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RESEARCH ARTICLE

ANEMIA AND HEART FAILURE: STATE-OF-THE-ART REVIEW

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ABSTRACT

Anemia is a frequent co-morbidity in patients with heart failure, associated with an increased risk of hospitalization, morbidities, and mortality, making its correction an important factor in improving the quality of life and clinical data, in patients who have both of these pathologies. This article reviews the multifactorial etiology of anemia in heart failure patients, including iron deficiency, chronic inflammation, abnormal levels of erythropoietin, and the abnormal activation of the Renin-Angiotensin-Aldosterone (SRAA) system, as the main cause of this pathology. The diagnostic guidelines, therapeutic alternatives based on different studies, are also discussed in this review article, especially iron preparations and erythropoietin stimulating preparations.

INTRODUCTION

Heart failure (HF) represents a highly prevalent worldwide disease. The risk for life in patients with heart failure remains high, which varies depending on race and ethnic groups, ranging from 20% to 45% after the age of 45. Various studies show that the incidence of HF with preserved ejection fraction is increasing, compared to HF with reduced ejection fraction, whose incidence is decreasing, while both subtypes of HF have similar rates of mortality from all causes (1). Anemia is defined by WHO as the level of Hgb<13 in adults male and Hgb<12 in adults female (2). The diagnostic criteria of anemia in patients with HF is the level of ferritin in the blood less than 30mcg/L in patients without chronic kidney disease and less than 100mcg/L in patients with chronic kidney disease or the level of ferritin 100-299mcg/L with transferrin saturation less than 20% (3).Anemia is a frequent co-morbidity of HF with reduced and preserved ejection fraction (4). Despite the comorbidities, anemia remains an independent predictor of mortality and morbidity in patients with chronic HFrEF or HFpEF or acute decompensated HF (5). The prevalence of anemia in patients with HF ranges from 9% to 69.9%, associated by an increased risk of hospitalization and a mortality rate of 46.8% in anemic patients, compared to non-anemic patients, which is 29.5% (5). Numerous studies show that the prevalence of anemia increases from 30% to 60% in the presence of co-morbid medical condition like chronic renal disease, and advanced age (6). The specific cause of anemia in patients with HF is still not completely clear, where it is thought about the multifactorial etiology of the disease, among which iron deficiency and chronic inflammation play the most important role (7). Different therapeutic alternatives for anemia in patients with HF include erythropoietin stimulating preparations, iron supplements and hemotransfusions (8).

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This review article aims to establish the relationship between anemia and HF, the discussion of diagnostic methods and therapeutic alternatives.

Pathophysiology: The pathogenesis of anemia in HF is multifactorial, and has been linked to the chronic inflammation, presence of hematinic deficiencies, specifically iron deficiency (ID) anemia, impaired erythropoietin levels, or pseudo-anemia due to the activation of the renin-angiotensin-aldosterone system(RAAS).

Iron Deficiency Anemia (IDA): Iron is a vital element involved in numerous physiological processes such as oxygen transport, electron transport during oxidative phosphorylation within the mitochondria, oxygen storage, gene regulation, and cellular immunity. Most iron is used during hematopoiesis. However, iron is also indispensable for maintaining cellular energy and metabolism in extra-hematopoietic tissues (22). Iron deficiency (ID) is one of the most common nutritional deficiencies worldwide, affecting approximately one-third of the general population. Definition of iron deficiency in heart failure differs from other conditions of chronic inflammation and is defined as: ferritin <100 µg/L or ferritin of 100-299 µg/L with a transferrin saturation <20%.It can be absolute, when total body iron is decreased, or functional, when total body iron is normal or increased but inadequate to meet the needs of target tissues because of sequestration in the storage pool (iron maldistribution) (9). Absolute iron deficiency is defined by severely reduced or absent iron stores and was identified in 15% of individuals with heart failure (12). Absolute iron deficiency in HF is mainly caused by reduced dietary intake, malabsorption, and chronic blood loss (11). Functional iron deficiency is defined by adequate iron stores but insufficient iron availability for incorporation into erythroid, which was found in 18% of heart failure patients (12). Functional iron deficiency in HF results from mechanisms similar to those responsible for the anemia of chronic disease or inflammation (11). However, the deficiency of other nutrients like folic acid and vitamin B12 are less well described as contributing factors.

