Anemia and Iron Deficiency in Heart Failure

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KEYWORDS

• Anemia • Iron deficiency • Heart failure • Iron therapy • Erythropoiesis-stimulating agents

KEY POINTS

- Anemia is highly prevalent in patients with heart failure (HF), and is associated with poor prognosis.
- Among anemic HF patients, iron deficiency is the most common form of hematinic deficiency.
- Iron deficiency in HF patients, with or without anemia, confers increased risk of mortality and morbidity.
- Erythropoiesis-stimulating agents are no longer an option in the treatment in HF patients with anemia, based on the results of the RED-HF trial.
- Although intravenous iron supplementation improves functional outcomes in anemic HF patients, long-term, adequately powered, randomized, placebo-controlled trials of intravenous iron assessing morbidity and mortality are required before any firm recommendations about its use can be made.

INTRODUCTION

Anemia is a common comorbid condition in patients with heart failure (HF),[1,2] and is associated with adverse outcomes in this patient population.[3] The etiology of anemia in HF patients is multifactorial,[2,4] and in most of these patients more than one mechanism is involved. Iron deficiency is the commonest cause of anemia worldwide.[5] Even in anemic HF patients, iron deficiency is the most common form of hematinic deficiency, regardless of renal function status.[4] Iron deficiency, with or without anemia, confers increased risk of mortality and morbidity in HF patients, and iron supplementation improves functional status.[4] This article reviews current knowledge regarding anemia and iron deficiency in HF patients.

EPIDEMIOLOGIC INSIGHTS

Depending on the definition used and patient population studied, prevalence of anemia in HF patients varies from 9% to 70%.[1,2,6,7] There are no HF-specific criteria to define anemia, and definitions based on large samples from the third US National Health and Nutrition Examination Survey and the Scripps-Kaiser database propose the following: hemoglobin less than 13.7 mg/dL and less than 12.9 mg/dL in white and black men, respectively, and less than 12.2 mg/dL and less than 11.5 mg/dL in white and black women, respectively. Using the World Health Organization definition (hemoglobin <12 g/dL in women and <13 g/dL in men), a prevalence of 22% to 46% in HF patients have been reported.[3]

Anemia is associated with increased morbidity and mortality in HF patients. In a meta-analysis of HF patients, presence of anemia almost doubled the mortality risk (odds ratio 1.96; 95% confidence interval [CI] 1.74–2.21; $P<.001$).[3] In addition to increased risk of mortality, anemia in HF patients is also associated with increased risk of various morbidities such as cognitive

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impairment,[8] increased number of hospitalizations,[9] higher New York Heart Association (NYHA) functional class,[10] lower exercise capacity,[11] and worse quality of life.[12]

Iron deficiency is the most common form of hematinic deficiency among anemic HF patients.[4] Depending on the definition and diagnostic criteria used, the reported prevalence of iron deficiency in HF patients varies widely. In a study of 955 HF patients with 32% prevalence of anemia, 52% of the anemic and 17% of nonanemic patients had evidence of iron and/or ferritin deficiency, defined as iron less than 8 μmol/L and ferritin less than 30 μg/L.[13] In another prospective study of patients with decompensated advanced HF, bone marrow aspiration showed evidence of iron deficiency in 73% of patients.[14] A ferritin level of less than 100 μg/L, and a ferritin level of 100 to 300 μg/L along with transferrin saturation of less than 20%, have been used as a diagnostic criteria for iron deficiency.[15,16] Using these criteria, a prospective observational study of 546 patients identified iron deficiency in 37% of all patients with stable systolic HF; 57% of the anemic HF patients and 32% of the nonanemic HF patients.[15] Iron deficiency was more common in females and patients with advanced NYHA class, higher plasma N-terminal pro–brain natriuretic peptide (NT-proBNP) levels, and higher serum high-sensitivity C-reactive protein. In an international pooled cohort of 1506 patients with chronic HF, iron deficiency was present in 753 (50%) of the patients, 61.2% of anemic patients, and 45.6% of nonanemic patients.[16] In another study of patients with chronic HF, deranged iron homeostasis characterized by diminished circulating (decreased transferrin saturation) and functional (decreased mean cell hemoglobin concentration) iron status with adequate stores (ferritin levels) was seen in both anemic and nonanemic HF patients.[17]

From a prognostic standpoint, in HF patients both anemia and iron deficiency are associated with adverse outcomes such as reduced exercise capacity, increased rate of hospitalizations, and impaired quality of life. Many published studies have demonstrated a strong association between anemia and mortality in HF patients. A meta-analysis of 34 such studies demonstrated a significantly higher risk of mortality in anemic chronic HF patients in comparison with nonanemic patients, even after adjustment for potential confounders.[3]

Iron deficiency even without anemia is associated with an increased risk of mortality and morbidity. In a study of 157 patients with HF, patients with iron-deficiency anemia had a 4-fold increased risk of death compared with iron-replete patients with or without anemia and a 2-fold increased risk of death in comparison with those with nonanemic iron deficiency.[17] Similarly, in a prospective observational study of 546 patients, iron deficiency was associated with an increased risk of death or heart transplantations (adjusted hazard ratio 1.58; 95% CI 1.14–2.17; $P<.01$), independent of the presence of anemia.[15] Among the international pooled cohort of 1506 patients with chronic HF, iron deficiency (but not anemia) was a strong and independent predictor of mortality in the multivariable hazard models (hazard ratio 1.42; 95% CI 1.14–1.77; $P = .002$).[16] Iron deficiency also independently predicts exercise intolerance in patients with systolic chronic HF, although the strength of these associations is relatively weak.[18] Just as importantly, health-related quality of life was negatively affected in iron-deficient chronic HF patients, with demonstrable improvement after intravenous iron therapy, independent of anemia status.[19]

PATHOPHYSIOLOGIC INTERACTION

Although the pathogenesis of anemia in HF is not yet fully delineated, factors such as reduced erythropoietin (EPO) production, EPO resistance, chronic kidney disease, inflammation, diabetes, hemodilution, gastrointestinal malabsorption and blood loss, absolute and functional iron deficiency, and drugs such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers are believed to be contributing to the development of anemia in this patient population.[2,4,20,21]

Proinflammatory Cytokines

Elevated levels of circulating proinflammatory cytokines, such as tumor necrosis factor α, interleukin (IL)-1, and IL-6 observed in HF patients cause anemia of chronic disease.[22] Proinflammatory cytokines produce changes in EPO production, proliferation of erythroid progenitor cells, iron homeostasis, and the life span of red blood cells.[22]

Decreased EPO Production/EPO Resistance

Activation of the renin-angiotensin-aldosterone system and the sympathetic nervous system in HF patients leads to renal hypoperfusion and tissue hypoxia, causing increased EPO production. Elevated angiotensin II increases EPO production by causing renal hypoperfusion and also by direct stimulation of EPO production.[23] Chronic HF is associated with elevated proinflammatory cytokines, which may not only cause decreased EPO production but also resistance to its actions on bone marrow.[24,25] EPO levels in HF patients are