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STATE-OF-THE-ART PAPER

Anemia and Chronic Heart Failure

Implications and Treatment Options

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Anemia is a common comorbidity in patients with heart failure and is associated with worse long-term outcomes. Although the cause of anemia in heart failure is unclear, the weight of evidence suggests that renal dysfunction, along with neurohormonal and proinflammatory cytokine activation in heart failure, favors the development of anemia of chronic disease, with defective iron utilization, inappropriate erythropoietin production, and depressed bone marrow function. Similarly, the mechanisms by which anemia worsens heart failure outcomes are unknown but may be related to increased myocardial workload. If anemia is a mediator and not just a marker of poor outcomes, correcting anemia could become an important and novel therapeutic target to improve long-term outcomes in such patients. Indeed, several small-sized studies have shown the beneficial effects of empirically treating anemia in heart failure patients with recombinant erythropoietin and intravenous iron. However, the ideal threshold at which therapy should be initiated and the extent of correction considered safe and desirable in the individual patient with heart failure need to be known. These issues become more important because of increasing safety concerns that recombinant erythropoietin therapy for treating anemia may be associated with adverse cardiovascular outcomes in patients with chronic kidney disease and may worsen cancer in patients receiving chemotherapy to treat various types of cancer. Therefore, further prospectively designed studies are required to address some of these questions. Fortunately, 2 large mortality morbidity trials, TREAT (Trial to Reduce Cardiovascular Events with Aranesp Therapy) in patients with chronic kidney disease and RED-HF (Reduction of Events with Darbepoetin alfa in Heart Failure) in heart failure patients, are in progress and are likely to provide definitive answers. (J Am Coll Cardiol 2008;52:501–11) © 2008 by the American College of Cardiology Foundation

The annual mortality in patients with chronic heart failure (HF) who are randomized in clinical trials has shown a remarkable decrease to approximately 8% with the use of beta-blockers and renin-angiotensin-aldosterone antagonists (1). However, the mortality in clinical practice remains very high (2). One reason for this disparity is the exclusion of patients from clinical trials with comorbid conditions that contribute to high mortality. Anemia is one such comorbidity and a novel therapeutic target in HF. This review will summarize the magnitude of the problem of anemia in HF and examine the factors that are associated with the development of anemia and the mechanisms by which anemia may worsen HF. The risks and benefits of treating anemia with erythropoietin-stimulating agents (ESA), a subject of much recent debate, also will be discussed.

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Prevalence of Anemia in HF

The World Health Organization defines anemia as hemoglobin (Hgb) <13.0 g/dl in men and <12.0 g/dl in women (3). Using this definition, Sarnak et al. (4) found 9% (men 5%; women 13%) of a normal population ages 45 to 64 years in the U.S. to have anemia. However, a more appropriate age-, gender-, and race-specific definition identified anemia in approximately 5% of the NHANES (National Health and Nutrition Examination Survey) population (5). The prevalence of anemia during HF varies depending on the definition and sample selection, as summarized in previous reviews (6–8). In clinical trials and large HF registries, the prevalence ranged from 15% to 61% and 14% to 70% among hospitalized patients. During the course of 1 year, new anemia developed in 9.6% of SOLVD (Studies Of Left Ventricular Dysfunction) patients (9), 16.9% of Val-HeFT (Valsartan Heart Failure Trial) patients (10), and 14.2% of COMET (Carvedilol Or Metoprolol European Trial) patients (11). The prevalence of anemia is similar in patients with impaired or preserved left ventricular (LV) function (12–15). In a large community study, 58% of HF patients had anemia of chronic disease, on the basis of International Classification of Diseases-9th Edition (285.9) code alone (16).

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Abbreviations and Acronyms

BNP = brain natriuretic peptide
BP = blood pressure
CKD = chronic kidney disease
CRP = C-reactive protein
EF = ejection fraction
ESA = erythropoietin-stimulating agents
Hct = hematocrit
HF = heart failure
Hgb = hemoglobin
IL = interleukin
IV = intravenous
LV = left ventricular
MLHFQ = Minnesota Living with Heart Failure Questionnaire
RBF = renal blood flow
SVR = systemic vascular resistance

Anemia during HF has been associated with older age, diabetes, chronic kidney disease (CKD), greater New York Heart Association (NYHA) functional class, lower exercise capacity, worse health-related quality of life, greater edema, lower blood pressure, greater use of diuretics, and greater levels of neurohormones, proinflammatory cytokines, and C-reactive protein (CRP) (10,17–21). Importantly, Hgb has a weak inverse relation to ejection fraction (EF) (10,15), and an increase in Hgb over time is associated with a decrease, not an increase, in EF (10,22).