ID is recognized as major cause of anaemia in heart failure(HF) patients, regardless of sex, race, and left ventricular ejection function, which is an independent predictor of increased mortality and hospitalization, reaching a prevalence of 30–50% in patients with stable chronic heart failure (HF) regardless of their ejection fraction (7,10). Iron deficiency also has a prevalence of up to 80% in patients with acute HF (AHF) (38). Additionally, the prevalence of iron deficiency increases in severe HF (i.e., with higher New York Heart Association (NYHA) class (37)) and when anaemia is present (38). Myocardial dysfunction has been linked to chronic ID due to changes in structure and function of the myocardium due to impaired oxygen metabolism, cellular activities, and immune mechanisms.

Chronic Inflammation: Inflammatory anemia is normocytic normochromic anemia, established in the presence of an inflammatory disease, infection or malignancy. Inflammation is an important component of HF. The pathophysiology of this process is still unclear but it is thought to be related to the increase in the level of pro-inflammatory cytokines and hepcidin (7). The source of cytokine production in heart failure remains uncertain and several mechanisms have been proposed including endotoxin-induced immune activation due to bowel oedema, myocardial production due to haemodynamic overload and peripheral extramyocardial production due to tissue hypoperfusion and hypoxia (13). Tumor necrosis factor-α, interleukin-6 and several other proinflammatory cytokines, C-reactive protein, and hepcidine are increased in HF and inversely related to hemoglobin level, which are linked with a poorer prognoses and outcomes (7). Interleukin-6 and tumor necrosis factor-α also inhibit renal erythropoietin production by activating transcription factors GATA binding protein 2 (which binds nucleotide consensus sequence GATA in target gene promoters) and nuclear factor κ light-chain enhancer of activated B cells and may explain the blunted erythropoietin response. These cytokines also inhibit bone marrow erythroid progenitor cell proliferation (14). Additionally, IL-6 activates the synthesis of an acute phase protein, hepcidin in the liver which is involved in the downregulation of ferroportin (8), decreases the duodenal iron absorption and the release of iron from its stores in the reticuloendothelial system, causing functional and absolute iron deficiency anemia (15).

Renin-Angiotension-Aldosterone System (RAAS): The increased activity of RAAS in heart failure, initially improves cardiac output, however, over time it is associated with various negative effects, such as cardiac remodeling and activation of the sympathetic nervous system, progressively worsening the condition (18). The use of angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARBs) is a major way of managing HF, responsible for the mild reduction of hemoglobin (16) by decreasing the production of erythropoietin (17) and erythroid progenitors and by preventing the breakdown of the hematopoiesis inhibitor N-acetyl-seryl-aspartyl-lysyl-proline. Angiotensin II decreases P_{O_2} by reducing renal blood flow and increasing oxygen demand and thereby stimulates erythropoietin production. Also, bone marrow erythroid progenitor cell production was directly stimulates by Angiotensin II.

Erythropoietin Levels: Erythropoietin 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. The production of Epo is controlled by hypoxia-inducible transcription factors (HIF), which is mainly triggered in presence of renal hypoxia and low concentrations of hemoglobin (18). The cause for the impaired levels is multifactorial, such as: decreased erythropoietin (EPO) production in the setting of CKD, which is present in 63% of HF patients (20), the chronic inflammatory state in heart failure, which is associated with release of pro-inflammatory cytokines, causing impaired expression of Epo,leading to an Epo resistance in the bone marrow ultimately resulting in elevated levels of endogenous Epo (19), myocardial EPO synthesize in response to oxidative or metabolic stress or the presence of renal tissue impairment due to the presence of Epo receptors (EpoR) via the synthesis of HIF (15), and EPO production in response to angiotensin, despite the presence of angiotensin enzyme inhibitors (19).

