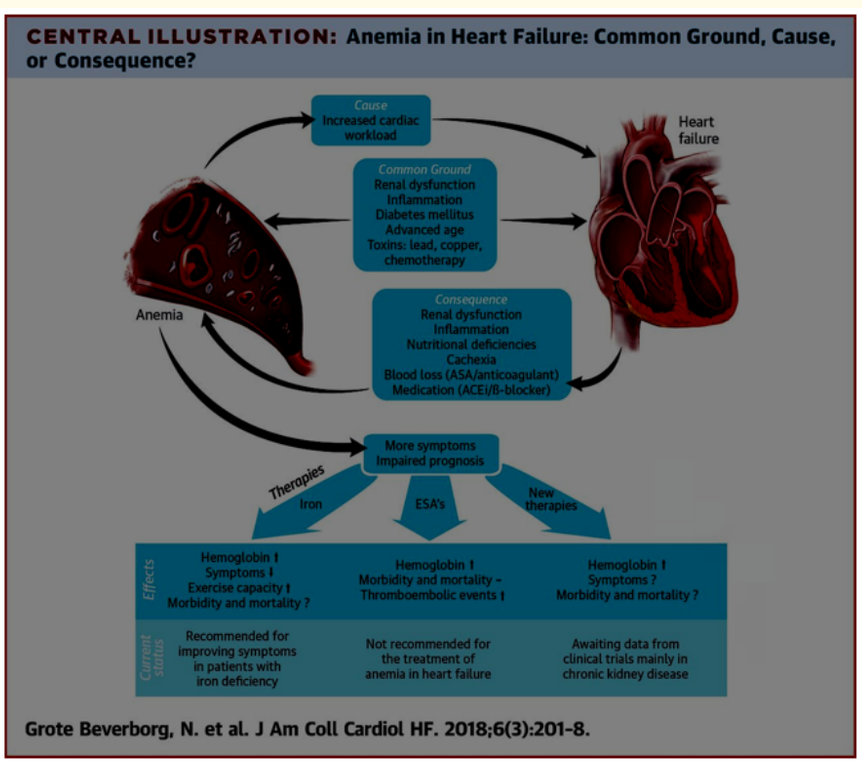

Figure 2

Newer strategies

These modalities act directly at the erythropoiesis process via erythropoietin receptor or hypoxia pathway and also indirectly via hepcidin pathway.