Potential Causes of Anemia During HF

Hematinic abnormalities. Serum vitamin B12 and folic acid levels are low in only a minority of anemic patients with HF (23–25). Malabsorption and aspirin-induced gastrointestinal bleeding can cause iron deficiency. Detailed studies of iron homeostasis are not available. Lacking standard criteria (i.e., transferrin saturation, soluble transferrin receptor or ferritin levels), the reported prevalence of iron deficiency has varied from 5% to 21% (16,17,23,24,26). In a recent study, 43% of patients had either low serum iron (<8 μmol/l) or ferritin (<30 μg/l), but microcytic anemia was observed in only 6% patients (27). In contrast, Nanas et al. (28) found depleted iron stores in the bone marrow of 73% patients despite normal serum iron, ferritin, and erythropoietin. The mean corpuscular volume was at the lower limit of normal, suggesting that microcytic anemia was not present in all patients. These findings might be explained by diversion of iron from the bone marrow to the other reticuloendothelial stores, where it is not available for erythropoiesis even though serum iron and ferritin are normal or increased, a feature of anemia of chronic disease (29). Therefore, either absolute or relative iron deficiency may be more common than previously thought.

Renal dysfunction and impaired erythropoietin production. Erythropoietin is produced primarily in the kidney by specialized peritubular fibroblasts situated within the cortex and outer medulla (30). The primary stimulus for erythropoietin production is low PO_2 that activates hypoxia-inducible factor-1 in the peritubular fibroblasts, which induces transcription of the erythropoietin gene. The kidney is very susceptible to hypoxia despite the fact that it receives nearly 25% of the cardiac output and uses less than 10% of the oxygen delivered. To maintain the osmotic gradient generated by the loop of Henle, the arterial and venous blood vessels supplying it run countercurrent and in close contact, which leads to shunt diffusion of oxygen between the arterial and venous circulations, causing PO_2 to decrease across the renal parenchyma, reaching around 10 mm Hg at the tips of the cortical pyramids where the erythropoietin is produced (30). This area is very sensitive to small changes in the PO_2, resulting from an imbalance between oxygen supply and oxygen demand related to increased proximal tubular sodium reabsorption caused by low renal blood flow (RBF) and glomerular filtration rate.

During HF, RBF is decreased (31), and some renal dysfunction is common (7,32), but structural renal disease that could reduce erythropoietin production is infrequent. Therefore, reduced RBF should increase erythropoietin. Indeed, erythropoietin is increased, in proportion to the severity of HF, but is lower than expected for the degree of anemia, suggesting a blunted erythropoietin production (17,33,34). Studies of the complex relationship between RBF and erythropoietin secretion during HF have been inconsistent (25,35,36).

Anemia and the renin-angiotensin system. Angiotensin II decreases PO_2 by reducing RBF and increasing oxygen demand, thereby stimulating erythropoietin production. Angiotensin II also stimulates bone marrow erythroid progenitor cells (37). Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers cause a modest reduction in Hgb (10,38) by decreasing erythropoietin (39) and by preventing the breakdown of the hematopoiesis inhibitor *N*-acetyl-seryl-aspartyl-lysyl-proline (40).

Proinflammatory state, bone marrow dysfunction, and anemia of chronic diseases. Tumor necrosis factor-α, interleukin (IL)-6, and several other proinflammatory cytokines (17,41) and CRP are increased in HF (42) and inversely related to Hgb (18). Interleukin-6 and tumor necrosis factor-α inhibit erythropoietin production in the kidney by activating GATA-2 and nuclear factor-κB (43), which could explain the blunted erythropoietin response in HF. These cytokines also inhibit proliferation of bone marrow erythroid progenitor cells (44). Indeed, bone marrow in rats with HF show impaired erythropoiesis and have decreased number of erythropoietic progenitor cells, but the mechanisms remain unknown (45). Moreover, IL-6 stimulates the production of hepcidin in the liver that blocks duodenal absorption of iron (29). Furthermore, IL-6 downregulates the expression of ferroportin, preventing the release of iron from body stores (29). Thus, an activated proinflammatory state, an essential component of anemia of chronic disease (29), can contribute to the development of anemia by several mechanisms (Fig. 1).

In 148 patients with stable HF, a specific cause of anemia was identified in only 43% of cases (17). Iron deficiency was found in only 5% of patients. In the remaining 57%, proinflammatory cytokine activation, inadequate erythropoietin production, and/or defective iron utilization was found despite adequate iron stores,