Evaluation of anemia in heart failure: Guidelines provide various recommendations around screening for anemia and iron deficiency given its prevalence in heart failure and the effects on quality of life, exercise tolerance, and outcomes. Since 2012, the ESC guidelines have recommended that all HF patients be screened for anaemia and ID using ferritin and TSAT giving it a Class I, level of evidence: C recommendation (25). The 2021 ESC HF guidelines recommend that every patient with HF should be periodically assessed for iron deficiency (and anaemia) including carrying out a full blood count, and measuring both serum ferritin concentration and transferrin saturation (TSAT) (recommendation class I, evidence level C) (30); serum iron levels by themselves should not be used for iron deficiency diagnosis, since serum iron levels can vary widely—even from hour to hour. This recommendation is a noteworthy update to the 2016 ESC HF guidelines since screening was previously only recommended for new cases of HF (21,22). Among the routine blood tests for comorbidities recommended for patients with suspected CHF, iron status (TSAT and ferritin) should also be tested (recommendation class I, evidence level C) (30). Furthermore, determination of iron status (TSAT and ferritin) is recommended at pre-discharge in patients with AHF (30). Other serum markers, such as mean corpuscular volume (MCV), mean corpuscular Hgb (MCH), and mean corpuscular Hgb concentration (MCHC), are not reliable indicators of iron status, either (23,24).

Management of anemia in heart failure: Many observational studies suggest that anemia is common in patients with HF and is associated with poor clinical status and worse prognosis. So, it's reasonable to consider treatment of anemia in aim to improve outcomes. Only a few options are available to increase hemoglobin.

RBC transfusion

Packed RBC transfusion can be used as a short-term therapy, transfusions are associated with many risks and provide only temporary benefit. Routine blood transfusion in asymptomatic patients, particularly those with nonacute anemia, therefore cannot be recommended (26).

Erythropoiesis-Stimulating Agents: So many trials were carried out to correct Hb in patients with HF, by using darbepoetin, in the belief that improvement in Hb will result in beneficial effects in these patients. Finally, a large trial RED-HF was launched where darbepoetin was given in HF patients with anaemia whose TSAT was over 20%. The trial was negative for improvements in cardiovascular outcomes, but there was a higher incidence of thromboembolic events and ischemic stroke (27). One of the largest trials, evaluating the effect of darbepoetin alfa in HF patients with anaemia, is the Study of Anemia in Heart Failure Trial (STAMINA-HeFT), a multicenter, randomized, doubleblind, placebo-controlled trial published in 2008 (28). This trial compared a placebo group to the group receiving darbepoetin alfa based on clinical benefits and outcomes (27,28). No significant changes in exercise duration, NYHA class, or quality of life were noted upon receiving darbepoetin alfa contrary to that observed in the RED-HF trial (27,28). The 2021 ESC HF guidelines state that in HF, erythropoiesis-stimulating agent (ESA) treatment of anaemia is not recommended in cases where there are no other indications for this therapy (recommendation class III) (30).

Iron therapy: Utilisation of oral iron for repletion of deficient iron in patients with HF was specifically evaluated in the 16-week, single, randomised, double-blind, placebo-controlled IRONOUT HF clinical trial (29). The IRONOUT-HF study showed that treatment with 150 mg oral iron polysaccharide twice daily failed failed to increase exercise capacity, with no significant improvement in the primary endpoint of peak oxygen consumption (peak VO_2) or in 6 MWT distance over 16 weeks. The lack of improvement is likely due to impaired absorption because of elevated hepcidin, which inhibits iron absorption by reducing transmembrane ferroportin on enterocytes, thereby preventing iron transfer from enterocytes to blood, and/or dose intolerance since the median ferritin levels remained below 100 ng/mL after 16 weeks indicating that iron deficiency was not reversed in