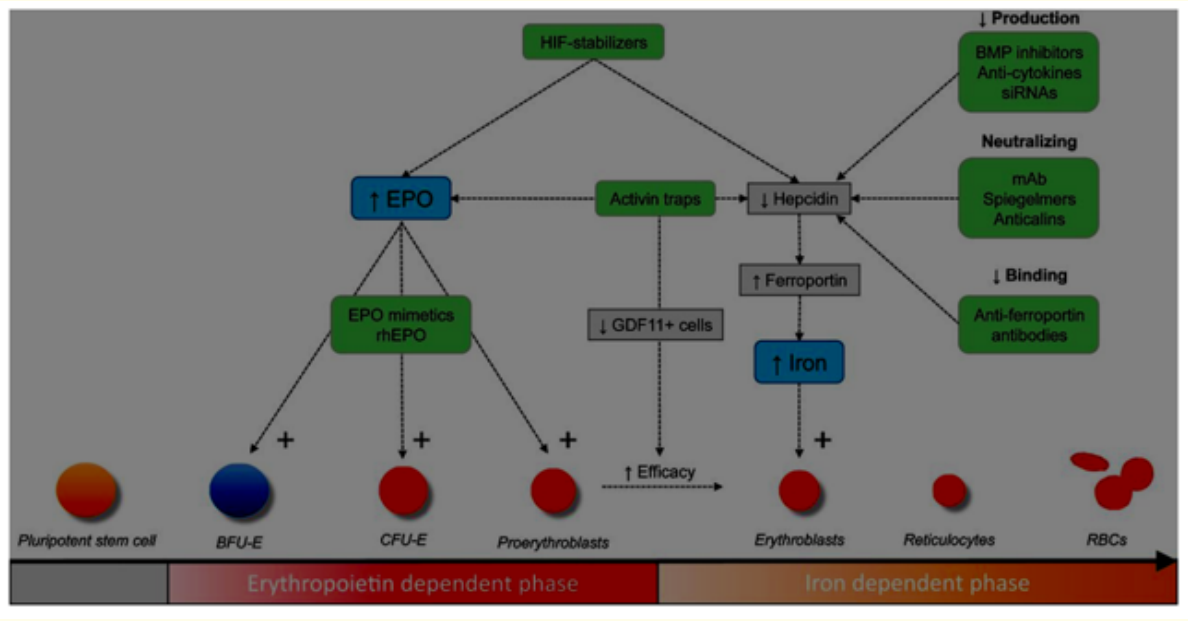

Figure 3: *Illustrates the mechanism of action of these newer strategies.*

Hepcidin

Antagonising hepcidin may result in increasing hemoglobin levels. It can be done by 3 important ways 1) decreasing production 2) Neutralising hepcidin 3) Preventing hepcidin- ferroportin interaction. One phase I trial showed that humanized monoclonal antibody against hepcidin (LY2787106) resulted in increase in serum iron levels and TSAT in cancer and anemia [31] Another hepcidin binding agent, Spiegelmer lexatepid (NOX-H94) has been shown to increase serum iron levels in patients subjected to inflammation by injecting polysachharides [32] In a small study, increase in the hemoglobin of > 1g/dla was observed after 4 weeks of treatment with lexaptepid in 5 of 12 patients [33].

Erythropoietin receptor targeting

Erythropoietin receptor targeting drugs like receptor antibodies, fusion proteins, peptides and activin receptor ligand traps directly target erythropoiesis. Activin traps are recombinant fusion proteins which bind transforming growth factor –beta including activin A and activin B thereby inhibiting signals [34]. Sotatercept, initially an osteoporosis agent has shown an increase in the hemoglobin level, red cell number and hematocrit. This drug has also shown benefits in elderly CKD population [35]. Growth differentiation factor -1 present on erythroid progenitors has been proposed as the target of these drugs. Another mechanism of increased erythropoiesis is by stimulationg erythroid differentiation directly through AT1 receptor or via induction of erythropoietin production by kidneys by increased expression of angiotensin II [36].

Hypoxia inducible factor stabilizers

These are the most promising drugs which rapidly degrade in the presence of oxygen and in hypoxic conditions induces transcription of > 60 genes including erythropoietin and vascular endothelial growth factor and induce erythropoiesis. Several studies of CKD patients have shown increased hb levels and decreased hepcidin levels after therapy. FG - 4592 or roxadustat was superior to epoetin alfa in increasing hemoglobin levels in CKD patients. Caution is warranted with kits use due to the adverse effects like promoted tumour growth related to its effects on angiogenesis. Further studies are needed to ensure its safety and efficacy.

Conclusion

Anemia in heart failure is a common entity found in almost one-third of all heart failure patients resulting into worse prognosis and poor quality of life. Anemia in such patients may be due to underlying renal disease, chronic inflammation, nutritional deficiencies and volume overload. It is emperical to identify these causes of anemia in patients of heart failure. The Therapies studied so far have no shown much clinical benefit by increasing the hemoglobin but underlying iron deficiency should be addressed and be treated with IV ferric carboxymaltose though data on hard clinical end points is still lacking. ESA has shown no added benefits on mortality and hospitalisation while it leads to deletirious effects in the form of increased thrombotic events and ischemic strokes which outweighs the marginal benefits. Few novel strateges are currently being explored which aim at targeting the erythropoiesis, more relevant data is awaited. In a nutshell, the treatment strategies have not shown much positive results, anemia in heart failure is still relevant considering its worse outcomes.

Conflicts of Interest

There is no conflict of interest.

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