more than half of subjects (29). Overall, the IRONOUT HF study findings demonstrated that supplementation with oral iron polysaccharide is not an effective strategy for iron deficiency treatment in patients with HFrEF (29), and consequently the 2021 ESC HF guidelines do not recommend oral iron use in patients with HF (30). Ferric carboxymaltose (FCM), a precision-engineered nanomedicine with a characteristic clinical profile (31), is the most extensively studied IV iron in randomised controlled clinical trials of patients with CHF (32,33,34,35). So, based in evidence, FCM is the only iron formulation specifically recommended for the treatment of iron deficiency the 2021 ESC HF guidelines (30). The largest randomised controlled trials to evaluate FCM in patients who were iron-deficient and had stable CHF (LVEF ≤ 45%) were the AFFIRM-AHF (32), FAIR-HF (33), CONFIRM-HF (34), and EFFECT-HF (35) studies, has shown that FCM IV improves New York Heart Association functional class, quality of life and exercise capacity (32,33,34,35,36). A meta-analysis of data from the four major randomized controlled trials conducted (FAIR-HF, CONFIRM-HF, EFFICACY-HF and FER-CARS-01), were evaluated for the main outcomes measures of recurrent CV hospitalizations and CV mortality in patients with HFrEF. Analyses showed that correction of iron deficiency with IV FCM was associated with lower rates of recurrent CV hospitalizations and CV mortality, heart failure (HF) hospitalizations and CV mortality, CV hospitalizations and all-cause mortality, and HF hospitalizations and all-cause mortality. These data suggest that iron deficiency is a modifiable risk factor with appropriate treatment (39). The 2021 ESC HF guidelines (30) recommend periodically and regularly evaluating iron deficiency and anaemia in all patients with HF as part of clinical evaluation (i.e., one to two times per year). Patients with decompensated HF should be screened for anaemia and iron deficiency, even when symptoms continue after optimised treatment for HF. IV iron should then be administered as needed.

New therapies: The new therapies which are being evaluated for management of anemia in HF include the molecules which target hepcidin, hypoxia pathway and the EPO receptor. Hepcidin can be antagonized by reducing its production, neutralizing it or preventing the hepcidin–ferroportion interaction. A fully humanized monoclonal antibody against hepcidin (LY2787106) and a hepcidin-binding agent, the Spiegelmer lexaptepid (NOX-H94) have shown promising results in phase 1 trials (40). EPO receptor targeting include mimetic peptides, gene therapy, fusion proteins, receptor antibodies and active receptor ligand traps. The proposed mechanisms of action makes erythropoiesis more efficient by reducing the number of growth differentiation factor-11-positive cells (41) or by increased expression of angiotensin II (42). These activin traps have not been studied in HF patients with anemia. One of the HIF stabilizers, roxadustat (FG-4592), has shown to increase EPO and Hb levels and decrease the hepcidin in CKD patients (43).

CONCLUSION

Anemia and ID (absolute or functional) are very common comorbidities in patients with HF and are associated with poor clinical status and worse outcomes. The specific cause of anemia in heart failure patients is still unclear and has been thought to be multifactorial. ESAs agents do not improve outcomes and may be associated with thromboembolic complications,and are therefore not recommended. Iron deficiency one of the most frequent comorbid conditions in HF, can exist with or without anaemia. The prompt diagnosis and appropriate correction of ID are crucial. In patients with HFrEF and absolute or functional ID with or without anemia, IV but not oral iron therapy may improve symptoms and outcomes. There is conclusive evidence that it reduces hospitalizations and improves quality of life. Although patients with HFpEF have similar prevalence of anemia and ID that is similarly associated with poor clinical status and worse outcomes, benefits of these therapies have not been tested in these patients. So, it's important for all patients with HF to be screened for anaemia and ID and to be treated in a way to help these patients improve their abilities and NYHA functional classes.

Conflicts of Interest: None to declare.

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